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Content

Anemia of Prematurity

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INTRODUCTION	Section 2 of 10

Background: Anemia frequently is observed in the infant who is hospitalized and premature. Although many causes are possible, anemia of prematurity (AOP) is the most common diagnosis. AOP is a normocytic, normochromic, hyporegenerative anemia that is characterized by the existence of a low serum erythropoietin (EPO) level in an infant who has what may be a remarkably reduced hemoglobin concentration.

Although common, AOP remains a controversial issue for clinicians. Few universally accepted signs or symptoms are attributable to AOP. Even less agreement exists regarding the timing, method, and effectiveness of current therapeutic interventions in individuals with AOP. With an increasing number of transfusion-related complications reported in the last 2 decades, caregivers and families of infants understandably are concerned about the use of blood products. This article reviews the pathophysiology of AOP, the means of reducing blood transfusions, and the current status of recombinant EPO.

Pathophysiology: The 3 basic mechanisms for the development of anemia in any patient are inadequate red blood cell (RBC) production, shortened RBC life span or hemolysis, and blood loss. AOP has its roots in each of these processes.

Inadequate red blood cell production

The first mechanism of anemia is inadequate RBC production. The location of EPO and RBC production changes during gestation of the fetus. EPO synthesis initially occurs in cells of monocyte or macrophage origin that reside in the fetal liver, with production gradually shifting to the peritubular cells of the kidney. By the end of gestation, the liver remains a major source of EPO.

In the first few weeks of embryogenesis, fetal erythrocytes are produced in the yolk sac. This site is succeeded by the fetal liver, which, by the end of the first trimester, has become the primary site of erythropoiesis. Bone marrow then begins to take on a more active role in producing erythrocytes. By approximately 32 weeks' gestation, the burden of erythrocyte production in the fetus is shared evenly by the liver and bone marrow. By 40 weeks' gestation, the marrow is the sole erythroid organ. Premature delivery does not accelerate the ontogeny of these processes.

Although EPO is not the only erythropoietic growth factor in the fetus, it is the most important. EPO is synthesized in response to both anemia and hypoxia. The degree of anemia and hypoxia required to stimulate EPO production is far higher for the fetal liver than for the fetal kidney. As a result, new RBC production in the extremely premature infant (whose liver remains the major site of EPO production) is blunted despite what may be marked anemia.

In addition, EPO, whether endogenously produced or exogenously administered, has a larger volume of distribution and is eliminated more rapidly by neonates, resulting in a curtailed time for bone marrow stimulation. Erythroid progenitors of premature infants are quite responsive to EPO when that growth factor finally is produced or administered.

Shortened red blood cell life span or hemolysis

Secondly, the average life span of a neonatal RBC is only one half to two thirds that of the RBC life span in an adult. Cells of the most immature infants may survive only 35-50 days. The shortened RBC life span of the neonate is a result of multiple factors, including diminished levels of intracellular ATP, carnitine, and enzyme activity; increased susceptibility to lipid peroxidation; and increased susceptibility of the cell membrane to fragmentation.

Blood loss

Finally, blood loss may contribute to the development of AOP. If the neonate is held above the placenta for a time after delivery, a fetal-placental transfusion may occur. More commonly, because of the need to closely monitor the tiny infant, frequent samples of blood are removed for various tests. Because the smallest patients may be born with as little as 40 mL of blood in their circulation, withdrawing a significant percentage of an infant's blood volume in a short period is relatively easy. In one study, mean blood loss in the first week of life was nearly 40 mL.

Taken together, the premature infant is at risk for the development of AOP because of limited synthesis, diminished RBC life span, and increased loss of RBCs.

Frequency: **In the US:** Frequency of AOP is related inversely to the gestational age and/or birthweight of the population. As many as 80% of infants with very low birthweight (VLBW) and 95% of infants with extremely low birthweight (ELBW) receive blood transfusions during their hospitalizations.

Mortality/Morbidity: Although a premature infant is unlikely to be allowed to become so anemic as to die, complications from necessary blood transfusions ultimately can be responsible for the death of a patient. Anemia is blamed for a variety of signs and symptoms, including apnea, poor feeding, and inadequate weight gain.

Race: Race has no influence on the incidence of AOP.

Sex: Although the presence of testosterone in the male infant is believed to be at least partially responsible for a slightly higher hemoglobin level at birth, this effect is of no significance with regard to individuals with AOP.

Age:

- The more immature the infant, the more likely the development of AOP. AOP typically is not a significant issue for infants born beyond 32 weeks' gestation.

- The nadir of the hemoglobin level typically is observed when the tiniest infants are aged 4-8 weeks.
- AOP spontaneously resolves by the time most patients are aged 3-6 months.

History: Few symptoms are universally accepted as attributable to AOP; however, the following are among the symptoms that clinicians attribute to AOP:

- Poor weight gain
- Apnea
- Tachypnea
- Decreased activity
- Pallor
- Tachycardia
- Flow murmurs

Physical: Debate regarding the presence or absence of physical findings in the infant with AOP is ongoing. Clinical trials designed to determine the efficacy of blood transfusions in relieving these findings have produced conflicting results.

- Poor growth

  o Inadequate weight gain despite adequate caloric intake often is attributed to AOP.
  o The response of weight gain to transfusions has been inconsistent in the literature.

- Apnea

  o If severe enough, anemia may result in respiratory depression manifested by increased periodic breathing and apnea.
  o While some studies have demonstrated a decrease in frequency of these symptoms subsequent to blood transfusions, others have found similar results with simple crystalloid volume expansion.

- Decreased activity: Lethargy frequently is attributed to anemia, with subjective improvement subsequent to transfusion.

- Metabolic acidosis

  o Significant anemia can result in decreased oxygen-carrying capacity less than the needs of the tissue, resulting in increased anaerobic metabolism with production of lactic acid.
  o Blood transfusions have been documented to decrease lactic acid levels in otherwise healthy infants who are anemic and premature. Some medical professionals have suggested using lactate levels as an aid in determining the need for transfusion.

- Tachycardia

  o Infants with AOP may respond by increasing cardiac output through increased heart rates, presumably in response to inadequate oxygen delivery to the tissues caused by anemia.
  o Blood transfusions have been associated with a lowering of the heart rate in infants who are anemic.

- Tachypnea
- Flow murmurs

- AOP results from a combination of relatively diminished RBC production, shortened RBC life span, and blood loss.
- Nutritional deficiencies of vitamin E, vitamin B-12, and folate may exaggerate the degree of anemia.

DIFFERENTIALS

Anemia, Acute
Anemia, Chronic
Birth Trauma
Head Trauma
Hemolytic Disease of Newborn
Parvovirus B19 Infection
Periventricular Hemorrhage-Intraventricular Hemorrhage

Other Problems to be Considered:

Bone marrow infiltration
Disseminated intravascular coagulation
G-6-PD deficiency
Glucose kinase deficiency
Iron deficiency
Spherocytosis
Vitamin E deficiency

Diamond-Blackfan anemia
Elliptocytosis
GI bleeding
Immune-mediated hemolysis
Pancytopenia
Twin-to-twin transfusion syndrome

WORKUP

Lab Studies:

- Complete blood count

  - The CBC demonstrates normal white blood cell (WBC) and platelet lines.
  - The hemoglobin is less than 10 g/dL but may descend to a nadir of 6-7 g/dL; the lowest levels generally are observed in the smallest infants.
  - RBC indices are normal (eg, normochromic, normocytic) for age.

- Reticulocyte count

  - The reticulocyte count is low when the degree of anemia is considered as a result of the low levels of EPO.
  - The finding of an elevated reticulocyte count is not consistent with the diagnosis of AOP.

- Peripheral blood smear: No abnormal forms are observed.
- Maternal and infant blood typing: In the evaluation of anemia, consider the possibility of hemolytic processes, such as the ABO blood group system and Rh incompatibility.
- Direct antibody test (Coombs): This test may be coincidentally positive; however, with such a finding, ensure that an immune-mediated hemolytic process is not ongoing.
- Serum bilirubin: With an elevated serum bilirubin level, consider other possible explanations for the anemia.

==Medical Care:== The medical care options available to the clinician treating an infant with AOP are prevention, blood transfusion, and recombinant EPO treatment.

Prevention

- Reducing the amount of blood taken from the premature infant diminishes the need to replace blood. When caring for the premature infant, carefully consider the need for each laboratory study obtained. Hospitals with care for premature infants should have the ability to determine laboratory values using very small volumes of serum.
- Manufacturers are developing an array of technologies that require extremely small amounts of blood for a steadily increasing number of tests. Likewise, devices that allow blood gases and serum chemistries to be determined at bedside via an analyzer attached to the umbilical artery catheter without loss of blood recently have been developed. The impact of such devices on the development of anemia and/or the need for transfusions has yet to be determined.
- The use of noninvasive monitoring devices, such as transcutaneous hemoglobin oxygen saturation, partial pressure of oxygen, and partial pressure of carbon dioxide, may allow clinicians to decrease blood drawing; however, no data currently support such an impact of these devices.

Blood transfusion

- Packed red blood cell (PRBC) transfusions: Despite disagreement regarding timing and efficacy, PRBC transfusions continue to be the mainstay of therapy for the individual with AOP. The frequency of blood transfusions varies with gestational age, degree of illness, and, interestingly, the hospital evaluated.
- Reducing the number of transfusions: Studies derived from individual centers document a marked decrease in the administration of PRBC transfusions over the past 2 decades, even before the use of EPO. This decrease in transfusions is almost certainly multifactorial in origin. One frequently mentioned component is the adoption of transfusion protocols that take a variety of factors into account, including hemoglobin levels, degree of cardiorespiratory disease, and traditional signs and symptoms of pathologic anemia. Using various audit criteria and indications for transfusions suggested by Canadian, American, and British authorities, the Medical University of South Carolina has instituted the following transfusion guidelines:
  - Do not transfuse for phlebotomy losses alone.
  - Do not transfuse for hematocrit alone, unless the hematocrit level is less than 21% with a reticulocyte count less than 100,000.
  - Transfuse for shock associated with acute blood loss.
  - For an infant with cyanotic heart disease, maintain a hemoglobin level that provides an equivalent fully saturated level of 11-12 g.
  - Transfuse for hematocrit levels less than 35-40% in the following situations:
    - Infant with severe pulmonary disease (defined as requiring >35% supplemental hood oxygen or continuous positive airway pressure [CPAP] or mechanical ventilation with a mean airway pressure of >6 cm water)
    - Infant in whom anemia may be contributing to congestive heart failure
  - In the following situations, transfuse for a hematocrit level that is 25-30% or less:
    - The patient requires nasal CPAP of 6 cm water or less (supplemental hood oxygen of <35% by hood or nasal cannulae).
    - The patient has significant apnea and bradycardia (defined as >9 episodes in 12 h or 2 episodes in 24 h, requiring bag-mask ventilation while receiving therapeutic doses of methylxanthines).
    - The patient has persistent tachycardia or tachypnea without other explanation for 24h.
    - Weight gain of patient is deemed unacceptable in light of adequate caloric intake without other explanation, such as known increases in metabolic demands or known losses in metabolic demands (malabsorption).
    - The patient is scheduled for surgery; transfuse in consultation with the surgery team.

- Reducing the number of donor exposures: In addition to reducing the number of transfusions, reducing the number of donor exposures is important. This can be accomplished as follows:
  - Use PRBCs stored in preservatives (eg, citrate-phosphate-dextrose-adenine [CPDA-1]) and additive systems (eg, Adsol). Preservatives and additive systems allow blood to be stored safely for up to 35-42 days. Infants may be assigned a specific unit of blood, which may suffice for treatment during their entire hospitalization.
  - Use volunteer-donated blood and all available screening techniques. The risk of cytomegalovirus (CMV) transmission can be reduced dramatically (but not entirely) through the use of CMV-safe blood. This can be accomplished by using either CMV serology-negative cells or blood processed through leukocyte-reduction filters. This latter method also reduces other WBC-associated infectious agents (eg, Epstein-Barr virus, retroviruses, *Yersinia enterocolitica*). The American Red Cross now is providing exclusively leukocyte-reduced blood to hospitals in the United States.

Recombinant erythropoietin treatment

- Multiple investigations have established that premature infants respond to exogenously administered recombinant human EPO with a brisk reticulocytosis. Modest decreases in the frequency of PRBC transfusions have been documented primarily in premature infants who are relatively large.
- Recent trials have evaluated the impact of EPO treatment in populations of the most immature neonates. These studies likewise have demonstrated that infants with VLBW are capable of responding to EPO with a reticulocytosis and that the drug appears to be safe. Conversely, the hemoglobin level of infants treated with EPO falls to at or below the hemoglobin level of the control group within 1 week of treatment cessation, and the impact on transfusion requirements ranges from nonexistent to small.
- No agreement regarding timing, dosing, route, or duration of therapy exists. In short, the cost-benefit ratio for EPO has yet to be clearly established, and this medication is not accepted universally as a standard therapy for the individual with AOP. When the family has religious objections to transfusions, the use of EPO is advisable.

Consultations: Neonatology and Pediatric hematology
Diet: Provision of adequate amounts of vitamin E, vitamin B-12, folate, and iron are important to avoid exacerbating the expected decline in hemoglobin levels in the premature infant.

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Drug Category: *Growth factors* -- Hormones that stimulate production of red cells from the erythroid tissues in the bone marrow.

Drug Name	Epoetin alfa (Epogen, Procrit) -- Used to stimulate erythropoiesis and decrease the need for erythrocyte transfusions in high-risk preterm neonates. Stimulates division and differentiation of committed erythroid progenitor cells. Induces release of reticulocytes from bone marrow into blood stream. Infants require supplemental iron and vitamin E. Some physicians also use folate.
Adult Dose	Mother: 400 U/kg/dose IV/SC 3 times/wk until postconceptional age 35w
Pediatric Dose	72 hours: 200 U/kg/d IV for 14 d 10 days: 200 U/kg/dose SC 3 times/wk for 6 wk 10-35 days: 100 U/kg/d IV 2 times/wk for 6 wk
Contraindications	Documented hypersensitivity; uncontrolled hypertension
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.

Precautions	Caution in porphyria, hypertension, history of seizures; decrease dose if hematocrit increase exceeds 4 U in any 2-wk period; multidose vials contain benzyl alcohol

Organic substances required by the body in small amounts for various metabolic processes. Used clinically for the prevention and treatment of specific deficiency states.

Drug Name	Ferrous sulfate (Feosol) -- Nutritionally essential inorganic substance.
Pediatric Dose	5 mg/kg/wk (based on elemental iron content) IV; alternatively, 6 mg/kg/d PO
Contraindications	Documented hypersensitivity
Interactions	Absorption is enhanced by ascorbic acid; interferes with tetracycline absorption; food and antacids impair absorption
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	GI upset; iron toxicity is observed with ingestion of large amount and can be fatal, especially in children; parenteral (IV) administration may cause several reactions, including headaches, malaise, fever, generalized lymphadenopathy, arthralgia, and urticaria; can cause severe anaphylaxis; other reactions include phlebitis at infusion site

Drug Name	Vitamin E (Aquasol E, Vitec) -- Protects polyunsaturated fatty acids in membranes from attack by free radicals and protects RBCs against hemolysis.
Pediatric Dose	25 IU/d PO initially; measure plasma tocopherol within 1 wk and adjust dose accordingly
Contraindications	Documented hypersensitivity
Interactions	Mineral oil decreases absorption; delays absorption of iron and increases effects of anticoagulants
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Pregnancy category C with large doses of vitamin E; vitamin E may induce vitamin K deficiency; necrotizing enterocolitis may occur with administration of large doses

Drug Name	Folic acid (Folvite) -- Important cofactor for enzymes used in production of RBCs
Pediatric Dose	50 mcg/d PO
Contraindications	Documented hypersensitivity
Interactions	Increase in seizure frequency and decrease in subtherapeutic levels of phenytoin reported when used concurrently
Pregnancy	A - Safe in pregnancy
Precautions	Pregnancy category C if dose exceeds RDA; benzyl alcohol present in some products as preservative; has been associated with fatal gasping syndrome in premature infants; resistance to treatment may occur in patients with alcoholism and deficiencies of other vitamins

Further Outpatient Care: After discharge from the hospital, ensure regular determination of hematocrit levels in infants with APO. Once a steady increase in the hematocrit level has been established, only routine checks are required.

In/Out Patient Meds: Administer and/or prescribe iron supplementation according to standard guidelines.

Transfer: Transfer generally is not required unless transfusions cannot be carried out in the hospital's nursery.

Deterrence/Prevention: Limit diagnostic blood draws to a minimum.

Complications:

- Transfusion-acquired infections (eg, hepatitis, CMV, HIV, syphilis)
- Transfusion-associated fluid overload and electrolyte imbalances
- Transfusion-associated exposure to plasticizers
- Transfusion-associated hemolysis
- Posttransfusion graft versus host disease

Prognosis: Spontaneous recovery in the individual with AOP occurs by age 3-6 months.

Patient Education:

- Explain the normal course of anemia.
- Explain criteria for and risks of transfusions.
- Explain advantages and disadvantages of EPO administration.

Medical/Legal Pitfalls:

- Failure to consider anemia as a possible cause of signs and symptoms
- Failure to notify the family about the patient's need for transfusion before the transfusion
- Failure to consider the family's religious beliefs regarding transfusions
- Failure to anticipate transfusion-acquired infections and complications

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Anemia of Prematurity excerpt

Apnea of Prematurity

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INTRODUCTION	Section 2 of 11

Background: A fetus makes breathing movements from early in pregnancy, although the purpose of fetal breathing is unknown. Breathing is intermittent in the fetus and becomes continuous after birth. The mechanisms that cause the transition from intermittent fetal breathing to continuous neonatal breathing remain unelucidated. All premature neonates, as well as most full-term neonates, have apnea, which is defined as pauses in their breathing pattern. In most instances, this apnea is brief and causes no physiologic changes.

Definition and classifications of apnea

Pathologic apnea is defined as apnea exceeding 20 seconds' duration or apnea of shorter than 20 seconds if it is accompanied by bradycardia or oxygen desaturation. Bradycardia in a premature neonate is considered significant when the heart rate slows at least 30 beats per minute (bpm) from the resting heart rate. An oxygen saturation level less than 85% is considered pathologic in this age group. In all cases, the decrease in saturation should persist for at least 5 seconds. These levels represent significant apnea, bradycardia, and oxygen saturation changes that rarely occur in healthy preterm neonates older than 36 weeks after conception.

Apnea is classified as central, obstructive, or mixed. Central apnea is defined as the cessation of both airflow and respiratory effort (see Image 1). Obstructive apnea is the cessation of airflow in the presence of continued respiratory effort. Mixed apnea contains elements of both central and obstructive apnea (see Image 2), either within the same apneic pause or at different times during a period of respiratory recording.

Apnea of infancy

Apnea of infancy (AOI) occurs when apnea persists in a neonate older than 37 weeks after conception. The physiologic aspects of apnea of prematurity (AOP) and AOI coincide, although further studies are needed to determine the exact nature of their relationship.

<mark>Periodic breathing</mark> :

Periodic breathing (PB) is defined as periods of regular respiration for as long as 20 seconds followed by apneic periods no longer than 10 seconds that occur at least 3 times in succession (see Image 3). In most cases, PB accounts for 2-6% of the breathing time in healthy term neonates and as much as 25% of the breathing time in preterm neonates. PB occurrence is directly proportional to the degree of prematurity. Kelly and coworkers found that PB occurred in 78% of patients examined at age 0-2 weeks; the incidence declined significantly to 29% at age 39-52 weeks. This condition does not occur in neonates during their first 2 days of life.

PB is more frequent during active sleep, but it can occur when neonates are awake or quietly sleeping. This pattern, common at high altitudes, is eliminated with the administration of supplemental oxygen and/or with the use of continuous positive airway pressure (CPAP). Because the prognosis is excellent, no treatment is usually required.

<mark>Pathophysiology:</mark> Inspiration is controlled by an off switch. During inspiration, the augmenting discharge of the central inspiratory activator to the inspiratory motor neurons and specialized right bundle (Rb) neurons suddenly causes the off-switch neurons to discharge, transiently inhibiting the central inspiratory activator and allowing passive exhalation. Pulmonary volume sensors and the rostral pontine pneumotaxic center also control the off switch.

The pathophysiology of AOP has been attributed to abnormal breathing control caused by neuronal immaturity of the brainstem. This immaturity probably is secondary to decreased afferent traffic from peripheral receptors to the reticular formation. When dendritic and other synaptic interconnections multiply, breathing control improves as the brain matures, and AOP tends to resolve. This resolution typically occurs 34-52 weeks after conception.

Indomethacin stimulates phrenic neural output in an anesthetized piglet model; this finding supports the concept that prostaglandins inhibit breathing early in neonatal life. The final output of the respiratory control nuclei in the medulla may be a complex function of many inhibitory and stimulatory inputs, both humoral and neural. The exact manner in which these are altered during AOP remains unknown.

Sleep

Although determining the sleep state in neonates younger than 34 weeks is controversial, apnea appears to occur predominantly during active (ie, rapid eye movement [REM]) and indeterminate or transitional sleep in preterm and full-term neonates. Several mechanisms have been proposed to explain the high incidence of apnea during active sleep. Chest-wall movements are predominantly out of phase or paradoxical during active sleep, unlike their state during quiet sleep. A decrease in the fractional catabolic rate (FCR) and a decrease of 6-10 mm Hg in PaO_2 have been observed in infants during active sleep, and both effects predispose an infant to apneic episodes. Moreover, ventilatory responses to increased carbon dioxide and decreased oxygen concentrations attenuate during active sleep.

Chemoreceptors

Preterm neonates respond to a decrease in the inspired oxygen concentration by transiently increasing the ventilation rate for approximately 1 minute and then returning to baseline or even depressed ventilation rates. A progressive decrease in the inspired oxygen concentration causes significant flattening of carbon dioxide responsiveness in preterm neonates. This unstable response to low concentrations of inspired oxygen may play an important role in the etiology of neonatal apnea. Central chemoreceptor activity is less developed in immature neonates younger than 33 weeks after conception. The sensitivity of the central chemoreceptor to CO_2 is reduced in premature neonates and increases progressively with gestational age to adult levels by term. The sensitivity to CO_2 is increased with higher O_2 concentrations and decreased in hypoxemia.

The primary problem for premature neonates may be the relative weakness of the peripheral chemoreceptor function, at least during the first few weeks of life. The central hypoxic depression of ventilation, mediated by the midbrain inhibitor, also disappears about 2-3 weeks after birth when the mature response of sustained hypoxic stimulation of ventilation becomes dominant.

Upper airway

Reflexes originating from the upper airway may directly alter the pattern of respiration in infants and play a crucial role in initiating and terminating apnea. Sensory input from these upper airway receptors travels to the CNS through cranial nerves V, VI, IX, X, XI, and XII and may have powerful effects on the respiratory rate and rhythm, heart rate, and vascular resistance. These observations suggest that afferent sensory input from the upper airway is necessary for airway patency.

Adenosine

Adenosine and its analogues cause respiratory depression. Adenosine antagonism also has been proposed as a mechanism to explain the therapeutic effect of theophylline.

Oxygen

Inhalation of low oxygen concentrations produces an immediate 1-minute-long increase in the ventilation rate, followed by a 5-minute-long decrease. Infants with borderline hypoxia tend to breathe periodically or have apneic spells. These apneic spells, which are frequently associated with bradycardias, can be relieved by increasing the inspired oxygen concentration. Hypoxia also can induce PB in these infants.

Hering-Breuer reflex

The Hering-Breuer reflex (ie, inflation reflex) decreases the frequency of inspiratory effort during distension of the lungs. This effect is reflex-mediated via afferent vagal fibers. The Hering-Breuer reflex is more active in neonates than in adults, to the extent that small increases in lung volume may cause apnea.

Bradycardia

Bradycardias observed during apnea may result from chemoreceptor-induced inhibition of the heart rate in the absence of ventilatory effort.

Swallowing

AOP can be distinguished from PB by the frequent swallowing-like movements in the pharynx during the apnea. The etiology of swallowing during apnea is unknown.

Frequency:

- **In the US:** Although not always apparent, AOP is the most common problem in premature neonates. Approximately 70% of babies born at less than 34 weeks' gestation have clinically significant apnea, bradycardia, or oxygen desaturation during their hospitalization. Apnea is more frequent in less mature infants. Apnea may occur during the postnatal period in 25% of neonates who weigh less than 2500 g at birth and in 84% of neonates who weigh less than 1000 g. Carlo and associates have shown that apnea onset may occur on the first day of life in neonates without respiratory distress syndrome. AOP frequency rates may be as high as 50% in premature babies. An estimated 50% or more of surviving infants who weigh less than 1500 g at birth have apneic episodes that must be managed with ventilatory support or pharmacologic intervention.

Mixed apnea accounts for approximately 50-75% of all cases of apnea in premature neonates, 10-20% of obstructive apneas, and 10-25% of central apneas. In 50% of all apneic episodes, central apnea is either preceded or followed by an obstructive component and leads to mixed apnea.

- **Internationally:** To the author's knowledge, no data are available to compare the incidences of AOP in other countries.

Mortality/Morbidity: Butcher-Puech and coworkers found that infants in whom obstructive apnea exceeded 20 seconds in duration had a higher incidence of intraventricular hemorrhage, hydrocephalus, prolonged mechanical ventilation, and abnormal neurologic development after their first year of life. In 1985, Perlman and Volpe described a decrease in the cerebral blood flow velocity that accompanies severe bradycardia (ie, heart rate <80 bpm). Infants with significant AOP do not perform as well in neurodevelopmental follow-up testing as similar premature infants without recurrent apneas.

Race: No racial predilection exists.

Sex: No sex predilection exists.

Age: AOP affects approximately 70% of neonates aged 34-35 weeks after conception. Although the frequency progressively decreases during their subsequent weeks of life, approximately 30-40% of neonates born prematurely still have AOP at the expected due date. Significant apnea and/or hypoxemic events have been well documented in premature neonates beyond term. The mean time for AOP resolution is approximately 50-52 weeks after conception.

Findings from other recent studies indicate that 6-22% of babies with a very low birth weight have apnea at term, and that 91% of premature neonates have apnea exceeding 12 seconds in duration at the time of hospital discharge. Of these babies, 31% also had bradycardia, and 6.5% required prolonged hospitalization because of the severity of their apnea and bradycardia. These findings show that AOP does not resolve at term in many low-birth-weight infants and that it may be present for some time after hospital discharge.

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History:

- Usually, the decrease in PO_2 in full-term neonates with apnea is directly proportional to the duration of apnea; it also is significantly greater in obstructive than in central apnea.
- All forms of apnea are difficult to detect visually, although obstructive apnea usually is more obvious to a trained observer.
- Precise apnea diagnosis requires multichannel recordings, which are most commonly used to measure nasal airflow and thoracic impedance, average heart rate, and oxygen saturation.
- Published findings show that even highly trained observers miss more than 50% of AOP episodes.

Physical: The physical examination should include observation of the infant's breathing patterns while he or she is asleep and awake.

- Monitor the baby's cardiac, neurologic, and respiratory status.
- Observe the infant during feeding periods for any signs of breathing difficulty, desaturation, or bradycardia.
- Reflex effects of apnea include characteristic changes in the heart rate, BP, and pulse

pressure. Bradycardia may begin within 1.5-2 seconds of apnea onset. Apneic episodes associated with bradycardia are characterized by heart rate decreases of more than 30% below the baseline rates. This reflex bradycardia is secondary to hypoxic stimulation of the carotid body chemoreceptor or a direct effect of hypoxia on the heart.

Causes: A premature neonate in whom all other causes of apnea have been excluded may be considered to have true idiopathic apnea. Although the etiology of AOP is not fully understood, several mechanisms have been proposed to explain this condition, including the following:

- AOP is considered the final response of incompletely organized and interconnected respiratory neurons to a multitude of afferent stimuli. Abnormal control of breathing is secondary to neuronal immaturity of the brain.
- In a premature neonate, protective respiratory reflex activity is decreased, and Hering-Breuer reflex activity is increased.
- Dopaminergic receptors may have an inhibitory role in peripheral chemoreceptor responses and central neural mechanisms elicited by hypoxia. Evidence from neonatal animal studies indicates that endogenous endorphins may depress the central respiratory drive. Although endogenous opiates may modulate the ventilatory response to hypoxia in newborn animals, a competitive opiate receptor antagonist, naloxone, has no benefit in the resuscitation of an asphyxiated human neonate. Naloxone appears to have no therapeutic role in AOP.
- Negative luminal pressures are generated during inspiration, and the compliant pharynx of the premature neonate is predisposed to collapse. Genioglossus activation failure has been most widely implicated in mixed and obstructive apnea in adults and infants. The ability of medullary chemoreceptors to sense elevated CO_2 levels is impaired; thus, an absent, small, or delayed upper airway muscle response to hypercapnia can possibly cause upper airway instability when accompanied by a linear increase in chest-wall activity. This impairment may predispose the infant to obstructed inspiratory efforts after a period of central apnea.

- Another important factor to consider is the excitation of chemoreceptors in the larynx by acid reflux. Laryngeal receptors send afferent fibers to the medulla and can elicit apnea when stimulated.
- Swallowing during a respiratory pause is unique to apnea and does not occur during PB. Accumulation of saliva in the pharynx hypothetically could prolong apnea with a chemoreflex mechanism and also elicit swallowing movements.
- Gastroesophageal reflux (GER) has been associated with recurrent apnea. Menon et al observed that regurgitation of formula into the pharynx after feeding is associated with an increased incidence of apnea in premature infants. Gastric fluids can possibly activate laryngeal chemoreflexes, leading to apnea. Aminophylline may also exacerbate reflux in patients with apnea. On the other hand, findings from several studies have not demonstrated a relationship between episodes of apnea and episodes of acid reflux into the esophagus.
- However, Newell et al demonstrated that effective control of GER in infants with xanthine-resistant AOP was associated with a significant decrease in number of apneas. In 1992, Booth suggested that the reduction of apneic episodes was due to the resolution of esophagitis because clinical improvement of apnea occurred 1-2 days after initiation of antireflux therapy.
- Many clinicians treat xanthine-resistant apnea with H2 blockers, metoclopramide, thickened formula, and upright positioning during feeding. However, to the author's knowledge, no controlled trials have demonstrated that antireflux medications are effective in preventing apnea.

DIFFERENTIALS	Section 4 of 11

Anemia of Prematurity
Neonatal Sepsis
Respiratory Failure
Respiratory Syncytial Virus Infection

Lab Studies:

- A CBC and cultures of blood, urine, and spinal fluid are necessary if a serious bacterial infection is suspected.
- Tests for serum ammonia, urine and serum amino acid, and organic acid levels are useful if a metabolic disorder is suspected.
- Serum electrolyte, calcium, and glucose levels can help in diagnosing a recent stressful condition, metabolic process, or chronic hypoventilation.
- A stool specimen test for botulism helps if the infant with apnea has associated constipation and hypotonia.

Imaging Studies:

- Chest radiography and/or radionuclide milk scanning can help if the child has persistent, yet unexplained, lower airway symptoms.
- Upper airway evaluation, including lateral neck radiography and otolaryngologic evaluation, is useful for cases of fixed or recurrent stridor, as well as cases of unexplained pathologic obstructive apnea.
- Imaging studies of the head are necessary when an intracranial hemorrhage is suspected or when findings include dysmorphic features, abnormal neurologic results, or mental status changes.
- A barium swallow study is useful if the infant has signs of swallowing dysfunction or anatomic anomalies (eg, esophageal web, tracheoesophageal fistula).
- A gastric emptying study and abdominal sonography are useful in patients whose clinical picture includes a generalized GI motility disorder or pyloric stenosis.

Other Tests:

- Perform a continuous multichannel recording to measure the chest-wall movement, nasal and/or oral airflow (or change in air temperature), oxygen saturation, and heart rate trend. (A 2-channel pneumogram that is used to measure only chest-wall excursion and heart rate trend provides insufficient information.) The following results are diagnostic:

    o Central apnea - Absence of nasal airflow and wall movement
    o Obstructive apnea - Lack of airflow despite chest-wall movement
    o Mixed apnea - Combined results of central and obstructive apnea

- If GER is suspected, obtain an intraesophageal pH recording by means of multichannel recording.
- Consider obtaining an electroencephalogram (EEG) in infants in whom apneic seizures are suspected or in whom persistent pathologic central apnea without an identifiable cause is present.
- Obtain an echocardiogram (ECHO), and consult a cardiologist if the history or physical examination results (eg, feeding difficulties, heart murmur, cyanosis) suggest cardiac disease.

- Electrocardiographic (ECG) results are useful in patients with severe unexplained tachycardia or bradycardia. Cardiac conduction abnormalities (eg, prolonged-QT syndrome) are rare but important causes of infant apnea.
- Evaluate unilateral choanal stenosis and choanal atresia by passing a 5-8F feeding tube through both nares. CT scanning is the method of choice for definitive diagnosis.

- Stimulation

  - Tactile stimulation usually is sufficient to terminate an apneic event.
  - Gently elevate the infant's jaw if the upper airway is obstructed.

- Oxygen administration
  - Supplemental oxygen administration or bag-mask ventilation is indicated for infants with signs of bradycardia or desaturation.
  - Medical treatment is indicated when apneic episodes number 6-10 or more per day or when the infant does not respond to tactile stimulation or requires bag-mask ventilation.

- CPAP use

  - CPAP has been used to treat apnea in preterm neonates, and it is indicated when the infant continues to have apneic episodes despite a therapeutic methylxanthine serum level.
  - CPAP is delivered with nasal prongs, a nasal mask, or a face mask with 3-6 cm of water pressure.
  - CPAP is used to effectively treat mixed and obstructive apnea, but it has little or no effect on central apnea. This limitation suggests that CPAP may reduce the frequency of apnea by means of several mechanisms, including stabilization of PaO_2 by increasing the functional residual capacity (FRC), by altering the influence of stretch receptors on respiratory timing, or by splinting the upper airway in an open position.

Methylxanthine administration may help reduce the incidence of events in a child with central apnea, although apnea in 15-20% of children does not respond to methylxanthines.

Home monitoring after discharge always is necessary for an infant whose apneic episodes continue despite methylxanthine administration. Infants undergoing methylxanthine therapy should rarely be sent home without a monitor because apnea may recur once they outgrow their therapeutic level. Some families, however, cannot manage a monitor in the home, and, in these cases, caffeine administration may be the only possible therapy. For more about follow-up care, see Follow-up Care.

Doxapram use should be reserved for infants in whom appropriate methylxanthine therapy and CPAP fail to control severe apneic events.

Drug Category: *Methylxanthines* -- These appear to stimulate skeletal and diaphragmatic muscle contraction, increase the ventilatory center's sensitivity to carbon dioxide, and stimulate the central respiratory drive.

Drug Name	Aminophylline (Aminophyllin) -- Stimulates central respiratory drive and peripheral chemoreceptor activity; may increase diaphragmatic contractility. Aminophylline salt is 78.9% theophylline, and theophylline PO is 80% bioavailable; dose adjustment may be necessary when changing from IV aminophylline to PO theophylline. Aminophylline is significantly interconverted to caffeine; if changing from IV to PO aminophylline, increase dosage by 20%. IV and PO aminophylline is effective in 80% of infants with central apnea.
Pediatric Dose	Loading dose: 4-6 mg/kg PO or IV infusion over 30 min Maintenance dose: 1.5-3 mg/kg/dose PO q8-12h or slow IVP q8-12h (start maintenance dose 8-12 h after loading dose) Therapeutic serum concentration (trough) for AOP: 7-12 mcg/mL
Contraindications	Documented hypersensitivity; uncontrolled arrhythmias; peptic ulcers; hyperthyroidism; uncontrolled seizure disorders
Interactions	Incompatible with cefotaxime, ceftriaxone, clindamycin, dobutamine, epinephrine, hydralazine, insulin, isoproterenol, methadone, methylprednisolone, penicillin G, and phenytoin; aminoglutethimide, barbiturates, carbamazepine, ketoconazole, loop diuretics, charcoal, hydantoins, phenobarbital, phenytoin, rifampin, isoniazid, and sympathomimetics may decrease effects of theophylline; theophylline effects may increase with allopurinol, beta-blockers, ciprofloxacin, corticosteroids, disulfiram, quinolones, thyroid hormones, ephedrine, carbamazepine, cimetidine, erythromycin, macrolides, propranolol, and interferon
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in peptic ulcers, hypertension, tachyarrhythmias, hyperthyroidism, and compromised cardiac function; do not inject IV solution >25 mg/min; greater risk of toxicity in pulmonary edema or liver dysfunction because of reduced clearance; monitor heart rate and blood glucose periodically; consider withholding next dose if heart rate >180 bpm; may produce GI irritation, hyperglycemia, CNS irritability, and sleeplessness; may be associated with renal calcifications when used concurrently with furosemide and/or dexamethasone; signs of toxicity include sinus tachycardia, failure to gain weight, vomiting, jitteriness, hyperreflexia, and seizures
Drug Name	Caffeine citrate (Cafcit) -- Increases respiratory center output, chemoreceptor sensitivity to CO_2, and cardiac output; serum half-life is 40-230 h; half-life is prolonged in cholestatic hepatitis.
Pediatric Dose	Loading dose: 20-40 mg/kg PO or IV over 30 min; equivalent to 10-20 mg/kg of caffeine base Maintenance dose: 5-8 mg/kg PO qd or slow IVP; equivalent to 2.5-4 mg/kg of caffeine base; start maintenance dose 24 h after loading dose
Contraindications	Documented hypersensitivity; products containing sodium benzoate
Interactions	Cimetidine may impair caffeine hepatic metabolism, increasing clearance and half-life; phenytoin induces hepatic metabolism of caffeine, decreasing its half-life and increasing clearance; increases metabolism of phenobarbital; increases its own metabolism; can reduce theophylline clearance by 25% and increase elimination half-life; may enhance cardiac inotropic effects of beta-adrenergic stimulating agents; slightly increases urine levels of VMA, catecholamines, and 5-hydroxyindoleacetic acid
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Restlessness, vomiting, and functional cardiac symptoms (eg, tachycardia, extrasystoles, palpitations) possible

Drug Name	Doxapram (Dopram) -- Stimulates respiratory drive by activating peripheral carotid chemoreceptors; increases tidal volume and slightly increases respiratory rate; stimulates medullary respiratory center with increasing doses; induces pressor response due to improved cardiac output (greater in hypovolemic patients).
Pediatric Dose	0.5-2.5 mg/kg/h continuous IV infusion
Contraindications	Documented hypersensitivity; epilepsy; mechanical obstruction; muscle paresis; flail chest, pneumothorax, other restrictive lung diseases; head injury; stroke; significant cardiovascular impairment; severe hypertension; intraventricular hemorrhage and kernicterus reported when used in a neonate's first week of life or when the bilirubin level is high.
Interactions	Delay infusion for at least 10 min after discontinuation of anesthetics known to cause myocardium sensitivity to catecholamines; may temporarily mask residual effects of muscle relaxants; additive pressor effect may occur if coadministered with MAOIs
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Caution in neonates; contains benzyl alcohol, which has been associated with a fatal gasping syndrome in premature neonates; incidence of hypertension and CNS symptoms increase at infusion rates >1.5 mg/kg/h

FOLLOW-UP	Section 8 of 11

Further Inpatient Care:

- Most neonatologists agree that babies should be apnea-free for 2-10 days before discharge. The minimum length of this apnea-free period has been subject to debate among clinicians. Darnall et al concluded that otherwise healthy preterm neonates continue to have periods of apnea separated by as many as 8 days before the last one before discharge. Infants with longer apnea intervals often have risk factors other than AOP.
- Home monitoring after discharge is necessary for an infant whose apneic episodes continue despite methylxanthine administration. Infants undergoing methylxanthine therapy rarely are sent home without a monitor because apnea may recur once they outgrow their therapeutic level. Without a monitor, caregivers may not know when apnea reappears.
- Some families, however, cannot manage a monitor in the home, and, in these cases, caffeine administration may be the only possible therapy. Seriously consider frequent follow-up for such infants, and readmit them for further study when blood levels approach the subtherapeutic range.

Further Outpatient Care:

- Home monitors

  - Among the several types of monitors now available for home use in the United States, the most common combines impedance pneumography with assessment of the average heart rate to provide cardiorespiratory monitoring. The most significant drawback of impedance monitors is their inability to detect obstructive apnea.
  - Standard home monitors detect respiratory signals and heart rates. Electrodes are placed directly on the infant's chest or inside an adjustable belt secured around his or her chest.
  - Recently developed units store records of events, which help the physician to evaluate home events. These devices also provide a record of compliance to show monitor use. The event recorder has a computer chip that continuously records respiratory and cardiac signals. Normal signals are erased, but any event that violates preset alarm parameters activates the monitor to save records of that event, as well as records of activities 15-75

seconds before and 15-75 seconds after the event. Additional channels are available to record pulse oximetry, nasal airflow, and body position (eg, prone, supine) findings. The monitor records are downloaded within 24 hours after a parent's report of an event or after excessive alarms.

- o Many units now have computer modems that instantly transmit data to the physician's office for evaluation. These easily installed devices are especially useful for families who have had problems with events or alarms.
- o Some devices, such as pulse oximeters, piezo belts, and pressure capsules, have been impractical to use or have had limited applications. Newer technologies and software programs, however, may soon make oximeters and similar devices more practical.
- o All monitoring devices are associated with false alarms, which occur when no true cardiorespiratory event has occurred. False alarms worry parents and, if they occur often, may discourage monitor use. Excessive false alarms usually can be minimized by alternative electrode placement and parental education.Image 4 illustrates an approach to apnea monitoring in the premature neonate. Monitoring depends on the frequency of observed events during hospitalization of the premature neonate, the size and stability of the infant at the time of discharge, and the degree of parental anxiety.
- o Careful follow-up is needed with all home monitoring of premature neonates. Physicians who have limited experience with home monitoring or who cannot interpret downloaded monitor recordings should seek assistance from a center or program with expertise in these areas.
- o Parents of infants with home monitors must have a clearly designated person to contact on a regular basis and during emergencies. Many programs or centers provide 24-hour assistance for families of children with home monitors.
- o The mean duration of home monitoring for premature neonates usually is less than 6 weeks. Reserve extended monitoring for infants whose recordings show significant cardiorespiratory abnormalities. Only in the rarest of circumstances should any child be monitored beyond age 1 year. Most often, children who require monitoring in such circumstances have other conditions that require additional technology, such as bronchopulmonary dysplasia with home mechanical ventilation.
- o For infants who require methylxanthine, stop drug therapy after 8 weeks without true events, but continue monitoring for 4 additional weeks. If no events are noted in that period, monitoring can be discontinued.

- Indications for home monitoring

  - o Historical evidence of significant apnea or an apparent life-threatening event (ALTE)
  - o Documentation of apnea on recording monitor or multichannel evaluation
  - o GER with apnea
  - o Sibling or twin of patient who died from sudden infant death syndrome (SIDS) or other postneonatal cause of death
    - The National Institutes of Health (NIH) consensus conference recommends monitoring the siblings of infants with SIDS only after 2 SIDS-related deaths have occurred in a family. Siblings of patients who died from SIDS routinely are monitored until 1 month past the sibling's age at death.
    - Monitoring to prevent SIDS in infants older than 1 year is not indicated, although proponents believe such monitoring reduces anxiety in parents of high-risk infants. Opponents of monitoring cite a lack of evidence that monitoring reduces the SIDS rate and argue that monitors are an intrusion into family life that is poorly tolerated by the family.

Complications:

- Infants born prematurely have increased risk for apnea and bradycardia after general anesthesia (or ketamine administration for sedation), regardless of their history of apnea.
- Because of this increased risk, defer elective surgery, if possible, until the infant's respiratory control mechanism is more mature (ie, approximately 52-60 weeks after conception).

Prognosis:

- The natural history of apnea in infants born prematurely shows a gradual decrease in the frequency of all types of apnea during the first month of postnatal life.
- In some infants, however, apnea may persist until they are aged 42 weeks after conception.

Patient Education:

- Family members and others involved in the care of an infant with AOP should be well trained in cardiopulmonary resuscitation (CPR).
- Many of the pitfalls of home monitoring can be avoided by providing 24-hour telephone access (ideal level of service) to a designated physician or nurse who is involved in the infant's care. In addition to this access, families should have frequent, regularly scheduled telephone calls from health care providers and home visits by a nurse or respiratory technician or follow-up appointments at a clinic.

| MISCELLANEOUS	Section 9 of 11

Special Concerns:

- SIDS-related concerns

  - Infants born prematurely account for approximately 10% of the birth population, yet they account for slightly more than 20% of SIDS deaths. The immature respiratory control so commonly seen in premature neonates has led to suggestions of a relationship between AOP and the risk of SIDS.
    - Premature infants in neonatal ICUs (NICUs) often cease breathing unexpectedly. Frequently, these events are accompanied by bradycardia and oxygen desaturation. In many instances, the infant might not have resumed breathing without direct intervention.
    - The hypothesis that apnea is a cause of SIDS is attractive because the premature neonate does not struggle to resume breathing; this situation appears to be similar to that of many cases of SIDS.
    - To date, however, this theory of SIDS causation has not been proven. Furthermore, most infants who die from SIDS were full-term neonates who apparently had no apneic events prior to their death, according to parental reports. However, visual detection of apnea and PB typically is difficult, even for medical personnel, and parents may miss such episodes.
  - No simple, accurate method now exists to predict whether a premature infant is likely to die from SIDS.
    - Despite the development of many programs for home cardiorespiratory monitoring of premature neonates to reduce the rate of SIDS, to the author's knowledge, no prospective randomized control study has been conducted to show that home cardiorespiratory monitoring prevents SIDS.
    - Anecdotal data from some programs suggest that the incidence of SIDS is lower among premature neonates who are monitored extensively, but, to the author's knowledge, no data prove that home monitoring has causes this reduction in the incidence of SIDS.
    - Also unclear is whether this approach is a cost-effective adjunct to neonatal care. Even the programs that have reduced the incidence of SIDS have reported deaths among the babies who were monitored, and the cost of hospitalization has increased to such an extent that the expense of a single inpatient day may be as costly as several months of home cardiorespiratory monitoring.
  - In term neonates, the acknowledged peak age of death for those who die from SIDS is 2-4 months, with a mean age of 52 weeks after conception. The peak age of death for the premature infant is approximately 4-6 months, but the mean age of 52 weeks after conception is the same.

- A premature neonate, therefore, may have a longer risk period for SIDS after hospital discharge.
- Little data about the comparative risks of SIDS among preterm neonates born at different postconceptional ages exist. The similarity in postconceptional ages of death for both term and preterm neonates, however, suggests that a neurodevelopmental phenomenon may be among the etiologies of this as yet unexplained problem.

- Approaches to AOP and SIDS prevention

  o Accumulating evidence from many countries indicates the importance of 2 factors for SIDS prevention in term infants: placing infants supine for sleeping and preventing infant exposure to cigarette smoke, both during and after pregnancy. Unless clear contraindications exist, treat premature neonates in a similar manner. These interventions appear to reduce the SIDS incidence far more than the use of home monitoring. Monitoring, however, may be valuable in some clinical situations to treat AOP and to help families cope with the discharge of a low-birth-weight infant.
  o No evidence identifies AOP as an independent risk factor for SIDS, despite the ongoing controversy surrounding the relationship between apnea and SIDS.
    - Prolonged apnea has been reported in infants with near-miss SIDS (ie, infants who have had an ALTE).
    - Short apneic episodes, PB, and mixed and obstructive apnea have been identified in infants with near-miss SIDS; these observations suggest that a ventilatory control abnormality may contribute to SIDS.
    - These observations prompted the development of polygraphic monitoring to measure variables such as the heart rate, nasal airflow, chest and abdominal movement, and transcutaneous oxygen tension or oxygen saturation in an attempt to predict the SIDS risk in vulnerable infants.
    - A number of studies involving large cohorts of infants have failed to demonstrate that monitoring cardiorespiratory variables can be used to prospectively identify infants at risk for SIDS.
    - The SIDS risk is highest in infants aged 2-4 months, similar to the risk for an ALTE. Positive family histories for these events are present in both infants who died from SIDS and patients with apnea. Both have peak incidences during cold weather months, and both typically occur while the infant is asleep.
    - Posturing and cyanosis are often present, as does an increased incidence of prematurity, low birth weight, and evidence of poor prenatal care.
    - Findings from epidemiologic studies suggest that as many as 18% of SIDS cases occur in infants who were born prematurely.
    - Despite all of these common factors, large-scale trials that have been conducted to verify the relationship between apnea and SIDS have failed to delineate a ventilatory control abnormality that underlies SIDS.

  o A reduction in the postneonatal mortality rate and rate of SIDS has been associated with sleeping in a supine position rather than a prone position.
    - Several groups have documented physiologic benefits for prone positioning versus supine positioning in preterm neonates, including modest improvement in transcutaneously measured PO_2, more time in quiet sleep, decreased energy expenditure, less apnea, and greater ventilatory responses to inspired carbon dioxide.
    - To decrease the SIDS incidence, the American Academy Of Pediatrics has recommended placing healthy neonates on their sides or backs and to avoid placing infants in the prone position for sleeping.
    - Oyen et al, in the Nordic Epidemiological SIDS study, concluded that sleeping in both the prone and side positions increased the risk of SIDS. This risk is increased further in low-birth-weight infants, infants born before term, and infants aged 13-24 weeks.
    - The mechanism by which sleeping in the prone position could lead to SIDS is unclear.
  o At the present time, more infants born prematurely are monitored at home than any other pediatric population. As many as 15-20% of the 400,000 premature babies born annually are treated with home cardiorespiratory monitoring, primarily to treat apnea but also to prevent SIDS.

- o Despite the number of premature infants receiving home monitoring, this therapy has not been embraced universally and remains controversial. Advocates of home monitoring believe that monitoring can alert caretakers to potentially serious episodes of apnea and/or bradycardia before they cause harm, helping parents to cope with the anxiety of caring for an infant born prematurely.

- Opponents of monitoring cite the lack of evidence to indicate that these devices alter the outcome for these patients in any definable way. To the author's knowledge, no prospective study findings demonstrate that monitoring prevents SIDS. Furthermore, many physicians believe that the decision to use home monitoring creates a significant emotional burden for parents.
- Non-SIDS monitoring issues

  - o Since the introduction of NICUs, preterm neonates have received an extraordinarily high level of medical support to compensate for their varying degrees of organ immaturity at birth.
  - o Unfortunately, the effectiveness of current NICU technology cannot begin to approach the combined effectiveness of the placental circulation and maternal metabolism. As a result, some premature babies survive with varying degrees of injury to certain organ systems.
  - o Bronchopulmonary dysplasia (BPD), cardiac disease, periventricular leukomalacia and other neurologic problems, and feeding difficulties are among the many problems that may require home monitoring for ongoing medical care. In these cases, monitoring appears valuable to alert caretakers to physiologic changes (eg, bradycardia, tachycardia, hypoxemia, seizures) that may require intervention.
  - o Without home monitoring, many infants would be unnecessarily confined to the hospital, with far greater emotional and financial costs to the child and family than if they were at home. In such instances, home monitoring may be an effective and safe approach to medical care.
  - o Home monitoring also may be an effective diagnostic tool for children whose events are so sporadic that they cannot be detected easily in the hospital.

    - ▪ Newly developed, documented, monitoring devices can be used to detect and quantify these infrequent episodes of apnea or ALTE, while creating a more typical situation for the child.
    - ▪ The detection of frequent events may indicate the need for additional evaluation for a specific cause. Studies such as EEG, ECG, CNS imaging, and metabolic testing may be valuable in such instances.

  - o Whether the reduction of apnea with the use of monitoring devices and/or pharmacologic agents (eg, methylxanthines) improves neurodevelopmental outcomes in infants born prematurely is not known. Because of the complex nature of the infant's problems, the contribution of apnea to any developmental disability is difficult to estimate. Frequent apnea, especially when accompanied by bradycardia and oxygen desaturation, may adversely affect neurodevelopmental outcomes and should be resolved, if possible.
  - o Neonatologists are aware of the parents' substantial anxiety when they take their low-birth-weight infant home. With recent changes in inpatient care, many premature babies now leave the hospital with discharge weights of 1800-2000 g. In such circumstances, home monitoring may help the infant make the transition to the home setting. Carefully train all caretakers who have a child who is being monitored at home in how to use the monitor and how to perform CPR. Clearly inform parents that monitoring might not prevent SIDS.

Picture 1. Central apnea is defined as the cessation of both airflow and respiratory effort.
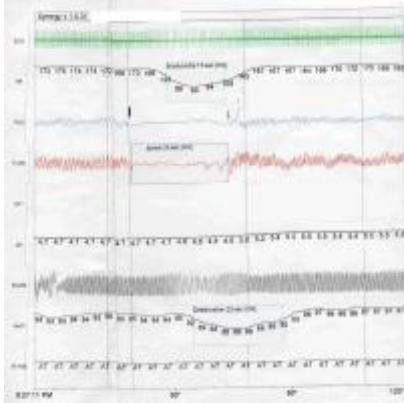
Picture 2. Mixed apnea contains elements of both central and obstructive apnea.
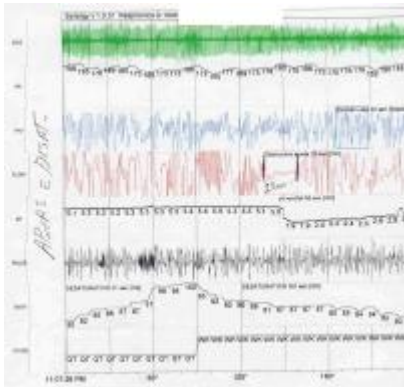
Picture 3. Periodic breathing is defined as periods of regular respiration for as long as 20 seconds followed by apneic periods no longer than 10 seconds that occur at least 3 times in succession.
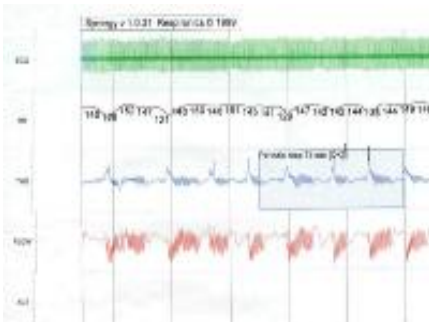
Picture 4. Apnea monitoring in a premature neonate

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Assisted Ventilation of the Newborn

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INTRODUCTION	Section 2 of 11

The primary objective of assisted ventilation is to support breathing until the patient's respiratory efforts are sufficient. Ventilation may be required during immediate care of the infant who is depressed or apneic or during prolonged periods of treatment of respiratory failure. Improved survival from advances in neonatal care has resulted in an increased number of infants at risk for chronic lung disease. Even though the etiology of lung injury is multifactorial, recent animal and clinical data indicate that lung injury depends in large part on the ventilatory strategies used. Optimal ventilatory strategies provide the best possible gas exchange with minimal or no lung injury or other adverse effects. This article highlights the concepts of pulmonary mechanics, gas exchange, control of breathing, and lung injury that can be used to optimize conventional mechanical ventilation (CMV).

GAS EXCHANGE	Section 3 of 11

Newborns are vulnerable to impaired gas exchange because of their high metabolic rate, propensity for decreased functional residual capacity (FRC) and decreased compliance, increased resistance, and potential for right-to-left shunts through the ductus arteriosus and/or foramen ovale. Thus, impaired gas exchange is common in newborns. Hypercapnia and hypoxemia may coexist, although some disorders may affect gas exchange differentially.

Hypercapnia

Hypercapnia usually is caused by hypoventilation or severe ventilation/perfusion (V/Q) mismatch. Carbon dioxide normally diffuses readily from the blood into the alveoli. Elimination of carbon dioxide from the alveoli is directly proportional to alveolar minute ventilation (see Picture 1), which is determined by the product of tidal volume (minus dead space ventilation) and frequency. Thus, the alveolar minute ventilation is calculated as follows:

Alveolar Minute Ventilation = (Tidal Volume - Dead Space) X Frequency

Tidal volume is the volume of gas inhaled (or exhaled) with each breath. Frequency is the number of breaths per minute. Dead space is the part of the tidal volume not involved in gas exchange, such as the volume of the conducting airways. Dead space is relatively constant. Thus, increases in either tidal volume or frequency increase alveolar ventilation and decrease partial pressure of carbon dioxide, arterial ($PaCO_2$). Because dead-space ventilation is constant, changes in tidal volume appear more effective at altering carbon dioxide elimination than changes in frequency. For example, a 50% increase in tidal volume (ie, 6-9 cc/kg) with a constant dead space (ie, 3 cc/kg) doubles alveolar ventilation (3-6 cc/kg X frequency). In contrast, a 50% increase in frequency increases alveolar ventilation by 50%, because an increase in dead space ventilation (dead space X frequency) occurs when frequency is increased.

Even though increases in minute ventilation achieved with large tidal volume increase alveolar ventilation more, the use of relatively small tidal volume and high frequencies usually are preferred as volutrauma can be minimized.

Hypoxemia

Hypoxemia is usually the result of V/Q mismatch or right-to-left shunting, although diffusion abnormalities and hypoventilation (eg, apnea) also may decrease oxygenation. V/Q mismatch is a major cause of hypoxemia in infants with respiratory distress syndrome (RDS) and other causes of respiratory failure. V/Q mismatch usually is caused by poor ventilation of alveoli relative to their perfusion. Shunting can be intracardiac (eg, congenital cyanotic heart disease) and/or extracardiac (eg, pulmonary). During conventional ventilation, oxygenation is determined largely by the fraction of inspired oxygen (FiO_2) and the mean airway pressure (MAP) (see Picture 2). MAP is the average airway pressure during the respiratory cycle and can be calculated by dividing the area under the airway pressure curve by the duration of the cycle as follows:

$$MAP = K\,(PIP - PEEP)\,\frac{T_I}{T_I + T_E} + PEEP$$

This formula includes the constant determined by the flow rate and the rate of rise of the airway pressure curve (K), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), inspiratory time (T_I), and expiratory time (T_E). This equation indicates that MAP increases with increasing PIP, PEEP, T_I to $T_I + T_E$ ratio, and flow (increases K by creating a more square waveform).

The mechanism by which increases in MAP generally improve oxygenation appears to be the increased lung volume and improved V/Q matching. Although a direct relationship between MAP and oxygenation exists, some exceptions are found. For the same change in MAP, increases in PIP and PEEP enhance oxygenation more than changes in the ratio of T_I to T_E (I/E ratio). Increases in PEEP are not as effective once an elevated level (>5-6 cm H_2O) is reached and may not improve oxygenation at all. In fact, a very high MAP may cause overdistention of alveoli, leading to right-to-left shunting of blood in the lungs. If a very high MAP is transmitted to the intrathoracic structures, which may occur with near normal lung compliance, cardiac output may decrease, and thus, even with adequate oxygenation of blood, systemic oxygen transport (arterial oxygen content X cardiac output) may decrease.

Blood oxygen content largely depends on oxygen saturation and hemoglobin level. Thus, transfusing packed red blood cells to infants with anemia (hemoglobin >7-10 mg/dL) who are receiving assisted ventilation is common practice. Oxygenation also depends on oxygen unloading at the tissue level, which is determined strongly by the oxygen dissociation curve. Acidosis, increases in 2,3-diphosphoglycerate, and adult hemoglobin levels reduce oxygen affinity to hemoglobin and thus favor oxygen delivery to the tissues.

Interaction between the ventilator and the infant strongly depends on the mechanical properties of the respiratory system.

Pressure gradient: A pressure gradient between the airway opening and the alveoli must exist to drive the flow of gases during both inspiration and expiration. The necessary pressure gradient can be calculated from the following equation:

$$\text{Pressure} = \frac{\text{Volume}}{\text{Compliance}} + \text{Resistance X Flow}$$

Compliance: Compliance describes the elasticity or distensibility (eg, of the lungs, chest wall, respiratory system) and is calculated from the change in volume per unit change in pressure as follows:

$$\text{Compliance} = \frac{\Delta \text{ Volume}}{\Delta \text{ Pressure}}$$

Therefore, the higher the compliance, the larger the delivered volume per unit changes in pressure. Normally, the chest wall is compliant in newborns and does not impose a substantial elastic load compared to the lungs. The range of total respiratory system compliance (lungs + chest wall) in newborns with healthy lungs is 0.003-0.006 L/cm H_2O, while compliance in babies with RDS may be as low as 0.0005-0.001 L/cm H_2O.

Resistance: Resistance describes the inherent capacity of the air conducting system (eg, airways, endotracheal tube [ETT]) and tissues to oppose airflow and is expressed as the change in pressure per unit change in flow as follows:

$$\text{Resistance} = \frac{\Delta \text{Pressure}}{\Delta \text{Flow}}$$

Airway resistance depends on (1) radii of the airways (total cross-sectional area), (2) length of airways, (3) flow rate, and (4) density and viscosity of gas. Unless bronchospasm, mucosal edema, and interstitial edema decrease their lumen, distal airways normally contribute less to airway resistance because of their larger cross-sectional area. Small ETTs that may contribute significantly to airway resistance also are important, especially when high flow rates that lead to turbulent flow are used. The range for total airway plus tissue respiratory resistance values for healthy newborns is 20-40 cm H_2O/L/s; in intubated newborns this range is 50-150 cm H_2O/L/s.

Time constant: Compliance and resistance can be used to describe the time necessary for an instantaneous or step change in airway pressure to equilibrate throughout the lungs. The time constant of the respiratory system is a measure of the time necessary for the alveolar pressure to reach 63% of the change in airway pressure, which can be calculated as follows:

$$\text{Time Constant} = \text{Resistance X Compliance}$$

Thus, the time constant of the respiratory system is proportional to the compliance and the resistance.

For example, the lungs of a healthy newborn with a compliance of 0.004 L/cm H_2O and a resistance of 30 cm H_2O/L/s have a time constant of 0.12 seconds. When a longer time is allowed for equilibration, a higher percentage of airway pressure equilibrates throughout the lungs. The longer the duration of the inspiratory (or expiratory) time allowed for equilibration, the higher the percentage of equilibration. For practical purposes, delivery of pressure and volume is complete (95-99%) after 3-

5 time constants. The resulting time constant of 0.12 seconds indicates a need for an inspiratory or expiratory phase of 0.36-0.6 seconds. In contrast, lungs with decreased compliance (eg, in RDS) have a shorter time constant. Lungs with a shorter time constant complete inflation and deflation faster than normal lungs.

The clinical application of the concept of time constant is clear, because very short inspiratory times may lead to incomplete delivery of tidal volume and, therefore, lower PIP and MAP, leading to hypercapnia and hypoxemia (see Picture 3). Similarly, insufficient expiratory time may lead to increases in FRC and inadvertent PEEP, which is evidence of gas trapping.

Gas trapping: A short expiratory time, a prolonged time constant, or an elevated tidal volume can result in gas trapping. Gas trapping may decrease compliance and impair cardiac output. Gas trapping during mechanical ventilation may manifest as decreased tidal volume, carbon dioxide retention, and/or lung hyperexpansion. Although PaO_2 may be adequate during gas trapping, venous return to the heart and cardiac output may be impaired; thus, oxygen delivery can be decreased.

Clinical situations that may suggest the presence of gas trapping include (1) use of a short expiratory time (eg, high ventilatory rates), (2) a prolonged time constant (eg, high resistance), (3) lung overexpansion on radiography, (4) decreased thoracic movement despite high PIP, and (5) impaired cardiovascular function (increased central venous pressure, decreased systemic blood pressure, metabolic acidosis, peripheral edema, decreased urinary output). Values of compliance and resistance differ throughout inspiration and expiration; thus, a single time constant cannot be assumed. Furthermore, with heterogeneous lung diseases such as bronchopulmonary dysplasia (BPD), different lung regions may have different time constants because of varying compliances and resistances, partly accounting for coexistence of atelectasis and hyperexpansion.

Chest wall motion: A technique to estimate time constant that may be helpful in everyday clinical practice is the use of chest wall motion as a semiquantitative estimate of tidal volume. At the bedside, chest wall motion can be measured with appropriately placed heart rate/respiration leads used for routine clinical monitoring (see Picture 4). Careful visual assessment of chest wall motion also can suffice. The shape of the inspiratory and expiratory phases can be analyzed. A rapid rise in inspiratory chest wall motion (or volume) with a plateau indicates complete inspiration. A rise without a plateau indicates incomplete inspiration. In this situation, prolongation of the inspiratory time results in more inspiratory chest wall motion and tidal volume delivery. Inspiratory plateau indicates that inspiratory time may be too long; shortening inspiratory time does not decrease inspiratory chest wall motion or tidal volume delivery and does not eliminate the plateau.

A short expiratory time leads to gas trapping. If gas trapping results from a short expiratory time, lengthening expiration improves ventilation. However, a very prolonged expiratory time does not improve ventilation. Indeed, in the absence of gas trapping, shortening expiratory time allows for more breaths to be provided per minute, which improves ventilation.

CONTROL OF BREATHING	Section 5 of 11

Important physiologic aspects of control of breathing need to be considered in order to better understand the interaction between the ventilator and the respiratory system. Respiratory drive is servocontrolled by the brain to minimize variations in arterial blood gases and pH despite changes in the efficiency of gas exchange and moment-to-moment changes in oxygen consumption and carbon dioxide production. Ventilation is maintained by fine adjustments in tidal volume and respiratory rate that minimize the work of breathing. This fine adjustment is accomplished by motor neurons in the central nervous system that regulate inspiratory and expiratory muscles. These neurons receive input largely from the chemoreceptors and the mechanoreceptors. These 2 components of respiratory control provide feedback to continuously adjust ventilation. Mechanical ventilation results in changes in chemoreceptor and mechanoreceptor stimulation.

Chemoreceptors

When $PaCO_2$ changes, ventilation is adjusted largely because of the activity of chemoreceptors in the brain stem. An increase in $PaCO_2$ increases respiratory drive. Because the chemoreceptors most likely sense the hydrogen ion concentration, metabolic acidosis and alkalosis have strong effects on respiratory drive that are somewhat independent of $PaCO_2$ values. Most of the changes in ventilation and respiratory drive produced by PaO_2 changes depend on the peripheral chemoreceptors, which include the carotid bodies and, to a lesser extent, the aortic bodies. In newborns, acute hypoxia produces a transient increase in ventilation that disappears quickly. Moderate or profound respiratory depression can be observed after a couple of minutes of hypoxia, and this decline in respiratory drive is an important cause of hypoventilation and/or apnea.

Mechanoreceptors

Particularly during neonatal life and infancy, considering the role of mechanoreceptors in the regulation of breathing also is important. Stretch receptors in airway smooth muscles respond to tidal volume changes. For example, immediately following inflation, a brief period of decreased or absent respiratory effort can be detected. This is called the Hering-Breuer inflation reflex, and usually it is observed in newborns during conventional ventilation, when a large enough tidal volume is delivered. The presence of the Hering-Breuer inflation reflex is a clinical indication that a relatively good tidal volume is delivered. This reflex is absent if the ventilator tidal volume is very small. For example, the reflex is absent if the ETT becomes plugged. The Hering-Breuer reflex is also time related (eg, a longer inspiration tends to stimulate the reflex more). Thus, for the same tidal volume, a breath with a longer inspiratory time elicits a stronger Hering-Breuer reflex and a longer respiratory pause. At slow ventilator rates, large tidal volumes stimulate augmented inspirations (head paradoxic reflex). This reflex demonstrates improved lung compliance, and its occurrence is increased by methylxanthine administration. This reflex may be one of the mechanisms through which methylxanthines facilitate weaning from mechanical ventilation.

Mechanoreceptors also are altered by changes in FRC. An increase in FRC leads to a longer expiratory time, because the next inspiratory effort is delayed. High continuous distending pressure (continuous positive airway pressure [CPAP] or PEEP) can prolong expiratory time and even decrease the respiratory rate because of the intercostal phrenic inhibitory and Hering-Breuer reflexes. Also, it is important to remember that during weaning from a ventilator, a high PEEP may decrease the spontaneous respiratory rate.

Other components of the mechanoreceptor system are the juxtamedullary (J) receptors. These receptors are located in the interstitium of the alveolar wall and are stimulated by interstitial edema and fibrosis as well as by pulmonary capillary engorgement (eg, congestive heart failure). Stimulation of the J receptors increases respiratory rate and may explain the rapid shallow breathing frequently observed in patients with these conditions. Another reflex that affects breathing is the baroreflex. Arterial hypertension can lead to reflex hypoventilation and/or apnea through aortic and carotid sinus baroceptors. Conversely, a decrease in blood pressure may result in hyperventilation.

VENTILATORY STRATEGIES	Section 6 of 11

Continuous positive airway pressure: CPAP has been an important tool in the treatment of newborns with RDS. The mechanisms by which CPAP produces its beneficial effects include increased alveolar volumes, alveolar recruitment and stability, and redistribution of lung water (see Table 1). The results are usually an improvement in V/Q matching. However, high CPAP levels may lead to adverse effects (see Table 1).

Multiple clinical trials have evaluated the use of CPAP in newborns with respiratory disorders. Meta-analyses generally conclude that CPAP is most beneficial early in established RDS. Prophylactic CPAP in preterm infants does not lead to a decreased incidence or severity of RDS and does not reduce the rate of complications or mortality.

Once the diagnosis of RDS is established, the administration of CPAP decreases oxygen requirements, decreases the need for mechanical ventilation, and may reduce mortality. However, the incidence of air leaks is increased among infants who receive CPAP. Optimal time to start CPAP depends on the severity of RDS. Early CPAP (ie, when the arterial-to-alveolar oxygen ratio is approximately >0.20) decreases the subsequent need for CMV and duration of respiratory assistance. Initiate CPAP in newborns with RDS when PaO_2 is approximately less than 50 mm Hg on a FiO_2 of 0.40 or more. Studies performed to determine whether CPAP facilitates successful extubation have not demonstrated consistent results.

Conventional mechanical ventilation: A complex interrelationship exists between the ventilator, the blood gas values, the mechanical characteristics of the respiratory system, and the infant's spontaneous respiratory efforts. Although attention often is focused on the effect of ventilator setting changes on blood gases, the ventilator changes may alter the pulmonary mechanics either acutely (eg, changes in PEEP affect compliance) or chronically (by predisposing to lung injury). Ventilator changes also may affect spontaneous breathing (eg, high PEEP decreases respiratory rate). An understanding of the basic pathophysiology of the underlying respiratory disorder is essential to optimize the ventilatory strategy. Aim for an adequate gas exchange without injuring the lungs; the ultimate goal is a healthy child without chronic lung disease.

A review of the major ventilatory parameters, which can be adjusted on pressure-limited time-cycled ventilators (ie, the most common type of ventilators used for CMV), is useful. These concepts also are applicable to volume ventilators.

Peak inspiratory pressure: Changes in PIP affect both PaO_2 (by altering MAP) and $PaCO_2$ (by its effects on tidal volume and thus, alveolar ventilation). Therefore, an increase in PIP improves oxygenation and decreases $PaCO_2$. Use of a high PIP may increase the risk of volutrauma with resultant air leaks and BPD; thus, exercise caution when using high levels of PIP. The level of PIP required in an infant depends largely on the compliance of the respiratory system.

A useful clinical indicator of adequate PIP is gentle chest rise with every breath, which should not be much more than the chest expansion with spontaneous breathing. While absent breath sounds may indicate inadequate PIP (or a blocked and/or displaced ETT or even ventilator malfunction), the presence of breath sounds is not very helpful in determining optimal PIP. Adventitious sounds, such as crackles, often indicate disorders of lung parenchyma associated with poor compliance (requiring higher PIP), while wheezes often indicate increased resistance (affects the time constant).

Always use the minimum effective PIP. Making frequent changes in PIP in the presence of changing pulmonary mechanics, such as after the administration of surfactant in the management of RDS, may be necessary. Babies with chronic lung disease often have nonhomogeneous lung disease, leading to varying compliance of different regions of the lung and, therefore, differing requirements for PIP. This partially accounts for the coexistence of atelectasis and hyperinflation in the same lung.

Positive end-expiratory pressure: Adequate PEEP helps to prevent alveolar collapse, maintains lung volume at end-expiration, and improves V/Q matching. Increases in PEEP usually increase oxygenation associated with increases in MAP. However, in infants with RDS, a very elevated PEEP (>5-6 cm H_2O) may not improve oxygenation further and, in fact, may decrease venous return, cardiac output, and oxygen transport. High levels of PEEP also may decrease pulmonary perfusion by increasing pulmonary vascular resistance. By reducing delta (amplitude) pressure (PIP minus PEEP), an elevation of PEEP may decrease tidal volume and increase $PaCO_2$. While both PIP and PEEP increase MAP and may improve oxygenation, they usually have opposite effects on $PaCO_2$. Generally, older infants with chronic lung disease tolerate higher levels of PEEP without carbon dioxide retention and with improvements in oxygenation. PEEP also has a variable effect on lung compliance and may impact the PIP required. With RDS, an improvement in compliance occurs with low levels of PEEP, followed by a worsening of compliance at higher levels of PEEP (>5-6 cm H_2O). A minimum PEEP of 2-3 cm H_2O is recommended, since endotracheal intubation eliminates the active maintenance of FRC accomplished by vocal cord adduction and closure of the glottis.

Rate: Changes in frequency alter alveolar minute ventilation and, thus, $PaCO_2$. Increases in rate and, therefore, in alveolar minute ventilation decrease $PaCO_2$ proportionally, and decreases in rate increase $PaCO_2$. Frequency changes alone (with a constant I/E ratio) usually do not alter MAP nor substantially alter PaO_2. Any changes in inspiratory time that accompany frequency adjustments may change the airway pressure waveform and thus alter MAP and oxygenation.

Generally, a high-rate, low-tidal volume strategy is preferred (see Table 2). However, if a very short expiratory time is employed, expiration may be incomplete. The gas trapped in the lungs can increase FRC, thus decreasing lung compliance. Tidal volume decreases as inspiratory time is reduced beyond a critical level depending on the time constant of the respiratory system. Thus, above a certain ventilator rate during pressure-limited ventilation, minute ventilation is not a linear function of frequency. Alveolar ventilation actually may fall with higher ventilatory rates as tidal volumes decrease and approach the volume of the anatomic dead space.

Inspiratory and expiratory times: The effects of changes in inspiratory and expiratory times on gas exchange are influenced strongly by the relationships of these times to the inspiratory and expiratory time constant, respectively. An inspiratory time 3-5 times longer than the time constant of the respiratory system allows relatively complete inspiration. A long inspiratory time increases the risk of pneumothorax. Shortening inspiratory time is advantageous during weaning (see Table 4). In a randomized trial, limitation of T_I to 0.5 second, rather than 1 second, resulted in significantly shorter duration of weaning. In contrast, patients with chronic lung disease may have a prolonged time constant. In these patients, a longer inspiratory time (near 0.8 s) may result in improved tidal volume and better carbon dioxide elimination.

Inspiratory-to-expiratory ratio: The major effect of an increase in the I/E ratio is to increase MAP and thus improve oxygenation (see Table 3). However, when corrected for MAP, changes in the I/E ratio are not as effective in increasing oxygenation as are changes in PIP or PEEP. A reversed (inverse) I/E ratio (inspiratory time longer than expiratory time) as high as 4:1 has been demonstrated to be effective in increasing PaO_2; however, adverse effects may occur (see Table 3).

Although a decreased incidence of BPD with the use of reversed I/E ratios may be possible, a large, well-controlled, randomized trial revealed only reductions in the duration of a high inspired oxygen concentration and PEEP exposure with reversed I/E ratios, with no differences in morbidity or mortality. Changes in the I/E ratio usually do not alter tidal volume, unless inspiratory and expiratory times become relatively too short. Thus, carbon dioxide elimination usually is not altered by changes in I/E ratio.

Fraction of inspired oxygen: Changes in FiO_2 alter alveolar oxygen pressure and thus, oxygenation. Because FiO_2 and MAP both determine oxygenation, they can be balanced as follows:

- During increasing support, first increase FiO_2 until approximately 0.6-0.7, when additional increases in MAP are warranted.
- During weaning, first decrease FiO_2 (to approximately 0.4-0.7) before reducing MAP, because maintenance of an appropriate MAP may allow a substantial reduction in FiO_2.

Reduce MAP before a very low FiO_2 is reached, because a higher incidence of air leaks has been observed if distending pressures are not weaned earlier.

Flow: Although not well studied in infants, changes in flow probably impact arterial blood gases minimally as long as a sufficient flow is used. Flows of 5-12 L/min are sufficient in most newborns, depending upon the mechanical ventilator and ETT being used. To maintain an adequate tidal volume, high flows are needed when inspiratory time is shortened.

Respiratory distress syndrome: RDS is characterized by low compliance and low FRC. An optimal conventional ventilation strategy may include conservative indications for conventional ventilation, the lowest PIP and tidal volume required, modest PEEP (3-5 cm H_2O), permissive hypercapnia ($PaCO_2$ 45-60 mm Hg), judicious use of sedation/paralysis, and aggressive weaning.

Chronic lung disease: BPD usually has heterogeneous time constants among lung areas. Resistance may be increased markedly, and frequent exacerbations may occur. A higher PEEP (4-6 cm H_2O) often is used, and longer inspiratory and expiratory times with low rates are preferred. Hypercarbia with compensated respiratory acidosis often is tolerated to avoid lung injury secondary to aggressive mechanical ventilation.

Persistent pulmonary hypertension of the newborn: Persistent pulmonary hypertension of the newborn may be primary or associated with aspiration syndrome, prolonged intrauterine hypoxia, congenital diaphragmatic hernia, or other causes. Ventilatory treatment of infants often is controversial and varies markedly among centers. In general, adjust FiO_2 to maintain PaO_2 at 80-100 mm Hg to minimize hypoxia-mediated pulmonary vasoconstriction; adjust ventilatory rates and pressures to maintain an arterial pH of 7.45-7.55 (sometimes combined with bicarbonate infusion). Take care to prevent extremely low $PaCO_2$ (<20 mm Hg), which can cause cerebral vasoconstriction and subsequent neurologic injury. Addition of inhaled nitric oxide to conventional ventilation reduces the need for extracorporeal membrane oxygenation.

STRATEGIES TO PREVENT LUNG INJURY	Section 8 of 11

Emphasis is being placed on the evidence that lung injury depends partially on the particular ventilatory strategies used. Ventilator-associated lung injury traditionally has been believed to result from the use of high pressures; thus, the term barotrauma. However, recent laboratory-based and clinical research has raised questions about this purported mechanism. Experimentally, investigators have used high and low volumes and pressures in an attempt to determine if volume or pressure is the major culprit responsible for lung injury in the immature animal. These studies consistently demonstrate that markers of lung injury (pulmonary edema, epithelial injury, hyaline membrane formation) are present with the use of high volumes and low pressures but not with the use of low volumes and high pressures. Thus, many investigators and clinicians prefer the term volutrauma to the more classic term barotrauma. The heterogeneity of lung tissue involvement in many respiratory diseases predisposes some parts of the lung to volutrauma. Oxidant injury may be another serious cause of lung injury. Immature and developing lungs are particularly susceptible to acquired injury.

Permissive hypercapnia: Permissive hypercapnia, or controlled mechanical hypoventilation, is a strategy for the treatment of patients receiving ventilatory assistance. When using this strategy, give priority to the prevention or limitation of overventilation rather than maintenance of normal blood gases and the high alveolar ventilation that frequently is used. Respiratory acidosis and alveolar hypoventilation may be an acceptable price for the prevention of pulmonary volutrauma. Two large retrospective studies designed to determine risk factors for lung injury in newborns concurred about the potential importance of this ventilatory strategy, since higher $PaCO_2$ values were associated with less lung injury. These 2 studies independently concluded that ventilatory strategies leading to hypocapnia during the early neonatal course resulted in an increased risk of lung (and possibly brain) injury. Thus, ventilatory strategies, which tolerate mild hypercapnia and/or prevent hypocapnia (particularly during the first days of life), result in a reduced incidence and/or severity of lung injury. However, larger clinical trials appear to be needed.

Low tidal volume ventilation: Focus ventilatory strategies for CMV in infants on prevention of overdistention, use of relatively small tidal volumes, maintenance of adequate FRC, and use of sufficient inspiratory and expiratory times. Because high maximal lung volume appears to correlate best with lung injury, selection of an appropriate PIP and the FRC (or operating lung volume) are

critical for the prevention of lung injury during pressure-limited ventilation. With the recognition that large tidal volumes lead to lung injury, relatively small tidal volumes now are recommended. Studies in healthy infants report tidal volume ranges of 5-8 cc/kg, while infants with RDS have tidal volumes of 4-6 cc/kg. Insufficient data are available to recommend a specific size of tidal volume in these infants. In infants with severe pulmonary disease, ventilate with small tidal volumes, because lung heterogeneity and unexpanded alveoli lead to overdistention and injury of the most compliant alveoli if a normal tidal volume is used. Maintenance of an adequate FRC also is necessary.

Technologic advances have resulted in better ventilators. Patient-initiated mechanical ventilation, patient-triggered ventilation, and synchronized intermittent mandatory ventilation are being used increasingly in newborns. High-frequency ventilation is another mode of ventilation that may reduce lung injury and improve pulmonary outcomes, though available studies fail to demonstrate consistent benefits.

Patient-triggered ventilation: The most frequently used ventilators in newborns are time-triggered at a preset frequency, but because of the available bias flow, the patient also can take spontaneous breaths. In contrast, patient-triggered ventilation (PTV), which also is called assist/control, uses spontaneous respiratory effort to trigger the ventilator. During PTV, changes in airway flow or pressure, chest wall or abdominal movements, or esophageal pressure changes are used as an indicator of the onset of the inspiratory effort. Once the ventilator detects inspiratory effort, it delivers a ventilator breath at predetermined settings (PIP, inspiratory duration, flow). Although improved oxygenation has been observed, PTV occasionally may have to be discontinued in some very immature infants because of weak respiratory efforts. A back-up (control) rate may be used to reduce this problem. Despite short-term benefit, large randomized controlled trials report that patient-triggered ventilation does not improve long-term outcomes in infants with RDS, although it may reduce the cost of care.

Synchronized intermittent mandatory ventilation: This mode of ventilation achieves synchrony between the patient and the ventilator breaths. Synchrony easily occurs in most newborns because strong respiratory reflexes during early life elicit relaxation of respiratory muscles at the end of lung inflation. Furthermore, inspiratory efforts usually start when lung volume is decreased at the end of exhalation. Synchrony may be achieved by nearly matching the ventilator frequency to the spontaneous respiratory rate or by simply ventilating at relatively high rates (60-120 min). Triggering systems can be used to achieve synchronization when synchrony does not occur with these maneuvers. Synchronized intermittent mandatory ventilation (SIMV) is as effective as CMV; however, no major benefits were observed in a large randomized controlled trial.

Proportional assist ventilation: Unless they are flow-cycled, both modes of patient-initiated mechanical ventilation discussed above (PTV, SIMV) are designed to synchronize only the onset of the inspiratory support. In contrast, proportional assist ventilation (PAV) matches the onset and duration of both inspiratory and expiratory support. Ventilatory support is in proportion to the volume and/or flow of the spontaneous breath. Thus, the ventilator selectively can decrease the elastic and/or resistive work of breathing. The magnitude of the support can be adjusted depending on the patient's needs. When compared to CMV and PTV, PAV reduces ventilatory pressures while maintaining or improving gas exchange. Randomized clinical trials are needed to determine if PAV leads to major benefits when compared to CMV.

Tracheal gas insufflation:The added dead space of the ETT and the ventilator adapter that connects to the ETT contribute to the anatomic dead space and reduce alveolar minute ventilation, leading to reduced carbon dioxide elimination. In smaller infants or in those with increasing severity of pulmonary disease, dead space becomes the largest proportion of the tidal volume. With tracheal gas insufflation (TGS), gas delivered to the distal part of the ETT during exhalation washes out this dead space and the accompanying carbon dioxide. TGS results in a decrease in $PaCO_2$ and/or PIP. If proven safe and effective, TGS should be useful in reducing tidal volume and the accompanying volutrauma, particularly in very premature infants and infants with very decreased lung compliance.

High-frequency ventilation: High-frequency ventilation (HFV) may improve blood gases because, in addition to the gas transport by convection, other mechanisms of gas exchange may become active at high frequencies (variable velocity profiles of gas during inspiration and exhalation, gas exchange between parallel lung units, increased turbulence and diffusion). Extensive clinical use of the various HFVs has occurred in newborns. High-frequency positive-pressure ventilators employ standard ventilators modified with low-compliance tubing and connectors, thus an adequate tidal volume may be delivered despite very short inspiratory time. High-frequency jet ventilation (HFJV) is characterized by the delivery of gases from a high-pressure source through a small-bore injector cannula. The fast gas flowing out of the cannula possibly produces areas of relative negative pressure that entrain gases from their surroundings. High-frequency flow interruption (HFFI) also delivers small tidal volumes by interrupting the flow of the pressure source, but in contrast to jet ventilation, HFFI does not use an injector cannula. High-frequency oscillatory ventilation (HFOV) delivers very small volumes (even smaller than dead space) at extremely high frequencies. Oscillatory ventilation is unique because exhalation is generated actively, as opposed to other forms of HFV, in which exhalation is passive. The largest randomized trial of HFV revealed that early use of HFOV did not improve outcome. However, the trend is toward decreases in BPD, increases in severe intraventricular hemorrhage and in periventricular leukomalacia, and small increases in air leaks with HFOV and/or HFFI. However, if used properly, HFV is a safe alternative for infants for whom CMV fails.

Summary: Many advances in neonatal care have led to increased survival of smaller and critically ill infants. CMV is being used on smaller and more ill infants for longer durations. Sound application of the basic concepts of gas exchange, pulmonary mechanics, and control of breathing is necessary to optimize mechanical ventilation. Employment of pathophysiology-based ventilatory strategies, strategies to prevent lung injury, and alternative modes of ventilation should result in further improvement in neonatal outcomes.

Table 1. CPAP or High Positive End-expiratory Pressure in Infants With RDS

Pros	Cons
Increased alveolar volume and functional residual capacity	Increased risk for air leaks
Alveolar recruitment	Overdistention
Alveolar stability	Carbon dioxide retention
Redistribution of lung water	Cardiovascular impairment
Improved ventilation/perfusion matching	Decreased compliance
	May increase pulmonary vascular resistance

Table 2. High Rate, Low Tidal Volume (Low Peak Inspiratory Pressure)

Pros	Cons
Decreased air leaks	Gas trapping or inadvertent positive end-expiratory pressure
Decreased volutrauma	Generalized atelectasis
Decreased cardiovascular adverse effects	Maldistribution of gas
Decreased risk of pulmonary edema	Increased resistance

Table 3. High I/E Ratio/Long Inspiratory Time

Pros	Cons
Increased oxygenation	Gas trapping/inadvertent positive end-expiratory pressure
May improve gas distribution in lungs with atelectasis	Increased risk of volutrauma and air leaks
	Impaired venous return
	Increased pulmonary vascular resistance

Table 4. Short Inspiratory Time

Pros	Cons
Faster weaning	Insufficient tidal volume
Decreased risk for pneumothorax	May need high flow rates
Allows use of higher ventilator rate	

PICTURES	Section 10 of 11

Picture 1. Relationships among ventilator-controlled variables (shaded circles) and pulmonary mechanics (unshaded circles) that determine minute ventilation during pressure-limited time-cycled ventilation. The relationships between the circles joined by solid lines are described by simple mathematical equations. The dashed lines represent relationships that cannot be calculated precisely without considering other variable such as pulmonary mechanics. Thus, simple mathematical equations determine the time constant of the lungs, the pressure gradient, and the inspiratory time. In turn, these determine the delivered tidal volume, which, when multiplied by the respiratory frequency, provides the minute ventilation. Alveolar ventilation can be calculated from the product of tidal volume and frequency when dead space is subtracted from the former (Adapted from Chatburn RL, Lough MD).
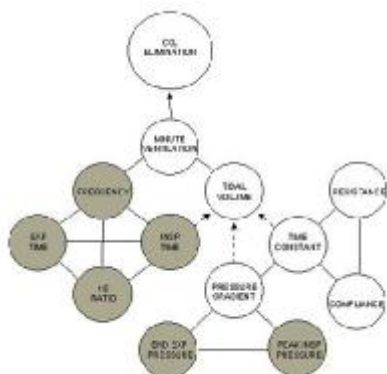
Picture 2. Determinants of oxygenation during pressure-limited time-cycled ventilation. Shaded circles represent ventilator-controlled variables. Solid lines represent the simple mathematical relationships that determine mean airway pressure and oxygenation, whereas dashed lines represent relationships that cannot be quantified in a simple mathematical way (From Carlo WA, Greenough A, Chatburn RL).
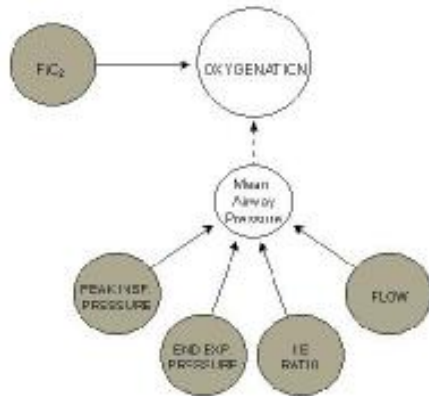
Picture 3. Effects of incomplete inspiration (A) or incomplete expiration (B) on gas exchange. An incomplete inspiration leads to decreases in tidal volume and mean airway pressure. Hypercapnia and hypoxemia may result. An incomplete expiration may lead to decreases in compliance and tidal volume and an increase in mean airway pressure. Hypercapnia with a decrease in PaO_2 may result. However, gas trapping and its resulting increase in mean airway pressure may decrease venous return, decreasing cardiac output and impairing oxygen delivery (From Carlo WA, Greenough A, Chatburn RL).
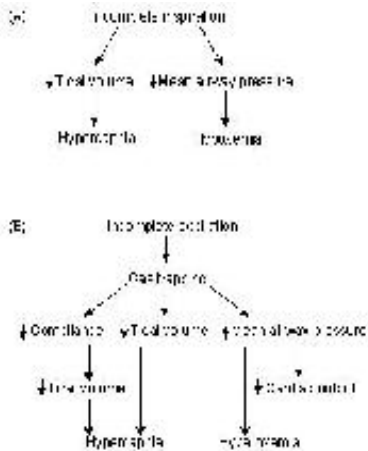
Picture 4. Estimation of optimal inspiratory and expiratory times based on chest wall motion (From Ambalavanan N, Carlo WA)
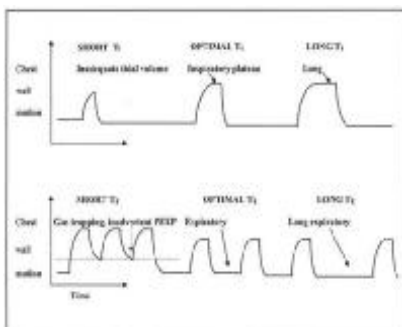
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Birth Trauma

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Synonyms and related keywords: birth injury, compression, traction, cephalhematoma, subgaleal hematoma, caput succedaneum, abrasions, lacerations, subcutaneous fat necrosis, brachial plexus injury, cranial nerve injuries, laryngeal nerve injury appears, spinal cord injury, clavicular fracture, long bone fracture, epiphysial displacement, intraperitoneal bleed, hepatic rupture

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INTRODUCTION	Section 2 of 10

Injuries to the infant resulting from mechanical forces (ie, compression, traction) during the process of birth are categorized as birth trauma. Factors responsible for mechanical injury may coexist with hypoxic-ischemic insult. One may predispose the infant to the other. Lesions that are predominantly hypoxic in origin are not discussed in this article. Significant birth injury accounts for fewer than 2% of neonatal deaths and stillbirths in this country. It still occurs occasionally and unavoidably with an average of 6-8 injuries per 1000 live births. In general, larger infants are more susceptible to birth trauma. Higher rates are reported for infants weighing more than 4500 g

Most birth traumas are self-limiting and have a favorable outcome. Nearly half are potentially avoidable with recognition and anticipation of obstetric risk factors. Infant outcome is the product of multiple factors. Separating the effects of a hypoxic-ischemic insult from those of traumatic birth injury is difficult.

Risk factors include large-for-date infants, especially larger than 4500 g; instrumental deliveries, especially forceps (midcavity) or vacuum; vaginal breech delivery; and abnormal or excessive traction during delivery.

Mortality/morbidity: Birth injuries account for fewer than 2% of neonatal deaths. From 1970-1985, rates of infant mortality resulting from birth trauma fell from 64.2 to 7.5 deaths per 100,000 live births, a remarkable decline of 88%. This decrease reflects, in part, the technologic advancements for today's obstetrician to recognize birth trauma risk factors by ultrasonography and fetal monitoring prior to attempting vaginal delivery. Use of potentially injurious instrumentation such as midforceps rotation and vacuum delivery has also declined. The accepted alternative is a cesarean delivery.

Causes: The process of birth is a blend of compression, contractions, torques, and traction. When fetal size, presentation, or neurologic immaturity complicates this event, such intrapartum forces may lead to tissue damage, edema, hemorrhage, or fracture in the neonate. The use of obstetric instrumentation may further amplify the effects of such forces or may induce injury alone. Under certain conditions, delivery by cesarean delivery can be an acceptable alternative, but it does not guarantee an injury-free birth. Factors predisposing to injury include the following:

- Prima gravida
- Cephalopelvic disproportion, small maternal stature, maternal pelvic anomalies
- Prolonged or rapid labor
- Deep transverse arrest of descent of presenting part of the fetus
- Oligohydramnios
- Abnormal presentation (breech)
- Use of midcavity forceps or vacuum extraction
- Versions and extractions
- Very low birth weight infant or extreme prematurity
- Fetal macrosomia
- Large fetal head
- Fetal anomalies

INJURIES WITH FAVORABLE LONG-TERM PROGNOSIS

- Soft tissue
    - Abrasions
    - Erythema petechia
    - Ecchymosis
    - Lacerations
    - Subcutaneous fat necrosis
- Skull
    - Caput succedaneum
    - Cephalhematoma
    - Linear fractures
- Face
    - Subconjunctival hemorrhage
    - Retinal hemorrhage
- Musculoskeletal injuries
    - Clavicular fractures
    - Fractures of long bones
    - Sternocleidomastoid injury
- Intra-abdominal injuries
    - Liver hematoma
    - Splenic hematoma
    - Adrenal hemorrhage
    - Renal hemorrhage
- Peripheral nerve
    - Facial palsy
    - Unilateral vocal cord paralysis
    - Radial nerve palsy
    - Lumbosacral plexus injury

SOFT TISSUE INJURY

Soft tissue injury is associated with fetal monitoring, particularly with fetal scalp blood sampling for pH or fetal scalp electrode for fetal heart monitoring, which has a low incidence of hemorrhage, infection, or abscess at the site of sampling.

Cephalhematoma

Cephalhematoma is a subperiosteal collection of blood secondary to rupture of blood vessels between the skull and the periosteum; suture lines delineate its extent. Most commonly parietal, cephalhematoma may occasionally be observed over the occipital bone.

The extent of hemorrhage may be severe enough to cause anemia and hypotension. Resolving hematoma predisposes to hyperbilirubinemia. Rarely, cephalhematoma may be a focus of infection leading to meningitis or osteomyelitis. Linear skull fractures may underlie a cephalhematoma (5-20% of cephalhematomas). Resolution occurs over weeks, occasionally with residual calcification.

No laboratory studies usually are necessary. Skull radiography or CT scanning is used if neurologic symptoms are present. Usually, management consists of observation only. Transfusion and phototherapy are necessary if blood accumulation is significant. Aspiration is more likely to increase the risk of infection. The presence of a bleeding disorder should be considered. Skull radiography or CT scanning is also used if concomitant depressed skull fracture is a possibility.

Subgaleal hematoma

Subgaleal hematoma is bleeding in the potential space between the skull periosteum and the scalp galea aponeurosis. Ninety percent of cases result from vacuum applied to the head at delivery. Subgaleal hematoma has a high frequency of occurrence of associated head trauma (40%), such as intracranial hemorrhage or skull fracture. The occurrence of these features does not correlate significantly with the severity of subgaleal hemorrhage.

The diagnosis is generally a clinical one, with a fluctuant boggy mass developing over the scalp (especially over the occiput). The swelling develops gradually 12-72 hours after delivery, although it may be noted immediately after delivery in severe cases. The hematoma spreads across the whole calvarium. Its growth is insidious, and subgaleal hematoma may not be recognized for hours. Patients with subgaleal hematoma may present with hemorrhagic shock. The swelling may obscure the fontanelle and cross suture lines (distinguishing it from cephalhematoma). Watch for significant hyperbilirubinemia. The long-term prognosis generally is good.

Laboratory studies consist of a hematocrit evaluation. Management consists of vigilant observation over days to detect progression. Transfusion and phototherapy may be necessary. Investigation for coagulopathy may be indicated.

Caput succedaneum

Caput succedaneum is a serosanguinous, subcutaneous, extraperiosteal fluid collection with poorly defined margins. It is caused by the pressure of the presenting part against the dilating cervix. Caput succedaneum extends across the midline and over suture lines and is associated with head moulding. Caput succedaneum does not usually cause complications. It usually resolves over the first few days. Management consists of observation only.

Abrasions and lacerations

Abrasions and lacerations sometimes may occur as scalpel cuts during cesarean delivery or during instrumental delivery (ie, vacuum, forceps). Infection remains a risk, but most heal uneventfully.

Management consists of careful cleaning, application of antibiotic ointment, and observation. Bring edges together using Steri-Strips. Lacerations occasionally require suturing.

Subcutaneous fat necrosis

Subcutaneous fat necrosis is not usually detected at birth. Irregular, hard, nonpitting, subcutaneous plaques with overlying dusky red-purple discoloration on the extremities, face, trunk, or buttocks may be caused by pressure during delivery. No treatment is necessary. Subcutaneous fat necrosis sometimes calcifies.

Brachial plexus injury

Brachial plexus injury occurs most commonly in large babies, frequently with shoulder dystocia or breech delivery. Incidence for brachial plexus injury is 0.5-2.0 per 1000 live births. Most cases are Erb palsy; entire brachial plexus involvement occurs in 10% of cases.

Traumatic lesions associated with brachial plexus injury are fractured clavicle (10%), fractured humerus (10%), subluxation of cervical spine (5%), cervical cord injury (5-10%), and facial palsy (10-20%). Erb palsy (C5-C6) is most common and is associated with lack of shoulder motion. The involved extremity lies adducted, prone, and internally rotated. Moro, biceps, and radial reflexes are absent on the affected side. Grasp reflex is usually present. Five percent of patients have an accompanying (ipsilateral) phrenic nerve paresis.

Klumpke paralysis (C7-8, T1) is rare, resulting in weakness of the intrinsic muscles of the hand; grasp reflex is absent. If cervical sympathetic fibers of the first thoracic spinal nerve are involved, Horner syndrome is present.

No uniformly accepted guidelines for determining prognosis exist. Narakas developed a classification system (types I-V) based on the severity and extent of the lesion, providing clues to the prognosis in the first 2 months of life. According to the collaborative perinatal study (59 infants), 88% of cases resolved in the first 4 months, 92% by 12 months, and 93% by 48 months. In another study of 28 patients with upper plexus involvement and 38 with total plexus palsy, 92% recovered spontaneously.

Residual long-term deficits may include progressive bony deformities, muscle atrophy, joint contractures, possible impaired growth of the limb, weakness of the shoulder girdle, and/or Erb engram flexion of the elbow accompanied by adduction of shoulder.

Workup consists of radiographic studies of the shoulder and upper arm to rule out bony injury. The chest should be examined to rule out associated phrenic nerve injury. Electromyography (EMG) and nerve conduction studies occasionally are useful. Fast spin-echo MRI can be used to evaluate plexus injuries noninvasively in a relatively short time, minimizing the need for general anesthesia. MRI can define meningoceles and may distinguish between intact nerve roots and pseudomeningoceles (indicative of complete avulsion). Carefully performed, intrathecally enhanced CT myelography may show preganglionic disruption, pseudomeningoceles, and partial nerve root avulsion. CT myelography is more invasive and offers few advantages over MRI.

Management consists of prevention of contractures. Immobilize the limb gently across the abdomen for the first week and then start passive range of motion exercises at all joints of the limb. Use supportive wrist splints. Best results for surgical repair appear to be obtained in the first year of life. Several investigators recommend surgical exploration and grafting if no function is present in the upper roots at 3 months of age, although the recommendation for early explorations is far from universal. Complications of brachial plexus exploration include infection, poor outcome, and burns from the operating microscope. Patients with root avulsion do not do well. Palliative procedures involving tendon transfers have been of some use. Latissimus dorsi and teres major transfers to the rotator cuff have been advocated for improved shoulder function in Erb palsy. One permanent and 3 transitory axillary nerve palsies have been reported from the procedure.

Cranial nerve and spinal cord injuries result from hyperextension, traction, and overstretching with simultaneous rotation. They may range from localized neurapraxia to complete nerve or cord transection.

Cranial nerve injury

Unilateral branches of the facial nerve and vagus nerve, in the form of recurrent laryngeal nerve, are most commonly involved in cranial nerve injuries and result in temporary or permanent paralysis.

Compression by the forceps blade has been implicated in some facial nerve injury, but most facial nerve palsy is unrelated to trauma.

Physical findings for central nerve injuries are asymmetric facies with crying. The mouth is drawn towards the normal side, wrinkles are deeper on the normal side, and movement of the forehead and eyelid is unaffected. The paralyzed side is smooth with a swollen appearance; the nasolabial fold is absent; and the corner of the mouth droops. No evidence of trauma is present on the face.

Physical findings for peripheral nerve injuries are asymmetric facies with crying. Sometimes evidence of forceps marks is present. With peripheral nerve branch injury, the paralysis is limited to the forehead, eye, or mouth.

The differential diagnosis includes nuclear genesis (Möbius syndrome), congenital absence of the facial muscles, unilateral absence of the orbicularis oris muscle, and intracranial hemorrhage.

Most infants begin to recover in the first week, but full resolution may take several months. Palsy that is due to trauma usually resolves or improves, whereas palsy that persists is often due to absence of the nerve.

Management consists of protecting the open eye with patches and synthetic tears (methylcellulose drops) every 4 hours. Consultation with a neurologist and a surgeon should be sought if no improvement is observed in 7-10 days.

Diaphragmatic paralysis secondary to traumatic injury to the cervical nerve roots supplying the phrenic nerve can occur as an isolated finding or in association with brachial plexus injury. The clinical syndrome is variable. The course is biphasic; initially the infant experiences respiratory distress with tachypnea and blood gases suggestive of hypoventilation (ie, hypoxemia, hypercapnia, acidosis). Over the next several days, the infant may improve with oxygen and varying degrees of ventilatory support. Elevated hemidiaphragm may not be observed in the early stages. Approximately 80% of lesions involve the right side and about 10% are bilateral.

The diagnosis is established by ultrasonography or fluoroscopy of the chest, which reveals the elevated hemidiaphragm with paradoxic movement of the affected side with breathing.

The mortality rate for unilateral lesions is approximately 10-15%. Most patients recover in the first 6-12 months. An outcome for bilateral lesions is poorer. The mortality rate approaches 50%, and prolonged ventilatory support may be necessary.

Management consists of careful surveillance of respiratory status, and intervention, when appropriate, is critical.

Laryngeal nerve injury

Disturbance of laryngeal nerve function may affect swallowing and breathing. Laryngeal nerve injury appears to result from an intrauterine posture in which the head is rotated and flexed laterally. During delivery, similar head movement, when marked, may injure the laryngeal nerve, accounting for approximately 10% of cases of vocal cord paralysis attributed to birth trauma. The infant presents with a hoarse cry or respiratory stridor, most often caused by unilateral laryngeal nerve paralysis. Swallowing may be affected if the superior branch is involved. Bilateral paralysis may be caused by trauma to both laryngeal nerves or, more commonly, by a CNS injury such as hypoxia or hemorrhage involving the brain stem. Patients with bilateral paralysis often present with severe respiratory distress or asphyxia.

Direct laryngoscopic examination is necessary to make the diagnosis and to distinguish vocal cord paralysis from other causes of respiratory distress and stridor in the newborn. Differentiate from other rare etiologies, such as cardiovascular or CNS malformations or a mediastinal tumor.

Paralysis often resolves in 4-6 weeks, although recovery may take as long as 6-12 months in severe cases. Treatment is symptomatic. Small frequent feeds, once the neonate is stable, minimize the risk of aspiration. Infants with bilateral involvement may require gavage feeding and tracheotomy.

Spinal cord injury

Spinal cord injury incurred during delivery results from excessive traction or rotation. Traction is more important in breech deliveries (minority of cases), and torsion is more significant in vertex deliveries. True incidence is difficult to determine. The lower cervical and upper thoracic region for breech delivery and the upper and midcervical region for vertex delivery are the major sites of injury.

Major neuropathologic changes consist of acute lesions, which are hemorrhages, especially epidural, intraspinal, and edema. Hemorrhagic lesions are associated with varying degrees of stretching, laceration, and disruption or total transaction. Occasionally, the dura may be torn, and rarely, the vertebral fractures or dislocations may be observed.

The clinical presentation is stillbirth or rapid neonatal death with failure to establish adequate respiratory function, especially in cases involving the upper cervical cord or lower brain stem. Severe respiratory failure may be obscured by mechanical ventilation and may cause ethical issues later. The infant may survive with weakness and hypotonia, and the true etiology may not be recognized. A neuromuscular disorder or transient hypoxic ischemic encephalopathy may be considered. Most infants later develop spasticity that may be mistaken for cerebral palsy.

Prevention is the most important aspect of medical care. Obstetric management of breech deliveries, instrumental deliveries, and pharmacologic augmentation of labor must be appropriate. Occasionally, injury may be sustained in utero.

The diagnosis is made by MRI or CT myelography. Little evidence indicates that laminectomy or decompression has anything to offer. A potential role for methylprednisolone exists. Supportive therapy is important.

BONE INJURY	Section 7 of 10

Fractures are most often observed following breech delivery and/or shoulder dystopia in macrosomia infants.

Clavicular fracture

The clavicle is the most frequently fractured bone in the neonate during birth and most often is an

unpredictable unavoidable complication of normal birth. Some correlation with birth weight, midforceps delivery, and shoulder dystocia exists. The infant may present with pseudoparalysis. Examination may reveal crepitus, palpable bony irregularity, and sternocleidomastoid muscle spasm. Radiographic studies confirm the fracture.

Healing usually occurs in 7-10 days. Arm motion may be limited by pinning the infant's sleeve to the shirt. Assess other associated injury to the spine, brachial plexus, or humerus.

Long bone fracture

Loss of spontaneous arm or leg movement is an early sign of long bone fracture, followed by swelling and pain on passive movement. The obstetrician may feel or hear a snap of fracture at the time of delivery. Radiographic studies of the limb confirm the diagnosis.

Femoral and humeral shaft fractures are treated with splinting. Closed reduction and casting is necessary only when displaced. Watch for evidence of radial nerve injury with humeral fracture. Callus formation occurs, and complete recovery is expected in 2-4 weeks. In 8-10 days, the callus formation is sufficient to discontinue immobilization. Orthopedic consultation is recommended.

Radiographic studies distinguish this condition from septic arthritis.

Epiphysial displacement

Separation of humeral or femoral epiphysis occurs through the hypertrophied layer of cartilage cells in the epiphysis. The diagnosis is made clinically based on the finding of swelling around the shoulder, crepitus, and pain when the shoulder is moved. Motion is painful, and the arm lies limp by the side. Because the proximal humeral epiphysis is not ossified at birth, it is not visible on radiography. Callus appears in 8-10 days and is visible on radiography.

Management consists of immobilizing the arm for 8-10 days. Fracture of the distal epiphysis is more likely to have a significant residual deformity than is fracture of the proximal humeral epiphysis.

INTRA-ABDOMINAL INJURY	Section 8 of 10

Intra-abdominal injury is relatively uncommon and can sometimes be overlooked as a cause of death in the newborn. Hemorrhage is the most serious acute complication, and the liver is the most commonly damaged internal organ.

Signs and symptoms of intraperitoneal bleed

Bleeding may be fulminant or insidious, but patients ultimately present with circulatory collapse. Intra-abdominal bleeding should be considered for every infant presenting with shock, pallor, unexplained anemia, and abdominal distension. Overlying abdominal skin may have bluish discoloration. Radiographic findings are not diagnostic but may suggest free peritoneal fluid. Paracentesis is the procedure of choice.

Hepatic rupture

The most common lesion is subcapsular hematoma, which increases to 4-5 cm before rupturing. Symptoms of shock may be delayed. Lacerations are less common, often caused by abnormal pull on peritoneal support ligaments or effect of excessive pressure by the costal margin. Infants with hepatomegaly may be at higher risk. Other predisposing factors include prematurity, postmaturity, coagulation disorders, and asphyxia. In cases associated with asphyxia, vigorous resuscitative effort (often by unusual methods) is the culprit. Splenic rupture is at least a fifth as common as liver laceration. Predisposing factors and mechanisms of injury are similar.

Rapid identification and stabilization of the infant are the keys to management, along with assessment of coagulation defect. Blood transfusion is the most urgent initial step. Persistent coagulopathy may be treated with fresh frozen plasma, transfusion of platelets, and other measures.

Hepatic rupture has no specific racial predilection and has equal sex distribution. Patients usually present immediately following birth, or rupture becomes obvious within the first few hours or days.

CONCLUSION	Section 9 of 10

Recognition of trauma necessitates a careful physical and neurologic evaluation of the infant to establish whether additional injuries exist. Occasionally, injury may result from resuscitation. Symmetry of structure and function should be assessed as well as specifics such as cranial nerve examination, individual joint range of motion, and scalp/skull integrity.

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Birth Trauma excerpt

Bowel Obstruction in the Newborn

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INTRODUCTION	Section 2 of 11

Bowel obstruction in the newborn is one of the most common and potentially dire newborn surgical emergencies. Successful management of a newborn with a bowel obstruction depends upon both timely diagnosis and prompt therapy. Many causes of bowel obstruction in the newborn can be readily diagnosed with physical examination and simple radiographic examinations. Crucial to the management of most newborn bowel emergencies is effective nasogastric or orogastric decompression.

Early consideration of the need for surgical intervention may mean the difference between intestinal salvage and catastrophe. Have a high index of suspicion; often, a surgeon's approach to a newborn with a potential bowel obstruction is to rule out the worst possibility first. Important signs to identify are stools containing occult blood, hypotension, metabolic acidosis, progressive respiratory failure, and thrombocytopenia.

A delay in diagnosis of a newborn bowel obstruction may exacerbate the compromise of dilated bowel upstream of the obstruction; result in clinical deterioration with dehydration, fever, and unconjugated hyperbilirubinemia; and predispose the child to complications such as aspiration pneumonia.

For example, a child with bilious emesis must be considered to have malrotation with volvulus until proven otherwise. A few hours may make the difference between full recovery and massive bowel necrosis. If a newborn in distress demonstrates evidence of a high-grade proximal small-bowel obstruction with some air past the duodenum, suspect volvulus and urgently consider an exploratory laparotomy.

Signs and symptoms of a newborn bowel obstruction may be subtle and nonspecific. Bilious gastric aspirates or emesis suggests an obstruction distal to the ampulla of Vater, usually in the proximal small bowel, and demands an immediate evaluation. As a rule, consider any infant or child with bilious vomiting to have a bowel obstruction until proven otherwise; emergent assessment is mandatory. Abdominal distention or tenderness is a less-specific finding and may indicate bowel obstruction or bowel compromise from other causes, such as septic ileus or necrotizing enterocolitis. An abnormal gas pattern visualized on abdominal radiography often leads to the diagnosis of bowel obstruction.

The importance of a thorough physical examination cannot be overstated. Inspection and palpation of the infant's abdomen and perineum often suggest a diagnosis. An incarcerated hernia, an anterior ectopic anus, or imperforate anus can be identified with careful perineal inspection. Inability to pass a nasogastric tube may be diagnostic of esophageal atresia. Diagnostic modalities, such as simple abdominal radiography, radiographic contrast studies, and abdominal ultrasonography, can be extremely helpful in identifying the cause of a neonatal bowel obstruction.

A more detailed discussion of the causes of bowel obstruction in the newborn can be divided into proximal bowel obstruction and distal bowel obstruction. Patients with proximal obstruction often present with different clinical scenarios than patients with distal obstruction, and different diagnostic approaches are indicated. Understanding the causes and evolution of neonatal bowel obstruction is enhanced by careful prenatal imaging and diagnosis.

Once a newborn presents with evidence of bowel obstruction, dividing the differential diagnoses into categories of surgical versus nonsurgical etiologies is useful.

PRENATAL DIAGNOSIS OF BOWEL OBSTRUCTION

Prenatal imaging, especially with ultrasonography, can be extremely effective in detecting of bowel obstruction. A fetus with proximal bowel obstruction may present with polyhydramnios that occurs when the normally large volume of amniotic fluid swallowed by the fetus remains in the amniotic sac. Approximately 50% of newborns with duodenal atresia have polyhydramnios. Polyhydramnios increases the risk of premature birth.

The high resolution of fetal ultrasonography and fetal magnetic resonance imaging (MRI) frequently enables identification of abnormal features of the bowel in the fetus. Both studies readily identify a dilated loop of bowel and are good predictors of a proximal bowel obstruction such as atresia or volvulus. In some situations, fetal diagnosis of a proximal bowel atresia may prompt amniocentesis because a strong relationship exists between some types of bowel obstruction and some chromosomal anomalies. For example, children with duodenal atresia have a higher incidence of trisomy 21. Thus, prenatal imaging of a bowel obstruction may complement other modalities of prenatal counseling for parents.

Ultrasonography is useful for identification of abnormal loops of bowel in the fetus. Unlike in the newborn, the fetal bowel is gasless, without swallowed air that distorts the image. As mentioned above, a dilated loop of small bowel may suggest an atresia or volvulus. A whirlpool appearance to the bowel and bowel mesentery may indicate malrotation with volvulus. Echogenic bowel suggests bowel compromise. In approximately one third of fetuses with echogenic bowel on prenatal ultrasonography, a malformation of the GI tract is later confirmed.

Some prenatal ultrasonographic or MRI features are associated with specific abnormalities in the fetus. A dilated proximal esophagus is often observed with esophageal atresia. Bowel within the thoracic cavity confirms a congenital diaphragmatic hernia. More subtle signs can be observed as well. Flecks of calcification throughout the peritoneal cavity suggest meconium peritonitis from prenatal bowel compromise and perforation and strongly suggest cystic fibrosis. Finally, the nonspecific finding of ascites can suggest compromised bowel in the fetus. Other nonsurgical causes of postnatal bowel dysfunction, such as hydrocephalus or renal disease, may also be observed on prenatal imaging studies.

The prenatal diagnosis of a bowel obstruction may directly improve postnatal outcome by expediting its surgical management. Immediate surgical intervention may be needed in patients with congenital diaphragmatic hernia, esophageal atresia, or malrotation with volvulus. Many children with a prenatal diagnosis of bowel obstruction are referred for delivery in a center where pediatric surgeons are readily available.

In situations where prenatal imaging has been used to diagnose an anatomic cause of bowel obstruction, focused resuscitation in the delivery room may facilitate preoperative stabilization. If positive pressure respiratory support is needed, rapid intubation without prolonged bag-mask ventilation may minimize bowel distention and improve outcome. A child born with a possible bowel obstruction should undergo immediate nasogastric decompression because progressive bowel distention from swallowed air may cause further compromise. Fluid sequestration in a dilated loop of obstructed bowel may require aggressive parenteral fluid administration to maintain the patient's hemodynamic stability. Preoperative laboratory studies, antibiotics, and vitamin K may also be an appropriate part of the delivery room resuscitation.

The diagnostic evaluation of a neonatal bowel obstruction must be expeditious because some causes of bowel obstruction rapidly cause ischemia leading to necrosis and bowel death. Bilious vomiting is perhaps the most common symptom that initiates an emergent workup for bowel obstruction. Physical signs, such as abdominal distention or tenderness, abdominal wall erythema, a palpable mass, or visible loop of bowel, also demand further investigation. In some situations, an exploratory laparotomy is the best diagnostic test. Most infants pass meconium in the first 12-24 hours after birth. No newborn should be discharged from the hospital before passing meconium.

The pattern of bowel gas on plain radiography can be used to differentiate between proximal and distal bowel obstruction. Duodenal atresia, a common cause of proximal small-bowel obstruction, often creates a double bubble sign on plain radiographic examination. A dilated stomach and obstructed duodenum, indented at the waist by the pylorus, produces this characteristic appearance. Plain radiography revealing malrotation with midgut volvulus may show a bowel gas pattern in the duodenum with an abrupt cutoff in the distal duodenum. A bird's beak sign may be observed. Radiography of jejunal atresia may also show a few dilated proximal loops of bowel with no distal bowel gas. If many nondilated loops of bowel are gas-filled but no air is observed in the rectum, a more distal cause of bowel obstruction is suggested.

Ultrasonography can be helpful in making the diagnosis in newborns with a palpable abdominal mass. Tumors, intestinal duplication, mesenteric cysts, ovarian masses, or cystic lymphatic malformations may be identified by ultrasonography. A mass in the inguinal region may represent an incarcerated inguinal hernia. The use of upper GI series, ultrasonography, and contrast enema are discussed below in the context of each specific cause of bowel obstruction.

An ileus, or functional bowel obstruction, may result from causes other than those requiring surgical intervention. Premature infants frequently demonstrate abdominal distention because of small amounts of subcutaneous fat making the abdominal wall more distensible and because of immature peristaltic function. Abdominal distention may also be the first sign of necrotizing enterocolitis, a particularly ominous disease process that can cause death in a neonate. Ileus can also be a symptom of neonatal sepsis, as well as a result of a central nervous system (CNS) lesion such as hydrocephalus or a subdural hematoma. Polycystic kidney disease may mechanically obstruct the bowel as well as predispose to an ileus. Metabolic disorders, such as hypothyroidism, are rare causes of chronic neonatal ileus that can masquerade as bowel obstruction for several months before the definitive diagnosis is made. Hirschsprung disease, the absence of ganglion cells in the distal bowel, can also cause chronic obstructive signs until the definitive diagnosis is finally made by rectal biopsy.

Most babies with a proximal bowel obstruction present with vomiting. Depending on the level of obstruction, abdominal distention may also be a feature. If the obstruction is distal to the drainage of the common bile duct at the ampulla of Vater in the second portion of the duodenum, the vomitus is likely to be bilious. The differential diagnosis for proximal bowel obstruction includes atresias, both duodenal and jejunoileal, as well as malrotation with volvulus. Responsibility rests with the clinician to expeditiously exclude the diagnosis of volvulus. Plain radiography of proximal bowel obstruction may demonstrate little gas beyond the proximal duodenum. Placement of a nasogastric tube may be both diagnostic and therapeutic. An upper GI contrast study through the nasogastric tube may be helpful.

Malrotation and volvulus

Because of the potential for midgut volvulus and loss of the entire small bowel, malrotation represents perhaps the most feared cause for proximal small-bowel obstruction. Midgut volvulus from malrotation is a life-threatening surgical emergency in the newborn. Remember that malrotation is not synonymous with volvulus. Malrotation occurs in approximately 1 in 6000 newborns; rotational abnormalities may be present in as many as 1% of the population. Volvulus represents the acute twisting of the intestines upon their mesentery and can occur in a patient with malrotation due to the lack of normal fixation of the bowel to the retroperitoneum. Patients who develop obstructive symptoms of malrotation usually present in the first month of life. Of those who are eventually symptomatic, 90% present in the first year of life. Associated anomalies include duodenal or jejunoileal atresia, Hirschsprung disease, and, rarely, mesenteric cysts.

Malrotation results from a failure of the GI tract to complete its normal rotation as it returns to the abdominal cavity at 8-10 weeks' gestation. The bowel develops outside of the abdominal cavity as a single long loop of bowel based on the pedicle of the superior mesenteric vessels. As the bowel returns to the abdomen, the proximal small bowel returns first and the duodenum rotates underneath the superior mesenteric vessels to assume a retroperitoneal position. Rotation continues as the large bowel returns to the peritoneal cavity, rotating over the vascular pedicle to place the ileocecal valve in the right lower quadrant and establishing the hepatic and splenic flexures.

Fixation points develop in the peritoneum at the duodenum, ligament of Treitz, ileocecal valve, and right and left paracolic gutters. This arrangement results in a broad fixed base of the small-bowel mesentery by 10 weeks' gestation. If the rotation of the bowel is incomplete or does not occur, normal mesenteric attachments are absent and abnormal peritoneal bands may develop. These bands may obstruct the duodenum and are known as Ladd bands. Most worrisome in malrotation is the lack of peritoneal attachments of the bowel. The unfixed bowel may twist around itself and compromise the blood supply of the superior mesenteric pedicle.

The initial presentation of a newborn with volvulus of the midgut may be bilious vomiting. The abdomen is initially soft and scaphoid and may or may not be tender on physical examination. As the obstruction progresses, the volvulus compromises flow in the superior mesenteric pedicle and the ischemic bowel becomes dilated, distended, and firm. The child may become hypotensive from sequestration of fluid within the obstructed bowel; peritonitis and shock may develop. Metabolic acidosis on laboratory evaluation may indicate bowel compromise. Prompt surgical intervention is required.

Some patients with malrotation present with a more indolent course of long-standing partial obstructive symptoms, constipation, and associated intestinal dysmotility. A history of chronic intermittent abdominal pain may also be associated with malrotation, presumably from intermittent partial volvulus.

Radiographic imaging that exhibits a characteristic pattern can confirm a diagnosis of malrotation in a stable patient. An upper GI series usually shows incomplete obstruction with extrinsic compression of the duodenum and torsion of the small bowel. The ligament of Treitz may be found in an abnormal position to the right of the midline or below the level of the pylorus. Obstructive bands may partially block the duodenum. The position of the splenic and hepatic flexure as well as the cecum may not

demonstrate the normal fixation pattern to the right and left paracolic gutters. Ultrasonography may also be helpful in confirming the diagnosis. Normally, the superior mesenteric artery (SMA) lies to the left of the superior mesenteric vein (SMV). An SMA that lies to the right or anterior to the SMV suggests malrotation. Contrast enema may demonstrate the abnormal position of the cecum but is no longer considered the best study to establish the diagnosis of malrotation.

Malrotation with midgut volvulus is a true surgical emergency in the newborn. Delay in operation may result in catastrophic loss of a large portion of the small bowel. In patients with severe midgut volvulus, the entire midgut is necrotic and the child cannot survive. Surgical treatment for malrotation is the Ladd procedure. A Ladd procedure includes evisceration of the midgut and immediate counterclockwise derotation of the gut to release the volvulus and reestablish flow of blood to the bowel. Obstructing Ladd bands from the colon to the duodenum are released.

The position of the mesentery does not allow the bowel to be placed in a normal position within the abdomen; therefore, the bowel is returned to the abdomen in a manner that spreads out the mesentery as much as possible. The duodenum and small bowel are placed on the right side of the abdomen, and the colon is placed on the left, with the cecum in the left lower quadrant. Because the ileocecal valve now is on the left side of the abdomen, the appendix is removed. Development of new postoperative adhesions may secure the bowel in this new configuration to avoid recurrent volvulus.

Morbidity and mortality from malrotation and volvulus are directly related to the extent of bowel necrosis. The mortality rate may be as high as 65% if more than 75% of the small bowel is necrotic at the time of laparotomy. Survivors may develop short bowel syndrome, with its associated complications of malabsorption and malnutrition. The Ladd procedure does not address the intestinal dysmotility associated with malrotation but rather prevents the risk of midgut volvulus. Thus, patients with constipation and motility problems from malrotation may not note improvement in their symptoms following the Ladd procedure.

Duodenal atresia

Duodenal obstruction from atresia or web affects as many as 1 in 6,000-10,000 infants. Polyhydramnios is present in as many as 50% of fetuses with duodenal obstruction and frequently leads to prenatal diagnosis of duodenal atresia. This polyhydramnios may lead to fetal distress and premature delivery in one third of patients. Vomiting, abdominal distention, and a dilated loop of bowel on plain radiography are consistent features of duodenal atresia or web. Some atresias may be obstructing incompletely; in these situations, a small amount of distal bowel gas may be observed on plain radiography.

Duodenal atresia is believed to occur from a failure of revacuolization of the lumen of the duodenum at 8-10 weeks' gestation. At earlier phases in fetal development, the lumen of the duodenum is obliterated by the proliferation of the layers of duodenal wall. Beginning at 8 weeks' gestation, a lumen is regenerated in the previously solid duodenum. If this process is incomplete, an atresia or web may occur.

Duodenal web results from an obstructive band of mucosa that stretches across the duodenal lumen. These webs may be incomplete, or a web may stretch out distally in the lumen of the duodenum like a windsock. Duodenal atresia may also occur from an improper rotation of the pancreas to the right of the duodenum and may be associated with an annular pancreas. Development of duodenal atresia follows a different embryologic pattern from that of jejunoileal atresias. Unlike jejunoileal atresias, which are believed to result from a mesenteric accident, in patients with duodenal atresia, the mesentery of the duodenum is intact.

The finding of duodenal atresia suggests an early error in development, and duodenal atresia may be associated with other congenital anomalies in as many as 50% of patients. Associated disease processes include trisomy 21 (40% of patients), imperforate anus, and congenital cardiac disease.

An infant with duodenal atresia may present with bilious or nonbilious vomiting. If a complete duodenal atresia or web lies upstream of the ampulla of Vater, the vomiting is nonbilious. In 85% of patients with

duodenal atresia, the obstruction lies distal to the ampulla or is incomplete. In these situations, vomiting is bilious. The abdomen is usually distended by the dilated duodenal loop but may be scaphoid if the obstruction is incomplete. Preoperative treatment for these patients includes fluid resuscitation and nasogastric decompression.

Consultation with a cardiologist and echocardiography may be helpful because of the high incidence of associated anomalies. If the obstruction is incomplete as evidenced by some distal gas on plain radiography, urgent laparotomy may be necessary to differentiate duodenal atresia from malrotation with volvulus. Surgery involves resection or bypass of the atretic segment. A web must be identified and completely resected to the degree that it no longer obstructs the distal lumen.

Many pediatric surgeons bypass rather than resect the atretic segment to avoid injury to the ampulla or to the pancreatic blood supply that usually is nearby. A severely dilated duodenum may require a tapering duodenoplasty to mitigate the poor long-term duodenal motility that can be observed in these dilated proximal segments. A nasoenteric feeding tube is often placed across the duodenal anastomosis for early decompression and late feeding.

Jejunoileal atresia

Atresia of the jejunum or ileum is more common than duodenal atresia, occurring in 1 in 1500 births. Small-bowel obstruction from jejunoileal atresia may also lead to polyhydramnios. Premature delivery is observed in one third of patients with intestinal atresia.

In contrast to duodenal atresia, jejunoileal atresia is widely considered to be a condition acquired during development, rather than a preprogrammed anomaly. In classic work on fetal dogs in 1955, Louw and Barnard demonstrated the pathophysiology by which intrauterine mesenteric vascular accidents produce atresia in the segment of intestine that is devascularized. The extent of atresia and the appearance of the atretic intestinal segment vary according to the timing and degree of the disruption of the mesenteric blood supply. Atresias may be focal or multiple throughout the small bowel. Interruption of the main superior mesenteric blood supply can result in atresia of most of the jejunum and ileum. Other abdominal conditions, such as gastroschisis or intrauterine intussusception, may be associated with intestinal atresia, presumably from kinking, stretching, or otherwise disrupting the blood supply to the fetal bowel. Chromosomal anomalies are rare (<1%) in children with jejunoileal atresia.

Infants with jejunoileal atresia may present with distention and vomiting. Thumb-sized loops of bowel with air-fluid levels can be observed on plain radiography. As many as 12% of newborns with jejunoileal atresia may have intra-abdominal calcifications observed on plain radiography. These calcifications are consistent with meconium peritonitis, resulting from necrosis and perforation of a devascularized loop of bowel. Blood flow to the segments immediately proximal and distal to the atresia may be compromised. For this reason, preoperative nasogastric decompression is vital to limit distention of the intestine proximal to the atresia. A delay in diagnosis or operation may distend and compromise the poorly vascularized, dilated, often bulbous bowel. Some surgeons insist on a contrast enema to exclude colonic atresia, while others examine the colon intraoperatively to ensure patency of the distal bowel.

Surgery for jejunoileal atresia involves resection and primary anastomosis of the atretic segments. Diverting ostomies are avoided if possible. As with surgery for duodenal atresia, tapering of the proximal dilated segment occasionally is necessary to limit the motility problems observed with dilated proximal bowel. If at all possible, the ileocecal valve is preserved. Long-term outcomes are generally excellent if sufficient bowel is present for absorption and growth.

Esophageal atresia and tracheoesophageal fistula

Esophageal atresia is a foregut malformation resulting from an error in separation of the esophagus from the respiratory tree. Newborn infants with esophageal atresia are unable to swallow their secretions and present with respiratory distress or an inability to nurse. Inability to pass a nasogastric tube is diagnostic of esophageal atresia.

The common association of a distal tracheoesophageal fistula predisposes a newborn to aspiration of acidic gastric contents and respiratory distress. Preoperative management must take into account the danger of respiratory collapse with positive pressure ventilation because ventilated breaths may preferentially shunt through the tracheoesophageal fistula into the stomach. Repair of esophageal atresia involves ligation of the tracheoesophageal fistula and anastomosis of the proximal and distal ends of the esophagus, if possible.

Occasionally, esophageal replacement with bowel or stomach is necessary. Anastomotic stricture, gastroesophageal reflux, and poor esophageal motility affect long-term outcome.

Hypertrophic pyloric stenosis

Gastric outlet obstruction from pyloric stenosis results from hypertrophy of the pylorus. This condition is acquired, although its etiology is not fully characterized. Hypertrophy of the pylorus is associated with reduced nitric oxide levels in the pyloric muscle tissue. Nitric oxide generally mediates relaxation of gastrointestinal smooth muscle so that pyloric obstruction may be related to a local reduction of nitric oxide levels in the pyloric muscle.

Most children with pyloric stenosis present with nonbilious vomiting and dehydration at 4-6 weeks, although hypertrophic pyloric stenosis can be observed in babies younger than 1 week. The thickened pylorus muscle is often palpable; ultrasonography and contrast studies may be helpful in diagnosis. Operative pyloromyotomy is curative.

DISTAL BOWEL OBSTRUCTION	Section 6 of 11

In contrast to obstruction in the duodenum or proximal small bowel, patients with a distal bowel or colonic obstruction often present in the newborn period with subacute clinical and radiographic features characterized by distention. In most patients with distal obstruction, the bowel is not immediately in danger of compromise, thus time is available for appropriate workup and diagnostic studies. Distention, rather than vomiting, is frequently the dominant clinical feature. Imperforate anus and other anorectal anomalies may be readily diagnosed on inspection of the perineum. Plain radiographic findings often suggest a distal obstruction with a pattern of proximal air-filled dilated small-bowel loops but no distal air. In these patients, a contrast enema may be both diagnostic and therapeutic.

A contrast enema, usually with hyperosmolar Gastrografin (diatrizoate), can help differentiate causes of distal bowel obstruction. The colonic and distal small-bowel lumen may be obstructed with thick meconium in patients with meconium ileus. Colon dilated proximal to a thick obstructing mass of meconium suggests meconium plug syndrome. A contrast enema may demonstrate a transition zone between small-caliber distal colon and more dilated proximal colon in patients with Hirschsprung disease. More proximal obstructions can produce a contrast enema picture of a small-caliber colon, termed congenital microcolon or small left colon syndrome.

Meconium ileus: Meconium ileus is the term used to describe neonatal presentation of distal small-bowel obstruction from thickened meconium in patients with cystic fibrosis. Meconium ileus is the earliest manifestation of cystic fibrosis in the newborn period. Cystic fibrosis is an autosomal recessive

condition characterized by abnormalities in cellular membrane physiology and chloride ion transport that contribute to progressive respiratory failure, derangements in cellular secretory patterns, and diminished mucosal motility.

Incidence of cystic fibrosis is 1 case per 3000 live births. Of newborns with cystic fibrosis, 10-20% present with meconium ileus. The gene for cystic fibrosis is carried by 3.3% of whites. Identified in 1985, the cystic fibrosis gene localized to the DF508 locus on chromosome 7 codes for a protein that acts as a cystic fibrosis transmembrane conductance regulator (CFTCR). Abnormalities in the CFTCR disrupt membrane function. In the GI mucosa of the newborn, this defect manifests as poor motility. Meconium may build up and obstruct the lumen of the distal small bowel and colon.

Because meconium does not pass readily into the distal GI tract, distal small-bowel obstruction may develop in utero. The involved segment of bowel may dilate and even perforate. A pseudocyst may wall off around the perforation. Prenatal ultrasonography or neonatal plain radiography may identify a soap bubble or ground glass appearance of inspissated meconium. Adhesions may develop from the perforation. The functional picture of tenacious thick meconium that does not pass is termed meconium ileus. Segmental obstruction of the small bowel from meconium ileus can also precipitate volvulus of the bowel upstream from the obstruction.

Treatment of meconium ileus involves evacuation of the meconium. In more than 50% of patients, nonsurgical management relieves the obstruction successfully. A contrast enema may be both diagnostic and therapeutic. For the enema to evacuate the meconium, fluid must be refluxed into the terminal ileum. Multiple enemas may be administered. Dilute Gastrografin with *N*-acetylcysteine may be administered by nasogastric tube from above to help loosen the meconium. Hyperosmolar solutions (1% acylcysteine) may be effective in drawing more fluid into the lumen of the bowel, thereby enhancing the ability to loosen the thick meconium. Hyperosmolar enemas may increase the risk of perforation. The risk of perforation reportedly is 3-10%.

Calcification on scout radiography suggests intrauterine perforation. Do not administer therapeutic contrast enemas in the presence of bowel perforation or compromise. A pseudocyst may develop around a bowel perforation during development. In these patients or in those who underwent unsuccessful initial management with enemas, postnatal laparotomy is indicated. An enterotomy with irrigation of the bowel contents may move the meconium through successfully. In some patients, an ostomy for diversion and access for proximal irrigation may be necessary. Long-term outcome depends upon management of the underlying cystic fibrosis.

Meconium plug syndrome

Some newborns present with bowel obstruction from plugs of meconium isolated to the colon. Most of these newborns are otherwise healthy babies, but all should undergo a contrast enema, which almost always is diagnostic (no pathology) as well as therapeutic (successful in loosening the meconium plug and resolving the obstruction). A plug of meconium isolated to the colon is usually unrelated to cystic fibrosis. Conditions that predispose to dysmotility of the neonatal bowel, such as maternal preeclampsia, maternal diabetes mellitus, maternal administration of magnesium sulfate, prematurity, sepsis, and hypothyroidism, may be responsible for the formation of the meconium plug.

In each of these conditions, the colon distal to the obstruction is narrowed and small in caliber. Because of the frequent association between maternal diabetes mellitus and colonic obstruction with a small left colon, this association is termed small left colon syndrome.

As with meconium ileus, a nonoperative approach with administration of enemas is favored to relieve the obstruction. The enemas can also serve to dilate the small-caliber distal colon. A need for laparotomy to evacuate the meconium suggests a diagnosis other than simple meconium plug syndrome. Hirschsprung disease can be associated with meconium plug syndrome in 4% of patients; therefore, a suction rectal biopsy may be indicated.

Hirschsprung disease is a disorder of the neuroenteric pathways within the distal large bowel that prevents bowel relaxation, resulting in a functional distal bowel obstruction. Hirschsprung disease is not an acquired disease as the name suggests, but rather is a congenital absence of neuroganglion cells from the distal intestine that affects 1 in 4500-7000 newborns. Hirschsprung disease is more common in white infants and affects males 4 times more frequently than females. In approximately 12.5% of patients, Hirschsprung disease may be familial, especially when the entire colon is affected, which is termed total colonic aganglionosis.

Functional bowel obstruction in Hirschsprung disease results from an inability of the colon to relax during peristalsis. The relaxation phase of peristalsis usually occurs as a reflex to the antegrade peristaltic wave. In Hirschsprung disease, the affected bowel cannot relax and, therefore, remains contracted. The relaxation phase reflex is controlled by neuroenteric ganglion cells, which are present in the submucosa layer of the intestine. Normally, at 7-12 weeks' development, neuroenteric ganglion cells migrate from the neural crest along the bowel distally to reach the distal rectum.

If these ganglion cells are not present, the peristaltic relaxation phase is not conducted to the affected distal segment of the bowel. The affected distal colon does not relax appropriately, and a functional obstruction develops. Because of the migration pattern of these ganglion cells, Hirschsprung disease usually affects a continuous segment of bowel extending from the rectum proximally to the level of normal ganglionated bowel. The extent of the aganglionic segment varies with each patient.

The genetic defect responsible for Hirschsprung disease has been linked to the *ret* protooncogene, located on the long arm of chromosome 10. Current understanding of the influence of the *ret* protooncogene on migration of the ganglion cells is evolving. Hirschsprung disease may also be linked to other disorders of bowel motility.

Diagnosis of Hirschsprung disease is suggested by contrast enema and confirmed by rectal biopsy. If Hirschsprung disease is suggested, perform a contrast enema. Older children with Hirschsprung disease show a characteristic transition zone between narrow-caliber aganglionic bowel and dilated upstream normally ganglionated bowel. A distinct transition zone is often difficult to observe in newborns. Failure to evacuate the contrast in 24 hours following the contrast enema may be diagnostic for Hirschsprung disease. Anal manometry may also suggest a diagnosis of Hirschsprung disease but is difficult to perform in the newborn period.

The criterion standard to confirm Hirschsprung disease is rectal biopsy. Rectal biopsy may be readily performed at the bedside in newborns with a specially designed rectal biopsy tool. This instrument suctions the rectal mucosa and submucosa into the tool and amputates the specimen without perforating the serosa of the rectum. Collection of the specimen via suction is replacing the more conventional open biopsy method of obtaining tissue for histopathologic examination. The specimen is examined for the presence of ganglion cells in the submucosal layer. In addition, acetylcholinesterase staining of the submucosa identifies abnormal hypertrophic nerve fibers in Hirschsprung tissue. All children with delayed passage of meconium with a suspicious finding on contrast enema should undergo rectal biopsy prior to discharge.

Constipation of varying severity is a feature of all patients with Hirschsprung disease. The length of the aganglionic segment greatly influences bowel dysmotility. Aganglionosis confined to a short segment of distal rectum may cause only mild constipation, while patients with longer segments of aganglionic bowel may present with complete functional obstruction in the newborn period.

Infants with Hirschsprung disease frequently present with enterocolitis. A child may exhibit explosive diarrhea, sepsis, and abdominal distention. The mucosal integrity of the massively dilated proximal bowel may be compromised, allowing bacterial invasion of the epithelium. Management of Hirschsprung enterocolitis includes aggressive washout of the distal segment to decompress the bowel. Intravenous antibiotics are administered. A diverting colostomy has been traditionally performed to aid with this process.

Treatment of Hirschsprung disease is surgical. Several different surgical approaches have been described that pull ganglionated bowel down to the rectum. Most pediatric surgeons have performed a colostomy to allow for decompression of the bowel. Most recently, a minimally invasive pull-through technique with a transanal approach but without formal laparotomy has gained acceptance. For many surgeons, newer laparoscopic techniques greatly facilitate performance of the transanal approach. This primary pull-through technique avoids both a formal laparotomy and a diverting ostomy and may be appropriate for newborns with Hirschsprung disease who have no evidence of enterocolitis.

Long-term complications of Hirschsprung disease include a continued risk for chronic constipation and enterocolitis, even after successful pull-through. Bowel dysmotility may persist in many patients despite successful removal of aganglionic bowel. Outcome for patients with Hirschsprung disease who have undergone a pull-through procedure is generally good in terms of both continence and stool frequency.

Colonic atresia

Colonic atresia is a rare condition usually associated with genitourinary anomalies or abdominal wall defects. Pathophysiology of colonic atresia parallels that of jejunoileal atresia in that it results from an intrauterine mesenteric vascular accident. Its rarity may result from better protection of the colon from segmental ischemia afforded by the well-developed vascular arcade that runs immediately adjacent to it. This provides a more generous collateral blood supply between the network of colonic arteries than that from the more radial blood supply of the small bowel. Diagnosis of colonic atresia may be made by contrast enema. Diverting colostomy may be necessary if the proximal colon is extremely dilated. Volvulus of the dilated colon proximal to an atretic colonic segment has been observed.

Imperforate anus

Routine inspection of a newborn should note the position and patency of the anus. Anorectal malformations range from slight anterior displacement of the anal opening to a completely imperforate anus. Many children with imperforate anus have an abnormal sacral progression as well as internal fistulas between the rectum and the genitourinary structures. All children with an anorectal malformation are predisposed to constipation. A newborn with imperforate anus should undergo plain radiography 12-24 hours after birth to assess the distal extent of bowel gas.

Preoperative workup for imperforate anus is focused on the proximity of the distal rectum to the anal skin and sphincter complex. Lateral radiography with the child in a prone position, invertography, may be helpful in classifying the imperforate anus. Many newborns with imperforate anus have a fistulous tract to the skin or genitourinary system. Low lesions that have a fistulous connection between perianal or perineal body skin and rectum may be primarily repaired with a perineal anoplasty. If the distal rectum is several centimeters above the anal skin or has a fistula to the vagina or urinary bladder, the imperforate anus is classified as intermediate or high. In intermediate or high imperforate anus, colostomy is performed in the newborn period.

Following colostomy for intermediate or high imperforate anus, the infant undergoes a staged repair of the imperforate anus to pull down the rectum into the center of the anal sphincter complex. Continence has been achieved with both anterior and posterior approaches. Currently, the most widely performed procedure is a posterior sagittal anorectoplasty as described by Pena in 1998. Outcome is dependent upon the precision of the surgery, the severity of the sacral and perineal musculature anomaly, and the degree of colonic dysmotility.

Anorectal malformations are part of the VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, limb) association of congenital anomalies. Diagnosis of an anorectal malformation requires an investigation for other associated midline anomalies. Cardiac echocardiography, renal and sacral ultrasonography, and plain radiography of the vertebrae and radii are recommended. Because esophageal atresia with tracheoesophageal fistula is part of the VACTERL spectrum, any infant with imperforate anus and respiratory distress should undergo full airway evaluation.

Although laparotomy in the newborn period poses a significant stress to the patient, most infants recover well following successful surgical correction of the cause of the bowel obstruction.

In the initial postoperative period, derangements in fluid balance, glucose metabolism, and respiratory status are common. Most infants have some third-space fluid sequestration following laparotomy and may require additional fluids in the postoperative period. Maintenance IV fluid requirements are initially at least 1.5 times normal. Nasogastric decompression until normal bowel function is established aids in the decompression of proximal bowel and facilitates healing of a bowel anastomosis. Following surgery for bowel obstruction, a transient ileus is invariably present. If postoperative bowel function is not expected to rapidly return, parenteral nutrition support is indicated. Patience before feeding a child may avoid anastomotic breakdown or postoperative obstruction.

Once bowel motility is reestablished, an infant frequently demonstrates intolerance to lactose and other complex carbohydrates. A predigested or lactose-free formula may initially aid in absorption. If the terminal ileum is resected, derangements in folate metabolism and the enterohepatic circulation may be observed. Wound care is usually straightforward, and empiric antibiotics are not generally recommended after the perioperative period.

In general, most infants with bowel obstruction who are expeditiously identified and treated have an excellent outcome. Survival usually depends on comorbidities, such as degree of prematurity, associated cardiac anomalies, and the presence of peritonitis or bowel compromise at the time of surgery. The survival rate for duodenal atresia is greater than 90%. Long-term survival in patients with volvulus and jejunoileal atresia depends upon the amount of bowel remaining after resection, but an 80-90% survival rate is expected. The rate of leaking anastomoses following repair of newborns with jejunoileal atresia is approximately 15%.

Total parenteral nutrition and better methods for central IV access have greatly improved outcomes for neonates who undergo surgery for bowel obstruction. Often, bowel function is not established for a prolonged interval postoperatively. While total parenteral nutrition can support an infant through this period, both long- and short-term complications are observed. Short-term complications from parenteral nutrition include catheter sepsis, respiratory insufficiency, and problems related to securing central venous access. Long-term problems include cholestasis, nutritional deficiencies, and development of oral aversion.

As with any laparotomy, postoperative adhesions may develop. Operative technique that avoids unnecessary manipulation of the bowel and spillage of enteric contents is perhaps the best prevention against the development of intraperitoneal scar tissue.

Poor motility is often observed following bowel resection for obstruction. Chronic dilation of the intestinal segment proximal to the obstruction may alter normal peristalsis across that segment of bowel. For example, persistent constipation and delayed intestinal transit may not resolve after relief of chronic partial volvulus via Ladd procedure. Interruption of vagal neuroenteric pathways by an atresia or surgical anastomosis may also contribute to abnormal intestinal motility.

Short bowel syndrome deserves special mention. Short bowel syndrome results when the remaining length of intestine cannot sustain normal absorptive functions. Normal length of the small bowel in a term infant is approximately 250 cm and in an adult is 600-800 cm. The estimated minimum jejunoileal length for sufficient bowel function in a term infant is 75 cm. Resection of more than 60% of the small bowel predisposes the child to malabsorption, resulting in failure to grow and develop normally.

Every effort is made intraoperatively to preserve bowel length. Some children with short bowel syndrome manage to survive with the aid of parenteral nutrition. Bowel lengthening procedures, creation of intraluminal valves, and manipulation of bowel recovery with nutritional and hormonal treatments can help wean the patient with short gut syndrome from dependence on parenteral nutrition. In patients with severe volvulus with infarction of the entire midgut or multiple intestinal atresias, the child may clearly not have enough bowel length to survive. A difficult ethical decision must be made at the time of operation whether to proceed with resection.

Bowel obstruction in the newborn can be a true surgical emergency. Urgent surgical consultation is appropriate in most patients with neonatal bowel obstruction, and catastrophic causes of both proximal and distal bowel obstruction must be excluded without delay. Prompt recognition and treatment of the source of obstruction can prevent complications ranging from gangrene and septic peritonitis to catastrophic bowel loss. Bilious vomiting in a newborn should trigger an immediate suspicion of malrotation with midgut volvulus and initiate an immediate workup or even exploratory laparotomy. The importance of radiographic imaging modalities, especially contrast studies and ultrasonography, cannot be overemphasized. Quick recognition and expeditious treatment usually results in successful resolution of neonatal bowel obstruction, with resultant favorable short- and long-term outcomes for the patient.

Picture 1. Bowel obstruction in the newborn. Malrotation.

Picture 2. Bowel obstruction in the newborn. Malrotation with volvulus. Proximal small intestine coiled around superior mesenteric vessels.
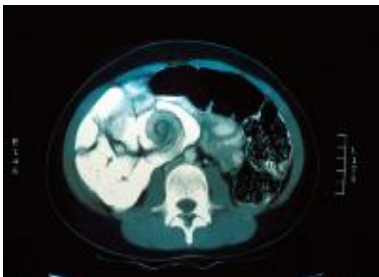
Picture 3. Bowel obstruction in the newborn. Duodenal atresia. Note double bubble and narrowing in second portion of the duodenum.

Picture 4. Bowel obstruction in the newborn. Jejunal atresia. Sharp transition between proximal dilated jejunum and distal unused intestine at point of atresia.

Picture 5. Bowel obstruction in the newborn. Jejunal atresia. Ischemic compromise of proximal segment.

Picture 6. Bowel obstruction in the newborn. Meconium plug. Contrast enema reveals dilated colon proximal to plug and can be therapeutic to relieve obstruction.

Picture 7. Bowel obstruction in the newborn. Imperforate anus.

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Breast Milk Jaundice

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Synonyms and related keywords: neonatal jaundice, indirect bilirubin, bilirubin, breastfeeding, uridine diphosphoglucuronic acid, UDPGA, UDPGA GT, unconjugated bilirubin pigment, conjugated bilirubin, hyperbilirubinemia, clinical jaundice, cholestatic jaundice, bilirubin level, phototherapy, breast milk, breastfeeding-associated jaundice, breastmilk jaundice

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INTRODUCTION	Section 2 of 9

Background: Arias first described breast milk jaundice in 1963. Breast milk jaundice is a type of neonatal jaundice associated with breastfeeding. Specifically, it is an elevation of indirect bilirubin in a breastfed newborn that develops following the first 4-7 days of life, persists beyond physiologic jaundice, and has no other identifiable cause. It should be differentiated from breastfeeding jaundice, which occurs before the first 4-7 days of life and is caused by insufficient production or intake of breast milk.

Pathophysiology: The etiology of breast milk jaundice is under investigation, but this type of jaundice is thought to be caused by a substance in the breast milk that inhibits uridine diphosphoglucuronic acid (UDPGA) glucuronyl transferase resulting in a prolonged unconjugated hyperbilirubinemia. Accumulation of unconjugated bilirubin pigment in the skin causes jaundice. Physiologic jaundice results from immaturity of newborn's liver and its inability to produce enough UDPGA glucuronyl transferase, the enzyme required to conjugate bilirubin. Conjugated bilirubin is water-soluble and can be excreted.

Frequency:

- **In the US:** Jaundice occurs in 50-70% of newborns. Moderate jaundice (bilirubin level >12 mg/dL) develops in 4% of bottle-fed newborns, compared to 14% of breastfed newborns. Severe jaundice (>15 mg/dL) occurs in 0.3% of bottle-fed newborns, compared to 2% of breastfed newborns.

- **Internationally:** International frequency is not extensively reported but is thought to be similar to that in the United States.

Race: Whether racial differences exist for breast milk jaundice is unclear, although an increased prevalence of physiologic jaundice exists in babies of Chinese, Japanese, Korean, and Native American descent.

Sex: No known sex predilection exists.

Age: Breast milk jaundice manifests within the first 4-7 days of life and can persist for 3-12 weeks.

History:

- Physiologic jaundice usually manifests in the first 2-4 days of life. This can be accentuated by breastfeeding, which in the first few days of life results in lower calorie intake, especially if milk production starts late. This is known as breastfeeding jaundice. Jaundice that manifests before the first 24 hours of life should be considered pathologic until proven otherwise. In this situation, a full diagnostic workup focusing on evaluation of sepsis and hemolysis should be undertaken.
- True breast milk jaundice manifests during the first 4-7 days of life. A second peak in bilirubin level is noted at approximately the 14th day of life.
- In clinical practice, differentiating between physiologic jaundice from breast milk jaundice is important so that the duration of hyperbilirubinemia can be predicted. Identifying the infants who become dehydrated secondary to inadequate breastfeeding is also important. These babies need to be identified early and given breastfeeding support and formula supplementation as necessary. Depending on serum bilirubin concentration, neonates with hyperbilirubinemia may become sleepy and feed poorly.

Physical:

- Clinical jaundice is usually first noticed in the sclera and the face. Then it progresses caudad to reach the abdomen and below. Gentle pressure on the skin helps to reveal the extent of jaundice, especially in darker-skinned babies; however, clinical observation is not an accurate measure of the severity of the hyperbilirubinemia.
- A rough correlation between blood levels and the extent of jaundice (face, approximately 5 mg/dL; mid abdomen, approximately 15 mg/dL; soles, 20 mg/dL) exists. Therefore, clinical decisions should be based on serum levels of bilirubin. Skin should have normal perfusion and turgor and show no petechiae.
- Neurologic examination, including neonatal reflexes, should be normal, although the infant may be sleepy. Muscle tone and reflexes (eg, Moro reflex, grasp, rooting) should be normal.
- Evaluate hydration status by an assessment of the percentage of birth weight that may have been lost, observation of mucous membranes, fontanelle, and skin turgor.

Causes:

- Supplementation of breastfeeding with dextrose 5% in water (D5W) actually can increase the prevalence or degree of jaundice.
- Late milk production and poor feeding lead to decreased caloric intake, dehydration, and increased enterohepatic circulation, resulting in higher serum bilirubin concentration.
- The biochemical cause of breast milk jaundice remains under investigation. Some research reported that lipoprotein lipase, found in some breast milk, produces nonesterified long-chain fatty acids, which competitively inhibit glucuronyl transferase conjugating activity.
- Glucuronidase has also been found in some breast milk, which results in jaundice.

Anemia, Acute   Biliary Atresia
Cholestasis   Galactosemia
Hemolytic Disease of Newborn   Hypothyroidism
Jaundice, Neonatal   Neonatal Sepsis
Polycythemia   Polycythemia of the Newborn

Other Problems to be Considered:

Hereditary nonspherocytic anemia   Spherocytosis
Acanthocytosis   Ovalocytosis
Hemangiomatosis   Large cephalhematoma
Dehydration   Inadequate breastfeeding
G-6-PD deficiency

Lab Studies:

- Measure total serum bilirubin in neonates who have jaundice that has progressed from the facies to the chest and in neonates at risk for hemolytic disease of the newborn.
- The following tests are to be considered if serum bilirubin is greater than 12 mg/dL (170 pmol/L). A total serum bilirubin rising faster than 5 mg/dL/d (85 pmol/L/d) or jaundice before 24 hours of life suggests pathologic jaundice.
- Fractionated serum bilirubin: A level of conjugated bilirubin greater than 2.0 mg/dL (34 pmol/L) suggests cholestasis, biliary atresia, or sepsis (see Jaundice, Neonatal).
- Complete blood count

  o Polycythemia (Hct >65%)
  o Anemia (Hct <40%)
  o Sepsis (WBC count <5 K/mL or >20 K/mL) with immature to total neutrophil ratio greater than 0.2
  o Urine specific gravity can be useful in the assessment of hydration status.

- If hemolysis is suspected, consider the following tests:

  o Blood type to evaluate for ABO and Rh incompatibility
  o Coombs test to evaluate for immune mediated hemolysis
  o Peripheral smear to look for abnormally shaped RBCs (ovalocytes, acanthocytes, spherocytes, schistocytes)
  o G-6-PD screen if ethnicity consistent

- Factors that suggest possibility of hemolytic disease include the following:

  o Family history of hemolytic disease
  o Onset of jaundice before 24 hours of life
  o Rise in serum bilirubin levels of more than 0.5 mg/dL/h
  o Pallor, hepatosplenomegaly
  o Rapid increase in serum bilirubin level after 24-48 hours (G-6-PD deficiency)
  o Ethnicity suggestive of G-6-PD deficiency
  o Failure of phototherapy to lower bilirubin level

- If sepsis is suspected, consider the following tests:

    - Blood culture
    - WBC differential
    - Platelet count

- Factors that suggest the possibility of sepsis include the following:

    - Poor feeding
    - Vomiting
    - Lethargy
    - Temperature instability
    - Apnea
    - Tachypnea

- Signs of cholestatic jaundice that suggest the need to rule out biliary atresia or other causes of cholestasis include the following:

    - Dark urine or urine positive for bilirubin
    - Light-colored stools
    - Persistent jaundice for more than 3 weeks

TREATMENT	Section 6 of 9

Medical Care:

- Treatment recommendations in this section apply only to healthy term infants with no signs of pathologic jaundice. In preterm, anemic, or ill infants and those with early (<24 h) or severe jaundice (>25 mg/dL or 430 pmol/L), different treatment protocols should be pursued .
- For healthy term infants with breast milk or breastfeeding jaundice and with bilirubin levels of 12 mg/dL (170 pmol/L) to 17 mg/dL, the following options are acceptable:

    - Increase breastfeeding to 8-12 times per day and recheck the serum bilirubin level in 12 hours. This is assuming that effective breastfeeding is occurring, including milk production, effective latching on of the baby, and effective sucking with resultant letdown of milk. Breastfeeding can also be supported with manual or electric pumps and the pumped milk given as a supplement to the baby.
    - Continue breastfeeding and supplement with formula.
    - Temporary interruption of breastfeeding is rarely needed and is not highly recommended.

- For infants with bilirubin levels from 17-25 mg/dL (294-430 pmol/L), add phototherapy to any of the previously stated treatment options.
- The most rapid way to reduce the bilirubin level is to interrupt breastfeeding for 24 hours, feed with formula, and use phototherapy; however, in most infants, interrupting breastfeeding is not necessary or advisable.
- Phototherapy can be administered with standard phototherapy units and fiberoptic blankets. Fiberoptic phototherapy can often be administered safely at home, which may allow for improved infant-maternal bonding. In locations where phototherapy is unavailable, natural sunlight is an alternative. Caution should be exercised as the intensity of sunlight is of course not standardized and risk of sunburn exists. Phototherapy can be discontinued when serum bilirubin drops below 15 mg/dL (260 pmol/L). It has been shown that average bilirubin level rebound is less than 1 mg/dL (17 pmol/L), so rechecking the level after discontinuation of phototherapy is not necessary. For an in-depth discussion of phototherapy.

Consultations:

- Consider consultation with a neonatologist when the serum bilirubin level rises above 20 mg/dL (430 pmol/L) or when signs and symptoms suggest pathological jaundice and the rate of rise in the serum bilirubin level is more than 0.5 mg/dL/h.
- Consultation with a lactation consultant is recommended in any breastfed baby who has jaundice. The expertise can be extremely helpful, especially in situations in which inadequate breastfeeding is contributing to the jaundice.

Diet:

- Continue breastfeeding, if possible, and increase frequency of feeding to 8-12 times per day.
- Depending on maternal preference, breastfeeding can be supplemented or replaced by formula at the same frequency. Supplementation with dextrose solution is not recommended because it may decrease caloric intake and milk production and consequently delay the drop in serum bilirubin concentration. Breastfeeding can also be supplemented by pumped breast milk.

Activity:

- No restrictions are necessary.
- Encourage parents to remove the child from the warmer or infant crib for feeding and bonding. Fiberoptic blankets allow holding and breastfeeding without interruption in treatment.

FOLLOW-UP	Section 7 of 9

Further Inpatient Care:

- If the patient has not been discharged with the parent, monitoring daily weights and serum bilirubin concentration for the need for phototherapy as well as assessment of caloric intake are important. Once serum bilirubin concentration is determined to be within a safe range (<20 mg/dL) and is not rising rapidly, home phototherapy is an option to consider as long as thorough outpatient follow-up (home visiting nursing assessment or office check-up and bilirubin level monitoring) are feasible.

Further Outpatient Care:

- If the infant is treated on an outpatient basis, measure serum bilirubin levels daily either in the clinic or in the home with home-health nurses until the bilirubin level is below 15 mg/dL (260 pmol/L).

Transfer: Transfer infants with pathologic jaundice or bilirubin levels greater than 25 mg/dL (430 pmol/L) to a center capable of performing exchange transfusions.

Complications: Kernicterus is rarely reported in breast milk jaundice.

Prognosis: Prognosis is excellent, although jaundice may persist for up to 12 weeks in breastfed infants.

Patient Education: Provide excellent breastfeeding education. Refer to a lactation consultant or La Leche League.

Medical/Legal Pitfalls:

- Failure to differentiate breast milk jaundice from pathologic jaundice
- Failure to appropriately treat elevated bilirubin levels
- Failure to identify and treat inadequate breastfeeding, with resultant dehydration

Special Concerns:

- Treat preterm infants (estimated gestational age <37 wk at birth) with phototherapy at lower bilirubin levels (see Jaundice, Neonatal).

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Bronchopulmonary Dysplasia

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INTRODUCTION	Section 2 of 11

Background: Bronchopulmonary dysplasia (BPD) is a chronic lung disease (CLD) that develops in preterm neonates treated with oxygen and positive pressure ventilation (PPV). Northway originally described BPD in 1967 with clinical, radiographic, and histologic lung changes in preterm infants who had respiratory distress syndrome (RDS) and were treated with oxygen and ventilator therapy.

Northway's original definition has been modified. Bancalari has refined Northway's definition using ventilation criteria, oxygen requirement at 28 days to maintain arterial oxygen concentration greater than 50 mm Hg, and abnormal findings on chest radiography. In 1988, Shennan proposed that the additional need for supplemental oxygen at 36 weeks corrected age may be a more accurate indicator of pulmonary outcome; this criterion decreases the large number of healthy very preterm infants included by Bancalari and others. A recent National Institute of Heart Disease (NIHD)/National Heart, Lung, and Blood Institute (NHLBI)/Office of Rare Diseases (ORD) workshop was summarized by Jobe and Bancalari in 2001; the definition of BPD was further modified with the diagnostic criteria based on gestational age less than 32 weeks' or greater than 32 weeks' gestation and the severity of BPD.

Currently, BPD is infrequent in infants with birth weight greater than 1200 g and in infants of greater than 30 weeks' gestation. Antenatal glucocorticosteroids, early surfactant therapy, and gentler modalities of ventilation have minimized the severity of lung injury, particularly in more mature infants. However, in some smaller infants who may have been exposed to chronic chorioamnionitis, its pathogenesis remains enigmatic.

Pathophysiology: The pathophysiology of BPD is multifactorial. Major organ systems affected include the lungs and the heart.

The alveolar stage of lung development in the human is from about 36 weeks' gestation to 18 months postnatally, with most alveolarization occurring within 5 to 6 months of term birth. Although primary septation forms saccules and secondary septal crests indicate alveolarization, some investigators think that septations are a continuous process. The intense pulmonary

microvasculature branching runs parallel with lung development; however, detailed understanding of their interactions and interactions with various growth factors is elusive.

In contrast to the findings of Northway, in the postsurfactant era, the lungs of infants dying of BPD show less fibrosis and more uniform inflation. The large and small airways are remarkably free of epithelial metaplasia, smooth muscle hypertrophy, and fibrosis. However, alveoli are less numerous and are larger, indicating an interference with septation, despite an increase in elastic tissue that is proportionate to the severity of the respiratory disease before death. Some specimens also have decreased pulmonary microvasculature development. Because most infants survive, the pathologic progression of the disease and the healing process are not fully understood.

Mechanical ventilation and oxygen interferes with alveolar and vascular development in preterm baboons and in lambs.

Infants with severe BPD have pulmonary hypertension and abnormal pulmonary vascular development.

In a Finnish study in 2000, Ramet et al showed that genetic polymorphism in their population may have increased the risk of developing BPD. Newly developed techniques of regulating genes important in lung development at precise times and the advancements in proteonomics applied to lung injury may provide a futuristic view of understanding this complex process.

==Frequency:== **In the US:** The frequency of BPD is dependent on the definition used and can be quite different between neonatal intensive care units (NICUs). An analysis of several surfactant trials reveals an incidence of BPD (ie, oxygen requirement at age 28 d with an abnormal finding on chest radiography) ranging widely from 17-57%; no significant difference between placebo- and surfactant-treated survivors was found. In 1998, Kresch et al performed a more recent meta-analysis of surfactant replacement therapy for infants weighing less than 2 kg, which demonstrated improved survival without BPD in infants receiving modified natural surfactant. Infants with severe BPD are often extremely immature and of very low birth weight, although term infants with significant respiratory failure may also be at increased risk. In fact, since the survival of very low birth weight infants has improved by surfactant supplementation, the actual prevalence of BPD has increased.

==Mortality/Morbidity:== Since the routine use of surfactant replacement has begun, survival of the most immature infants has improved. Along with other advances in technology and improved understanding of neonatal physiology, infants with BPD today appear to have less severe disease as compared to infants with BPD in years past. Infants with severe BPD remain at high risk for pulmonary morbidity and mortality during the first 2 years of life.

- Pulmonary mechanics

    o Pulmonary complications include increased airway resistance, decreased lung compliance, increase in airway reactivity, and increase in airway obstruction. Increased resistance and airway activity may be evident in the early stages of BPD. With worsening severity, airway obstruction can become significant, with expiratory flow limitations. In the early and mild stages of BPD, functional residual capacity (FRC) can be increased; however, increases in FRC are noted in severe BPD secondary to air trapping and hyperinflation.

    o Lung compliance is reduced in infants with BPD. Changes on pulmonary function tests (PFTs) correlate with radiographic findings. Compliance is often reduced in infants with BPD secondary to increased resistance, resulting in frequency dependence and tachypnea often observed in these infants. Serial PFTs may help assess therapeutic modalities employed to treat BPD, but they are fraught with variability and error related to excessive chest wall distortion and the location from which measurements are made.

History: BPD is a CLD that develops in both preterm and term neonates treated with oxygen and PPV for a primary lung disorder. Northway originally described BPD in 1967 with characteristic clinical, radiographic, and histologic lung changes in preterm infants who had RDS and were treated with oxygen and mechanical ventilation.

- Definition and frequency

  o The frequency of BPD is dependent upon the definition used and can vary significantly between NICUs. Other investigators have modified Northway's original definition of oxygen requirement at 28 days. Bancalari expanded Northway's definition to include the need for mechanical ventilation, oxygen requirement at 28 days (to maintain arterial oxygen >50 mm Hg), and an abnormal finding on chest radiography. In 1988, Shennan suggested that the need for supplemental oxygen at 36 weeks postconceptual age may be a more accurate predictor of long-term pulmonary outcome. In 1998, Palta and colleagues indicated that repeated episodes of wheezing (consistent with a diagnosis of asthma) severe enough to require treatment with bronchodilators or corticosteroids by age 1-2 years appears to be the most reliable way of predicting long-term pulmonary function.

  o Preterm infants are treated with oxygen and PPV. These infants may require only short periods of PPV and supplemental oxygen during the first 1-2 weeks of life. Other infants with severe RDS may respond poorly to surfactant replacement and have high ventilator and oxygen requirements, which increase toward the latter part of the first week or early in the second week of life. Chest radiography may reveal pulmonary interstitial emphysema (PIE), wandering atelectasis with concomitant hyperinflation, and cyst formation.

- Volutrauma and barotrauma

  o The mainstay of treatment for RDS has been surfactant replacement along with oxygen supplementation, continuous positive airway pressure (CPAP), and mechanical ventilation. The PPV required to recruit alveoli and prevent atelectasis in the immature lung may cause lung injury and activate the inflammatory cascade. Trauma secondary to PPV is generally referred to as barotrauma. With the more recent return to volume ventilation and the low versus high tidal volume ventilation strategy, some investigators have adopted the term volutrauma. Volutrauma suggests lung injury secondary to excess tidal volume from PPV.

  o The severity of lung immaturity and the effects of surfactant deficiency determine the need for PPV, surfactant supplementation, and resultant barotrauma/volutrauma. With severe lung immaturity, total alveolar number is reduced, thereby increasing the positive pressure transmitted to distal terminal bronchioles. In the presence of surfactant deficiency, surface tension forces are increased; some compliant alveoli may become hyperinflated, while other saccules with increased surface tension remain collapsed. With increasing PPV to recruit alveoli and improve gas exchange, the compliant terminal bronchiole and alveolar ducts may rupture, leaking air into the interstitium, with resultant development of PIE. The development of PIE was well demonstrated by Ackerman in 1984. The occurrence of PIE greatly increases the risk of BPD development.

  o Many different modes of ventilation as well as ventilator strategies have been studied to reduce barotrauma. In 1996, Bernstein compared synchronized intermittent mechanical ventilation (SIMV) to intermittent mechanical ventilation (IMV) in preterm infants with RDS. Infants weighing less than 1000 g ventilated with SIMV had less BPD. Others have employed high-frequency jet ventilation (HFJV) or high-frequency oscillatory ventilation (HFOV) to prevent barotrauma or to rescue infants when conventional ventilation (CV) has failed; results have been mixed.

- o Comparisons of these studies are difficult secondary to the ventilator strategy employed and the definition of BPD used. After surfactant administration, infants in the Provo multicenter HFOV trial were randomized to CV or HFOV with a lung recruitment strategy. This study found that patients randomized to HFOV had no CLD at age 30 days and needed less oxygen at discharge. Similarly, in 1997, Keszler and colleagues studied HFJV versus CV in preterm infants with RDS who were treated with surfactant. Although the study was terminated early, secondary to neurologic complications of another HFV trial using a different ventilator strategy, infants treated with HFJV had less BPD (ie, oxygen requirement at 36 weeks corrected age), less need for supplemental home oxygen therapy, and had no difference in severe neurologic injury (eg, grade III or IV intraventricular hemorrhage or periventricular leukomalacia [PVL]).
  - o Regardless of the HFV strategy that was used, avoidance of hypocarbia and optimization of alveolar recruitment may decrease the risk of BPD development and CNS abnormalities.

- Oxygen and antioxidants: Oxygen (O_2) can accept electrons in its outer ring to form oxygen free radicals. Oxygen free radicals can cause cell membrane destruction and DNA abnormalities. Neonates live in an oxygen-rich environment as compared to the fetus. Oxygen is ubiquitous and necessary for extrauterine survival. All mammals have antioxidant (AO) defense to mitigate oxygen free radical injury. Neonates are relatively AO deficient. The major AOs in humans are superoxide dismutase (SOD), glutathione peroxidase, and catalase. Antioxidant enzyme (AOE) levels tend to increase during the last trimester of pregnancy, similar to surfactant production. Increases in alveolar size and number, surfactant production, and AOEs prepare the fetus for transition from a relatively hypoxic placental respiratory environment to a relatively hyperoxic extrauterine life. Preterm birth exposes the neonate to high oxygen concentrations with low AO reserves, thereby increasing the risk of oxygen free radical injury.
Animal and human studies of supplemental SOD and catalase supplementation have shown reduced cell damage, increased survival, and possible prevention of lung barotrauma. Lipid peroxidation is increased in neonates who develop BPD. Lipid peroxidation can be measured in vivo by measurement of expired pentane and ethane. In 2000, Davis and others studied SOD supplementation in ventilated preterm infants with RDS.

- Inflammation

  - o Activation of inflammatory mediators has been demonstrated in humans and animal models of acute lung injury. Activation of leukocytes perhaps by oxygen free radicals, barotrauma, infection, and other stimuli may begin the process of destruction and abnormal lung repair that results in acute lung injury followed by development of BPD.
  - o Radiolabeled activated leukocytes have been recovered by bronchoalveolar lavage (BAL) in preterm neonates receiving oxygen and PPV. These leukocytes, as well as lipid byproducts of cell membrane destruction, activate the inflammatory cascade and are metabolized to arachidonic acid (AA) and lysoplatelet factor. AA is catabolized by lipoxygenase, resulting in cytokines and leukotrienes. These byproducts may also be metabolized by cyclooxygenase to produce thromboxane, prostaglandin, or prostacyclin. All of these substances have potent vasoactive and inflammatory properties and are elevated in tracheal aspirates of newly ventilated preterm infants who subsequently develop BPD.
  - o Metabolites of AA, lysoplatelet factor, prostaglandin, and prostacyclin may cause vasodilatation, increased capillary permeability with subsequent albumin leakage, and inhibition of surfactant function, thereby potentiating barotrauma.
  - o Collagenase and elastase are released from activated neutrophils and may destroy lung tissue directly. Hydroxyproline and elastin (breakdown products of collagen and elastin) have been recovered in the urine of preterm infants who develop BPD. Alpha1-proteinase inhibitor mitigates the action of elastases and is activated by oxygen free radicals. Increased activity as well as decreased alpha1-proteinase inhibitor function may worsen lung injury in neonates. A decrease in the prevalence

of BPD and in the need for continued ventilator support has been found in neonates treated with alpha1-proteinase inhibitor supplementation.

- o Di(2-ethylhexyl)phthalate (DEHP), a degradation product of used endotracheal tubes, may cause lung injury. Increases in alveolar growth, alveolar number, and surfactant production occur from 24-40 weeks' gestation. The self-perpetuating cycle of lung injury is accentuated in the extremely preterm neonate with immature lung development.
- o By contrast, in 1996, Yoon and colleagues found increased interleukin-6 in umbilical cord plasma of preterm infants who subsequently developed BPD, suggesting that intrauterine activation of the inflammatory cascade may predispose these infants to BPD.

- Infection: Maternal cervical colonization, preterm neonatal tracheal colonization, or both with *Ureaplasma urealyticum* have been implicated in BPD development. In 1988, Cassel and others found an 82% rate of *U urealyticum* colonization in infants who developed BPD as opposed to those infants with negative cultures. Heggie et al disputed these findings in 1994. Infection alone may activate the inflammatory cascade and damage the preterm lung, resulting in BPD. In 2000, Couroucli et al performed polymerase chain reaction (PCR) for some viruses, *U urealyticum,* and *Mycoplasma* species on tracheal aspirates within the first week of life in preterm ventilated infants. Positive PCR results for adenovirus were noted in infants who developed BPD.

- Nutrition

  - o Inadequate nutritional supplementation in the preterm neonate may compound the damage caused by barotrauma, inflammatory cascade activation, and deficient AO stores. Acute CLD may increase energy expenditures by preterm infants with limited reserves. Animal studies of newborn rats that were nutritionally deprived revealed decreased lung weights. AOE may protect the lung and help prevent or mitigate BPD. Trace elemental deficiency, especially copper, zinc, and manganese, in preterm neonates may predispose the infant to lung injury, and supplementation may provide protection. Vitamins A and E are nutritional AOs that may help prevent lipid peroxidation and maintain cell integrity. Supplementation of vitamin E in preterm neonates does not prevent BPD. Preterm neonates may be deficient of vitamin A, and trials of vitamin A supplementation to prevent BPD in preterm infants are ongoing.
  - o Extremely preterm infants may require large amounts of free water secondary to increased insensible water loss through thin immature skin. Excessive fluid administration increases the risk of symptomatic patent ductus arteriosis (PDA) development and pulmonary edema (PE). Increased ventilator settings and oxygen requirements necessary to treat PDA and PE may worsen pulmonary injury and increase the risk of BPD. Early PDA treatment may improve pulmonary function but does not affect the incidence of BPD.

- Genetics: Families with a strong family history of atopy and asthma may be at increased risk for BPD development, as well as increased severity. The histocompatability subtype locus anthocyanins 2 (A2) has been found in infants with BPD.
  - o In 1967, Northway and associates first described 4 different stages of severity. Stage 1 was similar to uncomplicated RDS. Stage 2 revealed pulmonary parenchymal opacities and a bubbly appearance to lungs. In stages 3 and 4, patients had areas of lung with atelectasis, areas of hyperinflation, bleb formation, and fibrous sheaths. Edwards in 1979 and Toce in 1984 have subsequently redefined Northway's original findings and correlated BPD scores with illness severity.
  - o More recently, CT scanning and MRI studies of infants with BPD have provided more detailed images of the damaged airway and lung. In 1999, Aquino and colleagues demonstrated scarring and air trapping with architectural distortion in 26 patients with a median age of 10 years who had a clinical history of BPD. The degree of abnormalities correlated with the physiologic assessments of pulmonary function.

- Cardiovascular changes: Endothelial cell proliferation, smooth muscle cell hypertrophy, and vascular obliteration have been demonstrated in infants with BPD who have died. Cor pulmonale may result from these vascular alterations. Serial ECG may reveal right ventricular hypertrophy, and echocardiography may demonstrate abnormal right ventricular systolic function and left ventricular hypertrophy. Persistent right ventricular hypertrophy or fixed pulmonary hypertension unresponsive to oxygen supplementation on cardiac catheterization portends a poor prognosis.
- Pulmonary mechanics: Increased resistance and airway activity may be evident in the early stages of BPD. With worsening severity, airway obstruction can become significant, with expiratory flow limitations. In the early and mild stages of BPD, FRC can be increased; however, increases in FRC are noted in severe BPD secondary to air trapping and hyperinflation. Lung compliance is reduced in infants with BPD. Changes on PFT results correlate with radiographic findings. Compliance is often reduced in infants with BPD secondary to increased resistance, resulting in frequency dependence and tachypnea often observed in these infants. Serial PFTs may help assess therapeutic modalities employed to treat BPD, but they are fraught with variability and error from excessive chest wall distortion as well as the locations from which measurements are made.

- Airway

  - The upper proximal airway (trachea and mainstem bronchi) of infants with BPD may have mild-to-severe abnormalities depending on the duration and frequency of intubation and ventilation. Diffuse or focal areas of mucosal edema, necrosis, or ulceration may be observed. The earliest changes noted on light microscopy include loss of cilia from columnar epithelium, dysplasia, or necrosis of these cells with breakdown of epithelial lining. Neutrophil and lymphocyte infiltration into the affected areas may be noted, along with goblet cell hyperplasia and increased mucus production. Granulation tissue and upper airway scarring may occur from deep suctioning and repeated endotracheal intubation, which may result in laryngotracheomalacia, subglottic stenosis, and vocal cord paralysis.
  - The terminal bronchioles and alveolar ducts may reveal the most significant pathophysiologic changes. Hyaline membranes appear during the acute phase of RDS, which may be incorporated into the underlying airway. Necrotizing bronchiolitis may occur as a result of edema, inflammatory exudate, and necrosis of epithelial cells. Inflammatory cells, exudate, and cellular debris may obstruct the terminal airways, thereby simultaneously resulting in airway obstruction and providing alveolar protection from oxygen and barotrauma/volutrauma. Activation and fibroblast proliferation may result in peribronchial fibrosis and obliterative fibroproliferative bronchiolitis, leading to airway narrowing and restriction in some conducting channels with obstruction in others.

- Alveoli: In the acute phase of RDS, some alveoli are collapsed secondary to increased surface tension and surfactant deficiency, while compliant alveoli may become hyperinflated and even rupture. Focal atelectasis, areas of hyperinflation, and inflammatory exudate may be observed. Normal alveolar architecture is subsequently distorted. Emphysematous blebs and alveolar and capillary destruction is observed with moderate-to-severe disease.
- Incidence: Determining the incidence of BPD is confounded by the definition used as well as the population being studied. An analysis of several surfactant trials reveals an incidence of BPD (ie, oxygen requirement at age 28 d with abnormal findings on chest radiography) ranging widely from 17-57%, with no significant difference between placebo- and surfactant-treated survivors. In 1998, Kresch et al performed a more recent meta-analyses of surfactant replacement therapy for infants weighing less than 2 kg, which demonstrated improved survival without BPD in infants receiving modified natural surfactant. Infants with severe BPD are often extremely immature and of very low birth weight, although term infants with significant respiratory failure may also be at increased risk. In fact, since the survival of very low birth weight infants has improved by surfactant supplementation, the actual prevalence of BPD has increased.

- Infants with BPD have abnormal findings on physical examination, chest radiography, pulmonary function testing, and histopathologic examination.
- Infants with severe BPD are often extremely immature and of very low birth weight.

   o They frequently respond to conventional ventilation and surfactant administration.
   o Extraordinary therapeutic modalities, such as HFV and inhaled NO, have been employed to improve survival of these infants with mixed success.
   o Oxygen and ventilator requirements often increase within the first 2 weeks of life.

- Other infants initially respond well to surfactant and various forms of ventilation strategies.

   o Over the course of the second to fourth weeks of life, oxygen assistance, ventilator assistance, or both often increases to maintain adequate oxygenation and ventilation.
   o Chest radiographs obtained in these infants may demonstrate decreased lung volumes, areas of atelectasis and hyperinflation, lung haziness, and PIE.

- Arterial blood gases may reveal acidosis, hypercarbia, and hyperoxia.
- Physical examination may reveal the following:

   o Tachypnea
   o Tachycardia
   o Increased work of breathing, with retractions, nasal flaring, and grunting

- Poor weight gain and increased energy intake requirements are frequently noted.
- Different scoring systems have been developed and studied to predict BPD, to gauge the severity of illness, and to predict the survival of patients with BPD.

Causes: See History for a detailed discussion of the following causes.

- Volutrauma and barotrauma
- Oxygen toxicity
- Inflammation
- Infection
- Nutrition

DIFFERENTIALS	Section 4 of 11

Atelectasis, Pulmonary
Hypertension
Patent Ductus Arteriosus
Pneumonia
Subglottic Stenosis
Tracheomalacia

Other Problems to be Considered:

Airway injury

Lab Studies:

- Arterial blood gases may reveal acidosis, hypercarbia, and hyperoxia.

Imaging Studies:

- Chest radiography is helpful in distinguishing BPD severity and in differentiating BPD from atelectasis, pneumonia, and air leak syndrome.
- More recently, CT scanning and MRI studies of infants with BPD have provided more detailed images of the damaged airway and lung.

Histologic Findings: In 1996, Cherukupalli and colleagues completed morphologic and biochemical lung analyses of infants with BPD. Four distinct pathologic stages have been identified, which are acute lung injury, exudative bronchiolitis, proliferative bronchiolitis, and obliterative fibroproliferative bronchiolitis.

Staging: In 1967, Northway and associates first described 4 different stages of severity. Stage 1 was similar to uncomplicated RDS. Stage 2 revealed pulmonary parenchymal opacities and a bubbly appearance to lungs. In stages 3 and 4, patients had areas of atelectasis, hyperinflation, bleb formation, and fibrosis. Edwards in 1979 and Toce in 1984 subsequently refined Northway's original findings and correlated BPD score with illness severity.

Medical Care: Future management of BPD will involve strategies stressing prevention. Because few accepted therapies currently exist that can significantly prevent the development of BPD, many different therapeutic modalities (ie, mechanical ventilation, oxygen therapy, nutritional support, medications) are employed to treat BPD. Fortunately, the practicing neonatologist has observed a reduced severity of BPD in the postsurfactant era. Maintaining infants on PPV and oxygen therapy for longer than 4 months and discharging them to long-term care facilities for prolonged mechanical ventilation is now unusual.

- Mechanical ventilation

  - Oxygen and PPV frequently are life-saving in extremely preterm infants; however, the early and aggressive use of nasal CPAP may eliminate the need for PPV and exogenous surfactant in some infants or facilitate weaning from PPV in other infants. Other investigators recommend brief periods of intubation primarily for exogenous surfactant administration followed quickly by extubation and nasal CPAP as a method of minimizing the need for prolonged PPV.
  - In infants requiring oxygen and PPV, minimize oxygen toxicity and barotrauma/volutrauma by careful and meticulous management. Monitor pH, partial pressure of carbon dioxide, and partial pressure of oxygen carefully; maintain pH at 7.20-7.40, partial pressure of carbon dioxide at 45-65 mm Hg, and partial pressure of oxygen at 50-70 mm Hg. Assessment of blood gases requires arterial, venous, or capillary blood samples. Indwelling arterial lines are often employed early in the acute management of RDS, and they provide the most accurate information about pulmonary function. Arterial puncture may not provide completely accurate samples secondary to patient agitation and discomfort. Capillary blood gases, if properly obtained, may correlate with arterial values; however, capillary samples may suffer from wide variability and poor carbon dioxide correlation.
  - Pulse oximetry and transcutaneous carbon dioxide measurement may provide useful information on assessing adequate ventilation and oxygenation with minimal patient

discomfort. Many new synchronized ventilators may provide important information regarding tidal and minute volumes and flow volume loops. Proper interpretation of this information may help to improve gas exchange and minimize oxygen toxicity and barotrauma/volutrauma. Humidify and warm inspired gas and appropriately note the continuous monitoring of inhaled oxygen in patient records. Synchronized ventilators often allow infants to set their own inspiratory time as well as rate in dynamic fashion to minimize infant discomfort.

- o Weaning from mechanical ventilation and oxygen is often difficult in infants with moderate-to-severe BPD, and few criteria have been defined to enhance the chances of successful extubation. When adequate tidal volumes and low inspired oxygen concentrations are noted, a trial of extubation and nasal CPAP may be indicated. Not uncommonly, atrophy and fatigue of respiratory muscles may result in extubation failure. A trial of endotracheal CPAP prior to extubation is controversial because of increased work of breathing and airway resistance. Optimization of methylxanthines, diuretics, and adequate nutrition all support and facilitate weaning the infant from mechanical ventilation. Meticulous primary nursing care is essential to ensure airway patency and facilitate extubation. Prolonged and repeated intubations, as well as mechanical ventilation, may be associated with severe upper airway abnormalities, such as vocal cord paralysis, subglottic stenosis, and laryngotracheomalacia.

- o Consider bronchoscopic evaluation in infants with BPD in whom extubation is repeatedly unsuccessful despite optimization of nutrition, medications, and ventilator settings. Surgical interventions (cricoid split, tracheostomy) for severe structural abnormalities are less frequently employed today than in the past.

- Oxygen therapy

  - o Pulmonary hypertension and cor pulmonale may result from chronic hypoxia and airway remodeling in infants with severe BPD. Oxygen is a potent pulmonary vasodilator acting through the stimulation of NO production, which causes smooth muscle cell relaxation via activation of cyclic guanosine monophosphate (GMP). Currently, pulse oximetry is the mainstay of noninvasive oxygen monitoring. Repeated episodes of desaturation and hypoxia may occur in infants with BPD on mechanical ventilation as a result of a decrease in respiratory drive, alterations in pulmonary mechanics, excessive stimulation, and bronchospasm.

  - o Hyperoxia may overwhelm the neonate's relatively deficient AO defenses and worsen BPD. Increased oxygen requirements are frequently needed during stressful procedures as well as during feedings. Wean oxygen slowly. The optimal range of oxygen saturation in BPD is controversial, but maintain saturation of arterial oxygen (SaO_2) at 90-95%. Some infants, especially those living at high altitudes, may require oxygen therapy for many months. Transfusion of packed RBCs may increase oxygen carrying capacity of preterm infants who are anemic (hematocrit [Hct] <30), but transfusion may further increase complication rates. The ideal hemoglobin level in critically ill neonates has not been well established.

  - o In 1988, Alverson and colleagues demonstrated increases in oxygen content and systemic oxygen transport and decreases in oxygen consumption and oxygen requirements in infants with BPD after blood transfusion. Hemoglobin levels do not correlate well with oxygen transport. Minimize the need for multiple transfusions and donor exposures by the use of erythropoietin therapy, iron supplementation, and a reduction in phlebotomy requirements.

- Nutritional support
  - o Infants with BPD have increased energy requirements. Early parenteral nutrition is often used to ameliorate the catabolic state of the preterm infant. Maximizing parenteral protein, carbohydrate, fat, vitamin, and trace metal intake is critical to prevent further lung injury and augment tissue repair. However, take care to avoid excessive nonnitrogen calories because this may lead to excessive carbon dioxide formation and complicate weaning. Early insertion of percutaneous central venous lines may help to improve the energy density of parenteral nutrition. Accomplish progressive increases in protein and fat supplementation to provide approximately 3-3.5 g/kg of body weight per day. Rapid and

early administration of high concentrations of lipids may worsen hyperbilirubinemia and BPD through pulmonary vascular lipid deposition and bilirubin displacement from albumin.

- o Excessive glucose loads may increase oxygen consumption, respiratory drive, and glucosuria. Calcium and phosphorus requirements are greatly increased in preterm infants. Most mineral stores in the fetus occur during the third trimester, leaving the extremely preterm infant calcium and phosphorus deficient and at increased risk of rickets. Supplemental furosemide therapy and limited intravenous calcium use may worsen bone mineralization and secondary hyperparathyroidism. Vitamin A supplementation may improve lung repair and decrease incidence of BPD. Supplement trace minerals (ie, copper, zinc, and manganese) because they are essential cofactors in the AO defenses.

- o Early initiation of small amounts of enteral feeds (even if umbilical lines are in place) followed by slow steady increases in volume appears to facilitate tolerance of feeds. The most immature and unstable preterm infant often experiences a difficult transition to complete enteral nutrition. Frequent interruption of feedings secondary to intolerance or instability complicates the management of these patients. Enteral feeding of breast milk provides the best nutrition while preventing feeding complications (ie, sepsis, necrotizing enterocolitis). The energy content of expressed breast milk and formulas can be enhanced to provide increased energy intake, while minimizing fluid intake. Infants may require 120-150 kcal/kg of body weight per day to gain weight. Diuretics may often be used to prevent or treat fluid overload.

- Medical therapies: Often, many different drug therapies are employed to treat infants with severe BPD. The efficacy, exact mechanisms of action, and potential adverse effects of these medications have not been definitively established.
  - o Diuretics
    - Furosemide (Lasix) is the treatment of choice for fluid overload in infants with BPD. It is a loop diuretic that has been demonstrated to decrease PIE and pulmonary vascular resistance (VR), improving pulmonary function. Daily or alternate day furosemide therapy improves respiratory function and may facilitate weaning from PPV, oxygen, or both.
    - Adverse effects of long-term Lasix therapy are frequent and include hyponatremia, hypokalemia, contraction alkalosis, hypocalcemia, hypercalciuria, cholelithiasis, renal stones, nephrocalcinosis, and ototoxicity. Careful parenteral and enteral nutritional supplementation is required to maximize the benefits instead of exacerbating the adverse effects of furosemide. Potassium chloride supplementation is favored over sodium chloride supplementation in cases of mild hyponatremia or hypokalemia.
    - Thiazide diuretics with inhibitors of Aldactone have also been used in infants with BPD. Several trials of thiazide diuretics combined with spironolactone have shown increased urine output with or without improvement in pulmonary mechanics in infants with BPD. In 2000, Hoffman reported that spironolactone administration does not reduce the need for supplemental electrolyte administration in preterm infants with BPD. In 1989, Englehardt and colleagues found no effect in pulmonary mechanics in infants with BPD. Adverse effects include electrolyte imbalance. Long-term efficacy studies comparing furosemide with thiazide and spironolactone therapy have not been performed to date.
  - o Smooth muscle agents (bronchodilators)
    - Albuterol is a specific beta2-agonist used to treat bronchospasm in infants with BPD. Albuterol may improve lung compliance by decreasing airway resistance secondary to smooth muscle cell relaxation. Changes in pulmonary mechanics may last as long as 4-6 hours.
    - Adverse effects include increases in BP and heart rate. Ipratropium bromide is a muscarinic antagonist that is related to atropine but may have more potent bronchodilator effects. Improvements in pulmonary mechanics have been demonstrated in BPD after ipratropium bromide inhalation. Combination therapy of albuterol and ipratropium bromide may be more effective than either agent alone. Few adverse effects are noted.
    - Cromolyn sodium inhibits release of inflammatory mediators from mast cells. Some studies have shown a decrease in inflammatory mediators in tracheobronchial aspirates of infants with BPD who were treated with this drug. Do not use cromolyn to

treat acute bronchospasm; however, it may be used as an agent to prevent bronchospasm from occurring. With current aerosol administration strategies, exactly how much medication is delivered to the airways and lungs of infants with BPD (especially if they are ventilator dependent) is unclear. Because significant smooth muscle relaxation does not appear to occur within the first few weeks of life, do not initiate aerosol therapy before this time unless profound respiratory illness exists.

- o Systemic bronchodilators
  - Methylxanthines are used to increase respiratory drive, decrease apnea, and improve diaphragmatic contractility. These substances may also decrease pulmonary VR and increase lung compliance in infants with BPD, probably through direct smooth muscle relaxation. They also exhibit diuretic effects.
  - All of the above effects may increase success at weaning from mechanical ventilation. Synergy between theophylline and diuretics has been demonstrated. Theophylline has a half-life of 30-40 hours, is metabolized primarily to caffeine in the liver, and may include adverse effects, such as increase in heart rate, gastroesophageal reflux, agitation, and seizures. Caffeine has a longer half-life than theophylline (approximately 90-100 h) and is excreted unchanged in the urine. Both are available in intravenous and enteral formulations. Caffeine has fewer adverse effects than theophylline.
  - Long-term comparison studies of these 2 agents are needed. Oral albuterol and subcutaneous terbutaline have also been used to treat infants with BPD but appear to offer no therapeutic advantage when compared to the methylxanthines.
- o Corticosteroids: These are produced by the adrenal gland. Mineralocorticoids are produced in the adrenal medulla and primarily affect fluid and electrolyte balance. Glucocorticoids possess strong anti-inflammatory properties and affect the metabolism of many tissues. Systemic and inhaled corticosteroids have been studied extensively in preterm infants to prevent and treat BPD.
  - Seven studies have evaluated the effect of dexamethasone versus placebo during the first 2 weeks of life to prevent BPD. Original work by Cummings et al in 1989 revealed that a 42-day course of dexamethasone resulted in a decrease need for oxygen and improved neurologic outcome compared to control subjects aged 6 and 15 months. In 1998, Papile et al reported on the effects of dexamethasone treatment at 2 weeks versus 4 weeks in 371 preterm infants.
  - Dexamethasone treatment initiated at 14 days reduced 28-day mortality and oxygen requirement at 1 month; however, Koroco et al found no difference in CLD at 36 weeks corrected age in 60 infants who received systemic and inhaled corticosteroids or saline placebo beginning at 7 days of life. In 1999, Garland et al reported findings on very early use of a 3-day course of dexamethasone begun within 48 hours of life to prevent BPD. He found that infants treated with dexamethasone had less BPD but noticed an increase in early intestinal perforations. The difference in intestinal perforations between groups prompted a dosage adjustment after the first interim analysis.
  - Dexamethasone has also been administered to preterm infants older than 3 weeks to treat presumed CLD (ie, 28-d oxygen requirement). The largest collaborative dexamethasone trial revealed a decrease in ventilator requirements but no difference in supplemental oxygen usage. Outcomes at age 3 years were similar.
  - Dexamethasone is the primary systemic synthetic corticosteroid that has been studied in preterm neonates. Dexamethasone has many pharmacologic benefits but significant adverse effects. Dexamethasone stabilizes cell and lysosomal membranes, increases surfactant synthesis, increases serum vitamin A concentration, inhibits prostaglandin and leukotriene, decreases PE, breaks down granulocyte aggregates, and improves pulmonary microcirculation. The adverse effects are hyperglycemia, hypertension, weight loss, GI bleeding or perforation synthesis, cerebral palsy, adrenal suppression, and death.
  - Approximately 30 randomized trials have been performed examining strategies to prevent or treat BPD. An excellent on-line review of most of Professor Halliday's studies is available at the National Institute of Child Health and Human Development. The dexamethasone trials may be grouped by time of dexamethasone administration; for example, early administration may be considered within 2 days of birth or within the first 2 weeks of life, and late administration may be considered after 2 weeks of

life. Recently, meta-analyses of these trials was presented at the <u>Society for Pediatric Research</u>.

- Neurodevelopmental follow-up studies of infants treated with dexamethasone suggest that although this therapy improves short-term pulmonary outcome, long-term outcome appears significantly worse.
- The routine use of dexamethasone in infants with BPD is not currently recommended unless severe pulmonary disease exists. A rapid tapering course starting at 0.25 mg/kg/d and lasting for 5-7 days appears to be adequate. If no response is observed after 3 days, then discontinue dexamethasone. Inhaled glucocorticoid therapy has been studied in neonates to prevent BPD. In 1999, Cole and colleagues found that early therapy with beclomethasone did not prevent BPD, but it did decrease the need for systemic steroids. Further studies and the development of more efficient aerosol delivery systems are definitely needed.

  o Vasodilators: NO is a short-acting inhaled gas that relaxes the pulmonary vasculature. NO is metabolized rapidly by RBCs, thereby minimizing systemic hypotension. NO in vitro may have direct effects on the tracheobronchial tree. In 1999, Banks and colleagues studied the effect of inhaled NO in 16 preterm infants with severe BPD. Eleven of 16 infants had improved oxygenation after 1 hour of inhalation, an effect that persisted in some infants. Further controlled studies are necessary to define the use of NO in the prevention and treatment of BPD.

- Because the routine use of surfactant replacement has begun, survival of the most immature infants has improved. Along with other advances in technology and improved understanding of neonatal physiology, infants with BPD now appear to have less severe disease. Infants with severe BPD remain at high risk for pulmonary morbidity and mortality during the first 2 years of life.
- Fortunately, pulmonary function slowly improves in most survivors with BPD, likely secondary to continued lung and airway growth and healing. Northway followed the cases of patients with BPD to adulthood. In 1992, Northway reported that these patients had airway hyperreactivity, abnormal pulmonary function, and hyperinflation noted on chest radiography. Rehospitalization for impaired pulmonary function is most common during the first 2 years of life. In 1990, Hakulinen et al found a gradual decrease in symptom frequency in children aged 6-9 years as compared to the first 2 years of life. Bader in 1987 and Blayney et al in 1991 found persistence of respiratory symptoms and abnormal PFT results in children aged 7 and 10 years. High-resolution chest CT scanning or MRI studies in children and adults with a history of BPD reveal lung abnormalities that correlate directly with the degree of pulmonary function abnormality.

Consultations: Infants with BPD have multisystem involvement. Therefore, consultations should be obtained from various pediatric subspecialists. They include a cardiologist, pulmonologist, gastroenterologist, developmental pediatrician, ophthalmologist, neurologist, physical therapist, and nutritionist. They may also assist the pediatrician with the ongoing care of these infants after patients are discharged from the hospital.

Diet: Infants with BPD have increased energy requirements.

- Early parenteral nutrition is often used to minimize the catabolic state of the preterm infant. The most immature and unstable preterm infant often has a difficult transition to complete enteral nutrition. Frequent interruption of feedings secondary to intolerance or patient instability complicates the management of these patients. Enteral feeding of breast milk may provide the best nutrition, while possibly preventing feeding complications (eg, sepsis, necrotizing enterocolitis).
- The energy content of expressed breast milk and formulas can be enhanced to provide increased energy intake, while minimizing fluid intake. Infants may require 120-150 kcal/kg of body weight per day to adequately gain weight.
- Diuretics may often be used to prevent or treat fluid overload.
- Early insertion of percutaneous central venous lines may help to improve energy density of parenteral nutrition. Accomplish progressive increases in protein and fat supplementation to provide approximately 3-3.5 g/kg of body weight per day and 3 g/kg of body weight per day.
- Rapid and early administration of high concentrations of lipids may worsen hyperbilirubinemia and BPD through pulmonary vascular lipid deposition and bilirubin displacement from albumin.

- Excessive glucose loads may increase oxygen consumption, respiratory drive, carbon dioxide production, and glucosuria.
- Calcium and phosphorus requirements greatly increase in preterm infants. Most mineral stores in the fetus occur during the third trimester, leaving the extremely preterm infant calcium and phosphorus deficient and at increased risk of rickets. Supplemental furosemide therapy and limited intravenous calcium use may worsen bone mineralization and secondary hyperparathyroidism.
- Vitamin A supplementation may improve lung repair and decrease incidence of BPD.
- Trace mineral supplementations (ie, copper, zinc, manganese) are essential cofactors in the AO defenses.

MEDICATION	Section 7 of 11

Many different drug therapies are employed to treat infants with severe BPD. The efficacy, exact mechanisms of action, and potential adverse effects of these medications have not been definitively established.

Thiazide diuretics with inhibitors of aldosterone have been used in infants with BPD. Several trials of thiazide diuretics combined with spironolactone have shown increased urine output with or without improvement in pulmonary mechanics in infants with BPD. In 2000, Hoffman reported that spironolactone administration does not reduce the need for supplemental electrolyte administration in preterm infants with BPD. Long-term efficacy studies comparing furosemide to thiazides plus spironolactone therapy have not been performed.

Bronchodilators are typically prescribed. Ipratropium bromide is a muscarinic antagonist that is related to atropine but may have more potent bronchodilator effects. Improvements in pulmonary mechanics have been demonstrated in BPD after ipratropium bromide inhalation. Combination therapy of albuterol and ipratropium bromide may be more efficacious than either agent alone. Few adverse effects are noted.

Systemic bronchodilators include methylxanthines, which are used to increase respiratory drive, decrease apnea, and improve diaphragmatic contractility. Methylxanthines are routinely used in preterm infants to treat BPD and apnea of prematurity. Methylxanthines have been shown to improve diaphragmatic contractility, improve lung compliance, and decrease pulmonary resistance in infants with BPD, probably through direct smooth muscle relaxation. They exhibit diuretic effects. All of the above effects may increase success at weaning from mechanical ventilation. Synergy between theophylline and diuretics has been demonstrated.

Theophylline has a half-life of 30-40 h, is metabolized primarily to caffeine in the liver, and may produce adverse effects (eg, increased heart rate, gastroesophageal reflux, agitation, seizures). Caffeine has a longer half-life than theophylline (approximately 90-100 h) and is excreted unchanged in the urine. Both are available in IV and parenteral formulations. Caffeine has fewer adverse effects than theophylline. Long-term comparison studies of these 2 agents are needed.

Oral albuterol and subcutaneous terbutaline have also been used to treat infants with BPD, but they appear to offer no therapeutic advantage when compared to the methylxanthines.

Systemic and inhaled corticosteroids have been studied extensively in preterm infants to prevent and treat BPD. Dexamethasone is the primary systemic synthetic corticosteroid that has been studied in preterm neonates.

In 1999, Banks and colleagues studied the effect of inhaled nitric oxide in 16 preterm infants with severe BPD. Eleven of 16 infants had improved oxygenation after 1 hour of inhalation, an effect that persisted in some infants. Further controlled studies are necessary to define nitric oxide use in the prevention and treatment of BPD.

Cromolyn sodium inhibits release of inflammatory mediators from mast cells. Some studies have shown a decrease in inflammatory mediators in tracheobronchial aspirates of infants with BPD who were treated with this drug.

Drug Category: *Diuretics* -- Promote excretion of water and electrolytes by the kidneys. Used to treat heart failure or hepatic, renal, or pulmonary disease when sodium and water retention has resulted in edema or ascites.

Drug Name	Furosemide (Lasix) -- DOC for fluid overload in infants with BPD. A loop diuretic demonstrated to decrease PIE and pulmonary VR, while improving pulmonary function. Daily or alternate day furosemide therapy improves respiratory function and may facilitate weaning from PPV, oxygen, or both. Increases excretion of water by interfering with chloride-binding cotransport system, which in turn inhibits sodium and chloride reabsorption in ascending loop of Henle and distal renal tubule.
Pediatric Dose	0.5-2 mg/kg/dose PO/IV bid-qod (qd in infants <31 wk postconceptual age)
Contraindications	Documented hypersensitivity; hepatic coma; anuria; state of severe electrolyte depletion
Interactions	Furosemide antagonizes muscle-relaxing effect of tubocurarine; auditory toxicity appears to be increased with coadministration of aminoglycosides and furosemide; hearing loss of varying degrees may occur; anticoagulant activity of warfarin may be enhanced when taken concurrently with this medication
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Observe for electrolyte imbalances; long-term administration causes hyponatremia, hypokalemia, contraction alkalosis, hypocalcemia, hypercalciuria, cholelithiasis, renal stones, nephrocalcinosis, and ototoxicity; potassium chloride supplementation is favored over sodium chloride supplementation in cases of mild hyponatremia or hypokalemia

Drug Category: *Bronchodilators* -- These act to decrease muscle tone in both the small and large airways in the lungs, thereby increasing ventilation. This category includes subcutaneous medications, beta-adrenergic agents, methylxanthines, and anticholinergics.

Drug Name	Albuterol (Proventil, Ventolin) -- A specific beta2 agonist used to treat bronchospasm in infants with BPD. May improve lung compliance by decreasing airway resistance secondary to smooth muscle cell relaxation. With current aerosol administration strategies, exactly how much medication is delivered to the airways and lungs of infants with BPD (especially if they are ventilator dependent) is unclear. Because significant smooth muscle relaxation does not appear to occur within the first few weeks of life, do not initiate aerosol therapy before this time unless profound respiratory illness exists
Pediatric Dose	0.1-0.2 mg (0.02-0.04 mL of 0.5% solution) per kg/dose inhaled via nebulization q4-6h Use 0.5% solution diluted with 1-2 mL of 0.45-0.9% NaCl
Contraindications	Documented hypersensitivity

Interactions	Beta-adrenergic blockers antagonize effects; inhaled ipratropium may increase duration of bronchodilatation by albuterol; cardiovascular effects may increase with MAOIs, inhaled anesthetics, tricyclic antidepressants, or sympathomimetic agents
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May cause tachycardia or reflex bronchospasm; changes in pulmonary mechanics may last as long as 4-6 h; adverse effects include increases in BP and heart rate
Drug Name	Caffeine citrate (Cafcit) -- A CNS stimulant used to treat infants with apnea of prematurity and infants with BPD. Caffeine may facilitate ventilator weaning.
Pediatric Dose	Loading dose: 20 mg/kg PO/IV Maintenance dose: 5 mg/kg/d PO/IV
Contraindications	Documented hypersensitivity
Interactions	Caution with cardiovascular, renal, or hepatic dysfunction; may act synergistically with diuretics; decrease dose if coadministered with theophylline; additive positive inotropic and chronotropic effects with beta-adrenergic agonists; cimetidine and fluconazole decrease clearance
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Monitor levels at least once per wk; long half-life (100 h); therapeutic levels range from 10-20 mcg/mL; seizure threshold may be altered with very high levels; may worsen gastroesophageal reflux
Drug Name	Theophylline (Elixophyllin, Theo-Dur) -- A systemic bronchodilator. Used to treat apnea of prematurity. May decrease diaphragmatic fatigue in infants with BPD. May improve skeletal muscle contractility. Some studies have suggested that theophylline may help facilitate weaning an infant with BPD from continuous mechanical ventilation. Monitor serum levels and adjust levels based on infant's response; generally, the therapeutic levels of theophylline are considered to be in the range of 5-12 mcg/mL. IV dose is based on theophylline equivalent.
Pediatric Dose	Loading dose: 3-5 mg/kg PO/IV Maintenance dose: 1-3 mg/kg/d PO/IV divided q8-12h
Contraindications	Documented hypersensitivity; uncontrolled arrhythmias; hyperthyroidism; uncontrolled seizure disorders
Interactions	Theophylline levels are affected by drugs that may induce or inhibit the CYP450 enzyme system in the liver; aminoglutethimide, barbiturates, carbamazepine, ketoconazole, loop diuretics, charcoal, hydantoins, phenobarbital, phenytoin, rifampin, isoniazid, and sympathomimetics may decrease effects of theophylline; theophylline effects may increase with allopurinol, beta-blockers, corticosteroids, thyroid hormones, ephedrine, carbamazepine, cimetidine, erythromycin, macrolides, propranolol, and interferon
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in hypertension, tachyarrhythmias, hyperthyroidism, and compromised cardiac function; do not inject IV solution faster than 25 mg/min; patients diagnosed with pulmonary edema or liver dysfunction are at greater risk of toxicity because of reduced drug clearance; may worsen gastroesophageal reflux; may lower seizure threshold at high levels

Drug Name	Ipratropium bromide (Atrovent) -- A muscarinic antagonist with potent bronchodilating effects. May improve pulmonary mechanics significantly in infants with BPD. Inhaled ipratropium bromide is poorly absorbed systemically.
Pediatric Dose	0.025-0.08 mg/kg inhaled via nebulization q6h (dilute in 1.5-2 mL of 0.9% NaCl)
Contraindications	Documented hypersensitivity
Interactions	Drugs with anticholinergic properties, such as dronabinol, may increase toxicity; albuterol increases effects of ipratropium
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Not indicated for acute episodes of bronchospasm; caution in narrow-angle glaucoma, prostatic hypertrophy, and bladder neck obstruction

Drug Category: *Corticosteroids* -- Produced by the adrenal gland. Mineralocorticoids are produced in the adrenal medulla and primarily affect fluid and electrolyte balance. Glucocorticoids possess strong anti-inflammatory properties and affect the metabolism of many tissues.

Drug Name	Dexamethasone (Decadron) -- Has many pharmacologic benefits but significant adverse effects. It stabilizes cell and lysosomal membranes, increases surfactant synthesis, increases serum vitamin A concentration, inhibits prostaglandin and leukotriene, decreases PE, breaks down granulocyte aggregates, and improves pulmonary microcirculation. Adverse effects are hyperglycemia, hypertension, weight loss, GI bleeding or perforation synthesis, cerebral palsy, adrenal suppression, and death. Routine use of dexamethasone in infants with BPD is not currently recommended unless severe pulmonary disease exists.
Pediatric Dose	Loading dose: 0.2-0.5 mg/kg PO/IV Maintenance dose: 0.1 mg/kg PO/IV q6-8h
Contraindications	Documented hypersensitivity; active bacterial or fungal infection
Interactions	Effects decrease with coadministration of barbiturates, phenytoin, and rifampin; dexamethasone decreases effect of salicylates and vaccines used for immunization
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Not routinely recommended for BPD secondary to possible detrimental long-term effects on neurologic outcome; increases risk of multiple complications, including severe infections; monitor adrenal insufficiency when tapering drug; abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteoporosis, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, euphoria, psychosis, myasthenia gravis, growth suppression, and infections are possible complications of glucocorticoid use

Drug Name	Nitric oxide (INOmax) -- A short-acting inhaled gas that relaxes the pulmonary vasculature. Produced endogenously from action of enzyme NO synthetase on arginine. Relaxes vascular smooth muscle by binding to heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cGMP, which then leads to vasodilation. When inhaled, NO decreases pulmonary vascular resistance and improves lung blood flow. Metabolized rapidly by RBCs, thereby minimizing systemic hypotension. In vitro may have direct effects on the tracheobronchial tree.
Pediatric Dose	Not established; currently investigational for BPD
Contraindications	Right-to-left shunting of blood; methemoglobin reductase deficiency
Interactions	NO donor compounds (eg, nitroprusside, nitroglycerin) may increase risk of developing methemoglobinemia
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Toxic effects include methemoglobinemia and pulmonary inflammation resulting from reactive nitrogen intermediates; caution in thrombocytopenia, anemia, leukopenia, or bleeding disorders; monitor PaO_2, methemoglobin, and NO_2; abrupt withdrawal causes rebound pulmonary hypertension

FOLLOW-UP	**Section 8 of 11**

Further Outpatient Care:

- Infection

    o Increased susceptibility to respiration infections is frequent in infants with BPD in the first 2 years of life.
    o Respiratory syncytial virus (RSV) infection in infants with BPD may cause severe illness and even death.
    o RSV immunoglobulin infusion and RSV antibody injection administered on a monthly basis may prevent or reduce risk of rehospitalization of infants with BPD and may mitigate illness severity.
    o The AAP has published guidelines on the use of these medications during RSV season (November-March) in preterm infants discharged from the NICU.

- Growth and development

    o Poor growth and delayed development are frequently observed in infants with BPD. Secondary to abnormal pulmonary function, increased energy requirements are noted. In addition, many of these infants may have worsening pulmonary function with liberalization of fluid intake. Use of diuretics, high-energy formulas and breast milk additives, or both are the mainstays of treatment in and out of the hospital.
    o In 1981, Markestad et al found the degree of catch-up growth correlated directly with respiratory function. Long-term survivors are at increased risk for neurodevelopmental disabilities.
    o Vohr and Singer et al found no difference in full-scale IQ scores between infants with BPD and control preterm infants.
    o Therapies used to treat BPD as well as other perinatal and postnatal events may impair neurodevelopmental outcome. In 1992, O'Shea et al reported on the outcome of infants with BPD who were treated with a 42-day course of dexamethasone. A 42-day course of dexamethasone was associated with an increased risk of cerebral palsy. Cummings' 1989 study refutes these findings.

- The multifactorial etiology of BPD compounds its prevention.
- Prenatal steroid therapy and postnatal surfactant use has improved survival and perhaps redirected severity of BPD.
- Postnatal corticosteroid use may facilitate ventilator weaning but is fraught with many adverse effects. Reconsider standard of care therapy with postnatal dexamethasone, weighing the risk-to-benefit ratio in each case.
- Use of exogenous surfactant has improved neonatal survival but may increase the prevalence of BPD in preterm infants.
- Meticulous attention to oxygen and PPV may modify BPD.
- Maximizing nutritional support, careful monitoring of fluid intake, and judicious diuretic use helps promote lung healing.
- Conclusive evidence of HFV use to prevent BPD is not currently available.
- Inhaled NO may improve oxygenation in some infants with BPD, but synergistic toxicity of hyperoxia and NO on pulmonary and surfactant systems has been demonstrated in vitro.
- Davis in 2000 and Rosenfeld et al in 1986 completed human studies of recombinant SOD supplementation to prevent BPD in preterm infants. In preliminary studies, prophylactic use of recombinant SOD revealed that it is safe and may modify disease severity. Results of the most recent phase III efficacy trial are soon to be forthcoming. Effective prevention of BPD has yet to be found.

Complications:

- Chorioamnionitis, PVL, severe intraventricular hemorrhage, ventriculomegaly, sepsis, and severe retinopathy of prematurity all are important confounding variables that can greatly affect infant outcome.

Prognosis:

- Most neonates with BPD ultimately survive; however, these infants are at increased risk for serious infections, airway hyperreactivity, cardiac dysfunction, and neurologic impairments.

  o Since the routine use of surfactant replacement has begun, survival of the most immature infants has improved. Along with other advances in technology and improved understanding of neonatal physiology, infants with BPD today appear to have less disease severity as compared to infants in years past. Infants with severe BPD remain at high risk for pulmonary morbidity and mortality during the first 2 years of life.
  o Fortunately, pulmonary function slowly improves in most survivors with BPD, likely secondary to continued lung and airway growth and healing. Northway followed the cases of patients with BPD to adulthood. Northway reported in 1992, that these patients had airway hyperreactivity, abnormal pulmonary function, and hyperinflation noted on chest radiography. Rehospitalization for impaired pulmonary function is most common during the first 2 years of life. In 1990, Hakulinen et al found a gradual decrease in symptom frequency in children aged 6-9 years as compared to the first 2 years of life. Bader in 1987 and Blayney et al in 1991 found persistence of respiratory symptoms and abnormal PFT results in children aged 7 and 10 years, respectively. High-resolution chest CT scanning or MRI studies in children and adults with a history of BPD reveal lung abnormalities that correlate directly with the degree of pulmonary function abnormality. Postsurfactant studies of infants with BPD have yielded similar results of improved pulmonary function with time. Northway reported cor pulmonale in 36% of survivors. Oxygen supplementation at home is not infrequently required, and failure to relieve pulmonary hypertension with oxygen may be associated with a poor prognosis.
  o Persistent right ventricular hypertrophy or fixed pulmonary hypertension unresponsive to oxygen supplementation on cardiac catheterization portends a poor prognosis.

MISCELLANEOUS	Section 9 of 11

Medical/Legal Pitfalls:

- Misdiagnosis of other confounding problems in infants with BPD can be catastrophic. For example, if an infant with BPD and superimposed fungal sepsis is treated with dexamethasone, the infant may experience serious complications or death.

PICTURES	Section 10 of 11

Picture 1. Bronchopulmonary dysplasia.

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Congenital Diaphragmatic Hernia

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INTRODUCTION	Section 2 of 10

Background: The topic of congenital diaphragmatic hernia (CDH) frequently appears in the medical literature since its first description in the early 18th century. Initial theories about the pathophysiology of this condition centered on the presence of the herniated viscera within the chest and the need for its prompt removal. In 1946, Gross reported the first successful repair of a neonatal diaphragmatic hernia in the first 24 hours of life. The medical literature for the next decade addressed CDH as a surgical problem and discussed various technical aspects of surgical repair, including techniques required to close large defects. In the 1960s, however, Areechon and Reid observed that the high mortality rate of CDH was related to the degree of pulmonary hypoplasia at birth. Over the past 20 years, pulmonary hypertension and pulmonary hypoplasia have been recognized as the 2 cornerstones of the pathophysiology of CDH. In recent years, evidence suggests that dysfunction of the surfactant system as well as cardiac maldevelopment may further complicate the pathophysiology of CDH.

Pathophysiology: The 3 basic types of CDH are the posterolateral Bochdalek hernia (occurring at approximately 6 weeks' gestation), the anterior Morgagni hernia, and the hiatus hernia. The left-sided Bochdalek hernia occurs in approximately 90% of cases. Left-sided hernias allow herniation of both small and large bowel as well as intra-abdominal solid organs into the thoracic cavity. In right-sided hernias, only the liver and a portion of the large bowel tend to herniate. Bilateral hernias are uncommon and usually fatal.

CDH is characterized by a variable degree of pulmonary hypoplasia associated with a decrease in cross-sectional area of the pulmonary vasculature and dysfunction of the surfactant system. The lungs have a small alveolar capillary membrane for gas exchange, which may be further decreased by surfactant dysfunction. In addition to parenchymal disease, increased muscularization of the intra-acinar pulmonary arteries appears to occur. In very severe cases, left ventricular hypoplasia is observed. Pulmonary capillary blood flow is decreased because of the small cross-sectional area of the pulmonary vascular bed, and flow may be further decreased by abnormal pulmonary vasoconstriction.

Internationally: CDH occurs in 1 of every 2000-4000 live births and accounts for 8% of all major congenital anomalies. The risk of recurrence of isolated CDH for future siblings is approximately 2%. Familial CDH rarely occurs and may be due to a multifactorial/threshold inheritance pattern or, in some cases, an autosomal recessive pattern. CDH can also occur as a part of Fryns syndrome, an autosomal recessive disorder with variable features, including diaphragmatic hernia, cleft lip or palate, and distal digital hypoplasia.

Mortality/Morbidity:

- Mortality is difficult to determine. This is partially because of the hidden mortality for this condition. Hidden mortality refers to infants with CDH who are so severely affected that they die prior to transfer to a surgical site. This bias may be especially important when evaluating institutional reports of outcome.
- Population-based studies report survival rates ranging from 25-60%. Infants with multiple anomalies have much lower survival rates than those with isolated defects.

Sex: Most studies report a male preponderance for isolated posterolateral CDH (male-to-female ratio of approximately 1.5:1).

Age:

- While CDH is most commonly a disorder of the newborn period, as many as 10% of patients may present after the newborn period and even during adulthood.
- Outcome in patients with late presentation of CDH is extremely good, with low or no mortality.

CLINICAL	Section 3 of 10

History:

- Infants may have an antenatal history of polyhydramnios.
- Infants most commonly present with a history of cyanosis and respiratory distress in the first minutes or hours of life, although a later presentation is possible.

Physical:

- Frequently, infants exhibit a scaphoid abdomen, respiratory distress, and cyanosis.
- In left-sided posterolateral hernia, auscultation of the lungs reveals poor air entry on the left, with a shift of cardiac sounds over the right chest.

Causes:

- The cause of CDH is largely unknown. No single gene mutation has been identified as producing or contributing to this anomaly.
- Posterolateral hernia may occur as an isolated defect or in association with other congenital anomalies. CDH can occur as part of a multiple malformation syndrome in up to 40% of infants, principally with cardiovascular, genitourinary, and gastrointestinal malformations. Lethal anomalies are present in up to 16% of infants.
- Karyotype abnormalities have been reported in 4% of infants with CDH, and CDH may be found in a variety of chromosomal anomalies including trisomy 13, trisomy 18, and tetrasomy 12p mosaicism. CDH may be associated with nonchromosomal disorders such as the de Lange syndrome.
- Retrosternal hernias are also associated with cardiovascular, genitourinary, and gastrointestinal malformation.

Aspiration Syndromes
Bronchogenic Cyst
Congenital Pneumonia
Cystic Adenomatoid Malformation
Disorders of the Thoracic Cavity and Pleura
Pleural Effusion
Pneumothorax
Pulmonary Hypertension, Persistent-Newborn

Lab Studies:

- Arterial blood gas

  - Obtain frequent arterial blood gas (ABG) measurements to assess for pH, $PaCO_2$, and PaO_2.
  - Note the sampling site because persistent pulmonary hypertension (PPHN) with right-to-left ductal shunting often complicates CDH. The PaO_2 may be higher from a preductal (right-hand) sampling site.

- Chromosome studies

  - Obtain chromosome studies because of the frequent association with chromosomal anomalies.
  - In rare cases, chromosomal disorders that can only be diagnosed by skin biopsy may be present. If dysmorphic features are observed on examination, a consultation with a geneticist is often helpful.

- Serum electrolytes: Monitor serum electrolytes, ionized calcium, and glucose levels initially and frequently. Maintenance of reference range glucose levels and calcium homeostasis is particularly important.

Imaging Studies:

- Chest radiography

  - Obtain a chest radiograph if CDH is suspected.
  - Placement of an orogastric tube prior to the study helps determine the position of the stomach.
  - Typical findings in left-sided posterolateral CDH include air- or fluid-filled loops of the bowel in the left hemithorax and shift of the cardiac silhouette to the right.
  - Examine the chest radiograph for evidence of pneumothorax.

- Cardiac ultrasonography

  - Perform ultrasonographic studies to rule out congenital heart diseases.
  - Because the incidence of associated cardiac anomalies is high (up to 25%), cardiac ultrasonography is needed to evaluate for associated cardiac anomalies.

- Renal ultrasonography: A renal ultrasonographic examination may be needed to rule out genitourinary anomalies.

- Cranial ultrasonography

    o Perform cranial sonography if the infant is being considered for extracorporeal support.
    o Ultrasonographic examination should focus on evaluation of intraventricular bleeding and peripheral areas of hemorrhage or infarct or intracranial anomalies.

Other Tests: Pulse oximetry

    o Continuous pulse oximetry is valuable in the diagnosis and management of PPHN.
    o Place oximeter probes at preductal (right-hand) and postductal (either foot) sites to assess for a right-to-left shunt at the level of the ductus arteriosus.

Procedures:

- Intubation and mechanical ventilation

    o Endotracheal intubation and mechanical ventilation are required for all infants with severe CDH who present in the first hours of life.
    o Avoid bag-and-mask ventilation in the delivery room because the stomach and intestines become distended with air and further compromise pulmonary function.
    o Avoid high peak inspiratory pressures and overdistension. Consider high-frequency ventilation if high peak inspiratory pressures are required.

- Arterial catheter placement: Place an indwelling catheter in the umbilical artery or in a peripheral artery (radial, posterior tibial) for frequent ABG monitoring.
- Central venous catheter placement

    o Place a venous catheter via the umbilical or femoral vein to allow for administration of inotropic agents and hypertonic solutions such as calcium gluconate.
    o Frequently, placing an umbilical venous catheter is difficult because of the altered position of the heart and liver. For the same reason, confirming correct position (in the low right atrium) can be difficult, and ultrasonography may be needed.

Histologic Findings: Both lungs appear abnormal, although histologic changes are more severe on the affected side. Bronchi are less numerous, and the overall number of alveoli is reduced. In addition, the lungs appear to be less mature with fewer mature alveoli. Pulmonary vascular abnormalities occur in addition to parenchymal abnormalities. These vascular abnormalities are characterized by both a reduction in the cross-sectional area of the pulmonary vascular bed and an abnormal increase in muscularization of pulmonary arteries and arterioles.

TREATMENT	Section 6 of 10

Medical Care: Because of associated PPHN and pulmonary hypoplasia, medical therapy is directed toward optimizing oxygenation while avoiding barotrauma.

- If the infant has CDH, or if the diagnosis is suspected in the delivery room, immediately place a vented orogastric tube and connect it to continuous suction to prevent bowel distension and further lung compression. For the same reason, avoid mask ventilation and immediately intubate the trachea. Avoid high peak inspiratory pressures and alert the resuscitation team to the possibility of early pneumothorax if the infant does not stabilize. Many infants benefit from exogenous surfactant administration during the first few hours of life.

    o Infants with CDH have immature lung development and may be surfactant deficient. Administration of exogenous surfactant in the delivery room or shortly thereafter may be useful.

- o Inhaled nitric oxide may be used in infants with hypoxia not responding to assisted ventilation and surfactant therapy to lower their pulmonary vascular resistance. However, the use of nitric oxide has not been shown to reduce mortality or the need for extracorporeal membrane oxygenation (ECMO) in infants with CDH. Therefore, it should be used with extreme caution if ECMO is not immediately available.
  - o Use ECMO when optimal ventilator and medical therapy do not maintain acceptable oxygenation and perfusion. Fewer than 100 centers in the United States provide ECMO, which is an adaptation of cardiopulmonary bypass performed via catheters inserted into the neck vessels. Recent developments allow support with a double lumen catheter in the internal jugular vein, thus avoiding ligation of the right common carotid artery.

- Provide meticulous attention to detail for subsequent medical care, including continuous monitoring of oxygenation, blood pressure, and perfusion. Provide care using a minimal stimulation approach, which reduces handling and invasive procedures such as suctioning. Maintain reference range glucose and ionized calcium concentrations. If necessary, support blood pressure using volume expansion and inotropic agents. An adequate circulating volume is necessary to maintain right ventricular filling and cardiac output; however, once circulating volume is normalized, repeated boluses of crystalloid solutions, colloid solutions, or both do not provide additional benefit. Inotropic support with dopamine, dobutamine, or both may be helpful in maintaining adequate systemic blood pressure while avoiding excessive volume administration.
- Mechanical ventilation is almost always required. Target ventilator strategies to avoid high peak inspiratory pressures and synchronize ventilation with the infant's respiratory effort. High-frequency ventilation may be helpful in some instances to avoid the use of high peak inspiratory pressures, although this modality is best used at a center with experience in assessing and maintaining optimal lung distension.
- The appropriate targets for PaO_2 and $PaCO_2$ are controversial. PaO_2 concentrations greater than 50 mm Hg typically provide for adequate oxygen delivery at the tissue level. Aiming for higher PaO_2 concentrations may lead to increased ventilator support and barotrauma. Similarly, because of pulmonary hypoplasia, infants with CDH often have hypercarbia. Whether to maintain a low $PaCO_2$ for pulmonary vasodilation (see below), to allow permissive hypercapnia, or to maintain normocarbia is controversial. No reliable controlled studies exist, and debate continues in the medical literature.
- Alkalinization is a popular therapy because of its ability to produce a rapid pulmonary vasodilation. Forced alkalosis can be accomplished using hyperventilation and hypocarbia by alkali infusions or their combination, although benefits have never been demonstrated in any prospective clinical trial. In many centers, these therapies are considered controversial. For instance, hypocarbia constricts the cerebral vasculature and reduces cerebral blood flow. Extreme alkalosis and hypocarbia are strongly associated with later neurodevelopmental deficits, including a high rate of sensorineural hearing loss. A recent study by Walsh-Sukys and colleagues indicates that the use of alkali infusions may be associated with increased use of ECMO and an increased use of oxygen at 28 days of age.
- The use of paralytic agents is also highly controversial. Paralysis may promote both atelectasis of dependent lung regions and ventilation-perfusion mismatch.

Surgical Care:

- Postnatal repair

  - o Until recently, specialists believed that reduction of the herniated viscera and closure of the diaphragmatic defect should be performed emergently following birth. More recent research demonstrates that a delayed surgical approach that enables preoperative stabilization decreases morbidity and mortality. This change is due to the recent understanding that pulmonary hypoplasia, PPHN, and surfactant deficiency are largely responsible for the outcome of CDH and that the severity of these pathophysiologies is largely predetermined in utero. The pathophysiology does not appear to be exacerbated postnatally by herniated viscera in the chest as long as bowel decompression is continuous using a nasogastric tube.

- In addition, several reports indicate that circulatory stability, respiratory mechanics, and gas exchange deteriorate after surgical repair. The ideal time to repair a CDH is unknown. Some suggest that repair 24 hours after stabilization is ideal, but delays of up to 7-10 days are often well tolerated. Many surgeons now prefer to operate on these neonates when echocardiographic evidence for normal pulmonary artery pressures is maintained for at least 24-48 hours.

- Chest tube placement

  - Chest tube drainage is necessary when a tension pneumothorax is present; however, the role and mode of routine chest drainage is controversial.
  - Some clinicians report improved survival when chest drainage is not used. Others think that balanced intrathoracic drainage, in which a closed gated pressure system is used to maintain intrathoracic pressure within the normal physiologic range, may minimize risk of pulmonary injury.

- Lung transplantation

  - Transplantation of a single lung has been successful. Lung transplantation may allow the remaining hypoplastic lung to increase in size and recover from injury while still allowing adequate oxygenation and ventilation. The transplanted lobe may be removed after physiologic recovery in the neonatal and infantile period. ECMO support can provide for stability of gas exchange prior to transplantation.
  - Auxiliary transplantation of a parental lobe to the infant with pulmonary hypoplasia has been studied in a neonatal swine model, but it has not been reported in a human infant.

MEDICATION	Section 7 of 10

Drug Category: *Surfactants* -- CDH may be associated with pulmonary immaturity and abnormal surfactant profiles before delivery; therefore, surfactant administration after birth may be useful. Following inhaled administration, surface tension is reduced and alveoli are stabilized, thus decreasing the work of breathing and increasing lung compliance. Many clinicians decrease the dose of surfactant by 50% because of decreased lung volume.

Drug Name	Beractant (Survanta) -- A semisynthetic bovine lung extract containing phospholipids, fatty acids, and surfactant-associated proteins B (7 mcg/mL) and C (203 mcg/mL).
Pediatric Dose	100 mg/kg (ie, 4 mL/kg) intratracheally divided in 4 aliquots administered at least 6 h apart; consider decreasing to 2 mL/kg in CDH
Contraindications	None known
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	For intratracheal administration only; must be warmed to room temperature and only be administered by experienced personnel under carefully supervised conditions with constant monitoring of vital signs and oxygen saturation (SaO_2) by pulse oximetry; if infant is compromised, SaO_2 decreases, or both, administration is discontinued and the infant is adequately ventilated and oxygenated

Drug Name	Calfactant (Infasurf) -- Natural calf lung extract containing phospholipids, fatty acids, and surfactant-associated proteins B (260 mcg/mL) and C (390 mcg/mL).
Pediatric Dose	3 mL/kg intratracheally; may repeat q6-12h; not to exceed 3-4 doses; may consider decreasing because of pulmonary hypoplasia
Contraindications	None known
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	For intratracheal administration only; should only be administered under carefully supervised conditions with constant monitoring of vital signs and SaO_2 by pulse oximetry; if infant is compromised, SaO_2 decreases, or both, administration is discontinued and the infant is adequately ventilated and oxygenated

Drug Name	Dopamine (Intropin) -- Dopamine increases blood pressure primarily by stimulation of alpha-adrenergic receptors; however, its mechanism of action in newborn infants remains controversial because of developmental differences in endogenous norepinephrine stores and expression and function of alpha-adrenergic receptors. Dosage must be individualized.
Pediatric Dose	2-20 mcg/kg/min IV continuous infusion
Contraindications	Documented hypersensitivity; pheochromocytoma; ventricular fibrillation
Interactions	Phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong effects of dopamine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Doses >10 mcg/kg/min may cause pulmonary vasoconstriction; correct hypovolemia prior to infusion; vasoconstriction occurs with IV infiltration, causing severe local tissue ischemia and sloughing, best administered via a central venous catheter

Drug Name	Dobutamine (Dobutrex) -- Increases blood pressure primarily via stimulation of beta1-adrenergic receptors. It appears to have a more prominent effect on cardiac output than on blood pressure.
Pediatric Dose	2-25 mcg/kg/min IV continuous infusion
Contraindications	Documented hypersensitivity; idiopathic hypertrophic subaortic stenosis; atrial fibrillation or flutter
Interactions	Beta-adrenergic blockers antagonize effects of dobutamine; general anesthetics may increase toxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Hypovolemic state should be corrected before infusion

Drug Category: *Opioid analgesics --* Used for deep sedation to allow adequate mechanical ventilation. They may be particularly useful in decreasing sympathetic pulmonary vasoconstriction in response to noxious stimuli such as suctioning.

Drug Name	Fentanyl (Duragesic, Sublimaze) -- Synthetic opioid that is 75-200 times more potent than morphine. It is highly lipophilic and protein-bound. Prolonged exposure leads to accumulation in fat and delays the weaning process. By itself fentanyl causes minor cardiovascular compromise, although the addition of benzodiazepines or other sedatives may result in decreased cardiac output and blood pressure.
Pediatric Dose	Intermittent: 1-5 mcg/kg IV q2h by slow bolus Continuous infusion: 1-10 mcg/kg/min IV
Contraindications	Documented hypersensitivity; hypotension; potentially compromised airway when establishing rapid airway control would be difficult
Interactions	Phenothiazines may antagonize analgesic effects of opiate agonists; tricyclic antidepressants may potentiate adverse effects of fentanyl when both drugs are used concurrently
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in hypotension, respiratory depression, constipation, nausea, emesis, and urinary retention; acute muscle rigidity (chest syndrome) may occur following rapid infusion; tolerance develops rapidly, withdrawal symptoms may develop if used for >5 d

Drug Category: *Neuromuscular relaxing agents --* Paralysis is sometimes necessary in the infant who is unstable despite adequate sedation; however, the use of paralysis is controversial and should be reserved for unusual cases in which the infant cannot be treated with appropriate sedation.

Drug Name	Pancuronium (Pavulon) -- Relatively long-acting nondepolarizing muscle relaxant. Onset of action is 1-2 min, and duration of action is 45-90 min. Excretion is renal (80%) and hepatic (20%), and duration of action may be longer if renal or hepatic failure is present.
Pediatric Dose	0.05-0.15 mg/kg/dose IV bolus
Contraindications	Documented hypersensitivity; myasthenia gravis or related syndromes
Interactions	Increased effect with magnesium sulfate, furosemide, aminoglycosides, amphotericin, ketamine, cyclosporine, inhalation anesthetics, or antiarrhythmics; decreased effect with calcium, carbamazepine, phenytoin, corticosteroids, theophylline, or caffeine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May cause tachycardia, hypotension, and excessive salivation; caution with conditions that may potentiate neuromuscular blockade (eg, electrolyte abnormalities, neuromuscular disease, acidosis, renal or hepatic failure)

Drug Name	Vecuronium (Norcuron) -- Has few to no adverse hemodynamic adverse effects and may be preferred over pancuronium as a muscle relaxant in the infant with PPHN; however, it is more expensive than pancuronium. Intermediate-acting nondepolarizing muscle relaxant. Onset of action is 1-2 min, and duration of action is 45-90 min. Primary route of excretion is hepatic.
Pediatric Dose	0.05-0.15 mg/kg/dose IV q1-2h; alternatively, may be used as a continuous infusion
Contraindications	Documented hypersensitivity; myasthenia gravis or related syndromes
Interactions	Increased effect with magnesium sulfate, furosemide, aminoglycosides, amphotericin, ketamine, cyclosporine, inhalation anesthetics, or antiarrhythmics; decreased effect with calcium, carbamazepine, phenytoin, corticosteroids, theophylline, or caffeine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	In myasthenia gravis or myasthenic syndrome, small doses of vecuronium may have profound effects; caution with conditions that may potentiate neuromuscular blockade (eg, electrolyte abnormalities, neuromuscular disease, acidosis, hepatic failure)

Drug Category: _Pulmonary vasodilating agents_ -- Recently approved as a therapeutic modality for infants with PPHN, nitric oxide is an important mediator of vascular tone. It is delivered as an inhaled gas. At least 2 multicenter studies did not show that inhaled nitric oxide decreases mortality or the need for extracorporeal support in infants with CDH; however, it may be useful in stabilizing an infant while evaluating or transferring for ECMO.

Drug Name	Nitric oxide (INOmax) -- The FDA approved nitric oxide for the treatment of PPHN in December 1999. Produced endogenously from action of enzyme nitric oxide (NO) synthetase on arginine. Relaxes vascular smooth muscle by binding to heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cGMP, which then leads to vasodilation. When inhaled, NO decreases pulmonary vascular resistance and improves lung blood flow. Optimal dose is unknown, although most investigators agree that doses >20 ppm are not beneficial and may be harmful. Administration should occur under controlled conditions with access to ECMO if needed. NO_2 and methemoglobin levels should be monitored frequently, and weaning should occur gradually. Abrupt discontinuation may be associated with severe rebound pulmonary hypertension.
Pediatric Dose	1-20 ppm inhalation Deliver by system that measures concentrations of NO in breathing gas, with constant concentration throughout respiratory cycle, and that does not cause generation of excessive inhaled nitrogen dioxide
Contraindications	Right-to-left shunting of blood; methemoglobin reductase deficiency
Interactions	Concomitant administration with NO donor compounds (eg, nitroprusside, nitroglycerin) may have additive effects and increase risk of methemoglobinemia
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Methemoglobinemia and pulmonary inflammation resulting from reactive nitrogen intermediates; abrupt discontinuation of NO may lead to worsening oxygenation and increasing PAP; toxic effects include methemoglobinemia and pulmonary inflammation resulting from reactive nitrogen intermediates; caution in thrombocytopenia, anemia, leukopenia, or bleeding disorders; monitor for PaO_2, methemoglobin, and NO_2; abrupt withdrawal causes rebound pulmonary hypertension

Further Inpatient Care:

- Pulmonary care

  - Some severely affected infants have chronic lung disease. These infants may require prolonged therapy with supplemental oxygen and diuretics, an approach similar to that for bronchopulmonary dysplasia.
  - The use of steroids, particularly high doses for prolonged periods, is controversial and may actually hinder appropriate lung and brain development.

- Neurologic evaluation

  - Following recovery, a neurologist or developmental pediatrician should examine the patient, including an evaluation for CNS injury by head CT scanning.
  - Because the incidence of hearing loss is high, perform an automated hearing test prior to discharge.

- Feeding: Incidence of significant gastroesophageal reflux is very high. While most infants can be managed medically, surgical intervention with Nissen or Thal procedures is sometimes required.

Further Outpatient Care:

- Growth: Failure to thrive is common in a significant percentage of survivors and is most common in severely affected infants. Possible causes include increased caloric requirements because of chronic lung disease, poor oral feeding because of neurologic delays, and gastroesophageal reflux.

- Developmental follow-up

  - Because of the risk for CNS insult and sensorineural hearing loss, infants should be closely monitored for the first 3 years of life, preferably in a specialty follow-up clinic.
  - Reassess hearing at 6 months of life (and later if indicated) because late sensorineural hearing loss occurs in a high percentage of patients.
  - Evaluate the patient prior to entering school to determine if any subtle deficits may predispose the patient to learning disabilities.

Transfer:

- Transfer to an ECMO center

  - Guidelines for ECMO consultation are available from the Extracorporeal Life Support Organization (ELSO).
  - Baseline criteria for ECMO consideration include evaluation for risk factors because of the invasive nature of the therapy and need for heparinization. Infants should be older than 34 weeks' gestation, have a weight greater than 2000 g, have no major intracranial hemorrhage on cranial sonography, have been on mechanical ventilator support for fewer than 10-14 days, and have no evidence for lethal congenital anomalies or inoperable cardiac disease.
  - Timing is always difficult, but referral and transfer should occur prior to refractory hypoxia. Early consultation and discussion with the ECMO center is strongly recommended.

- Pulmonary recovery: Overall reported survival varies among institutions. When all resources, including ECMO, are provided, survival rates range from 40-69%.
- Long-term morbidity: Significant long-term morbidity, including chronic lung disease, growth failure, gastroesophageal reflux, and neurodevelopmental delay, may occur in survivors.

MISCELLANEOUS	Section 9 of 10

Special Concerns:

- Antenatal diagnosis

  - Using ultrasonography, CDH may be diagnosed antenatally as early as the second trimester. A detailed examination (level II ultrasonography) is typically necessary.
  - Antenatal diagnosis allows the mother to make important decisions, including consideration of both antenatal therapy and delivery in a facility with a neonatal intensive care unit (NICU) that offers all possible therapies (including ECMO) for the newborn infant.

- Antenatal surgical intervention

  - In utero correction reverses pulmonary hypoplasia, pulmonary vascular abnormalities, and left ventricular hypoplasia in the fetal lamb model.
  - Human clinical trials at the Fetal Treatment Center of the University of California at San Francisco reported survival in more than 2 dozen individual cases. However, whether antenatal repair is more effective than repair after delivery has not been confirmed, and risk of premature delivery is substantial. Antenatal repair is not currently offered as a treatment option.

- In utero tracheal occlusion

  - Ligation or occlusion of the fetal trachea is a new fetal treatment. The fetal lung secretes fluid by active ion transport through gestation, and this lung fluid provides a template for lung growth. Occlusion of the fetal trachea traps this fluid and stimulates lung growth, either by retention of growth factors within the lung or stimulation of local growth factors by the gentle distension provided by the fluid.
  - In the fetal lamb model, this procedure reverses both pulmonary hypoplasia and vascular abnormalities but does not correct left ventricular hypoplasia. This may be because the mass effect of the hernia viscera on heart development is replaced by the mass effect of the overdistended lungs. These findings have led to the use of this technique in a small number of human fetuses.
  - Tracheal occlusion is more straightforward than in utero repair of the diaphragmatic defect and has been performed uteroscopically. More needs to be learned about this procedure, and a randomized clinical trial is underway.
  - The selection criteria for in utero surgical intervention remain controversial. Most recently, the position of the fetal liver and the size of the fetal lungs relative to the fetal head are promising as indicators of severe disease. Optimal timing during gestation and length of occlusion are still under investigation.

PICTURES	Section 10 of 11

Picture 1. This is a radiograph of a 1-day-old infant with a moderate-sized congenital diaphragmatic hernia. Note the air- and fluid-filled bowel loops in the left chest, the moderate shift of the mediastinum into the right chest, and the position of the orogastric tube.

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Counseling the Breastfeeding Mother

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OVERVIEW	Section 2 of 11

In the time before managed care and "drive-through" deliveries, the vast majority of newborns remained in the hospital for several days after birth and were typically examined by their physician when they were aged 2 weeks. In theory, this longer hospitalization allowed ample time to ensure that the baby was receiving adequate nutrition and had demonstrated the ability to appropriately latch on and suckle at the breast once the mother's milk became available. In addition, the longer stays gave the staff more opportunities to reassure the mother, answer her questions, and provide her with support and encouragement.

However, rates of breastfeeding in the United States declined during the periods of prolonged postpartum recuperation, with the lowest rates occurring in the 1950s. Reports of breastfeeding infants who were failing to thrive decreased, but at the same time fewer infants were being breastfed. Women who continued to breastfeed received supportive breastfeeding care from a variety of sources, including their social network.

With the recent reemergence of breast milk as the ideal source of infant nutrition, more women are choosing to breastfeed. Women were once supported by others with personal knowledge about breastfeeding; however, this has been replaced with generations of women and men who are experts about formula feeding. Lack of community knowledge about breastfeeding and shorter hospital stays have led to more breastfeeding failures.

Because women and their infants are now being discharged earlier, it is essential that the tradition of the first follow-up at age 2 weeks be replaced with earlier more carefully planned assessments of the breastfeeding mother-infant dyad. Such early follow-up makes lactation success more likely and leads to a healthier infant. Careful follow-up depends on the health care provider's knowledge of the mechanics of breastfeeding, the evaluation of successful lactation, and the interventions required if difficulties develop.

This article reviews the mechanics of breastfeeding, correct breastfeeding techniques, and sufficient versus insufficient milk supplies. A discussion of early follow-up of the breastfeeding mother-infant dyad and the warning signs of difficulties in that dyad are also included. Emphasis is placed on assessing the breastfeeding neonate and determining when neonatal jaundice is pathologic. Finally, common breastfeeding problems are discussed, with emphasis on their early recognition and management. For more information about the physiology of lactation and about the structure and biochemical features of human milk, please see the eMedicine article Human Milk and Lactation.

Understanding the actual mechanism of how babies get milk into their bodies is important. Suckling and breastfeeding often are areas that are taken for granted because of their seemingly instinctive nature. However, the mechanics should not be forgotten or deemphasized because they are essential for a successful and uncomplicated breastfeeding experience. This understanding is helpful in ensuring the use of proper breastfeeding technique.

Initiation of the breastfeeding cycle

When breastfeeding begins, the nipple, surrounding areola, and underlying breast tissue are brought deeply into the infant's mouth, with the baby's lips and cheeks forming a seal (see Image 1). During feeding, the suction created within the baby's mouth causes the mother's nipple and areola mammae to elongate to 2-3 times their resting length and to form a teat. The nipple and areola extend as far as the junction between the baby's hard and soft palates. The baby's jaw then moves his or her tongue toward the areola, compressing it. This process causes the milk to travel from the lactiferous sinuses to the infant's mouth. The baby then raises the anterior portion of the tongue to complete the process.

Afterward, the baby depresses and retracts the posterior portion of his or her tongue in undulating or peristaltic motions. This motion forms a groove in the tongue that channels milk to the back of the oral cavity and stimulates receptors that initiate the swallowing reflex. This backward movement creates a negative pressure, allowing milk to travel into the baby's mouth. Throughout the suckling cycle, the nipple should not move in the infant's mouth if it is positioned correctly.

Swallowing during the breastfeeding cycle

When the volume of milk is sufficient to trigger swallowing, the back of the infant's tongue elevates and presses against the posterior pharyngeal wall. The soft palate then rises, closing off the nasal passageways. The larynx then moves up and forward to close off the trachea, allowing milk to flow into the esophagus. The infant then lowers his or her jaw, the lactiferous sinuses refill, and a new cycle begins. A rhythm is created in which a swallow typically follows every 1-3 sucks.

Differences between suckling and sucking

Distinct differences between suckling from a breast and sucking from an artificial nipple are important to note. Suckling from the breast is an active process that involves participation of both the mother and her infant. In contrast, bottle-feeding is a more passive activity that results in the creation of a partial vacuum in the infant's mouth through sucking. The artificial teat taken into the infant's mouth has a distinct oral/tactile stimulation. When an infant sucks on an artificial nipple, the nipple fills his or her mouth and prevents the peristaltic tongue action that occurs with suckling at the breast. Milk flows from the artificial nipple into the mouth without tongue action; flow occurs from the rubber nipple even if the baby's lips are not sealed around the nipple. Because of these differences, an infant is more likely to have a desaturation episode during bottle-feeding than during breastfeeding.

Lawrence and Lawrence discuss the phenomenon of human imprinting or stamping, which occurs early in the postnatal period. Comfort sucking and the formation of a nipple preference are genetically determined behaviors that affect imprinting to the mother's nipple. The baby's initial recognition of his or her mother involves the distinctive features of the nipple. If an infant who is learning to breastfeed receives supplementation via a bottle or a pacifier, the nipple-recognition signals are mixed. Although some dispute the existence of nipple confusion, numerous documented cases support its existence. Certainly, studies have shown that supplementation and the introduction of a foreign nipple, such as a pacifier, are associated with decreased rates of continued breastfeeding.

CORRECT BREASTFEEDING TECHNIQUES	Section 4 of 11

Before the common breastfeeding positions and techniques are reviewed, an understanding of the importance of timing in initiating breastfeeding is essential. Studies show that a woman's likelihood of continuing breastfeeding beyond the first month is related to the initiation of breastfeeding immediately after delivery.

Oxytocin levels at 15, 30, and 45 minutes after delivery are elevated significantly, coinciding with the expulsion of the placenta. Studies have linked maternal bonding and oxytocin levels. Therefore, encouraging the mother to have contact with her infant at a time when suckling is paired with high oxytocin levels and better letdown seems appropriate. In addition, the infant is alert soon after delivery and has not entered the deep sleep period that ensues approximately 6-12 hours after birth. Finally, personnel are more available to assist the mother in initiating breastfeeding during this immediate postpartum period.

Successful latch-on of the infant during this period enhances a mother's confidence that she can breastfeed. If a mother received narcotic analgesics during delivery, the infant may be sleepy and less able to breastfeed; if so, the mother may need to wait until the infant is in a more alert state. The use of relaxation techniques during labor and other forms of anesthesia, such as epidural anesthesia, allows the infant to be delivered in a more fully awake state. This early breastfeeding session typically helps instill confidence in the mother. Any early problems can be identified, and the mother can be offered assistance to facilitate the lactation process.

Breastfeeding environment

The mother and infant should be allowed to breastfeed in a relaxed and supportive environment. Personnel should be readily available to facilitate the process. Constant interruptions and a deluge of visitors may disrupt the early breastfeeding experience. The father's assistance and support are strongly associated with the success of breastfeeding. In a study of 224 mothers who were interviewed regarding their feeding choice, the father was a key factor in the initiation of breastfeeding. When the father supported breastfeeding, more than 75% of the mothers chose to breastfeed; in contrast, when the father did not support breastfeeding, only 2% of the mothers chose to breastfeed.

Often, the father can assist the mother with the positioning of the infant, particularly if she is recovering from a cesarean delivery. Thus, the father's approval and involvement in the breastfeeding process is helpful in creating a supportive environment. Grandparents who support breastfeeding also facilitate the process; however, if they do not breastfeed, their attitude can adversely affect the breastfeeding mother. Therefore, the mother who is breastfeeding and learning to know her newborn should be surrounded by a supportive caring team of health care providers and family members.

Positioning the infant

Positioning the infant is one of the most fundamental components to successful breastfeeding. If no maternal or neonatal contraindications (eg, low Apgar scores, known tracheoesophageal fistula, heavily medicated mother) are present immediately after birth, the mother should be helped into a comfortable position. This position may be lying on her side on the hospital bed or sitting in a comfortable chair. The most common position involves cradling the infant next to the breast from which he or she will feed, with his or her head propped up by the mother's arm. The infant should be placed with his or her stomach flat against the mother's upper abdomen, in the same plane. Another holding position is the football hold, in which the infant is cradled in the mother's arm with his or her head in the mother's hand and the feet oriented toward the mother's elbow. Mothers recovering from cesarean delivery may prefer this position because less pressure is placed on her abdomen. The mother then presents her breast to the infant, and the suckling process is initiated.

Presenting the breast to the suckling infant

Two basic hand positions that the mother typically uses are the palmar grasp or C-hold and the scissor grasp. With the palmar grasp, the mother places her thumb above the areola, and she places her remaining fingers under the breast to form a "C" or "V." The scissor grasp involves the placement of her thumb and index finger above the areola with the remaining 3 fingers below. The mother should ensure that the nipple is not tipped upward when she presents it to the infant because improper latch-on and nipple abrasion may result. In addition, the grasp should not impede the infant's ability to place a sufficient amount of the areola into his or her mouth, which is necessary for adequate latch-on and suckling.

Achieving latch-on

Infants instinctually open their mouths wide when the nipple touches their upper or lower lip. The tongue extends under the nipple, and the nipple is drawn into the mouth, initiating the suckling reflex. The mother's nipple and areolar should be maneuvered to the infant's open mouth instead of pushing the infant's head toward the breast. Although this maneuver may appear simple, it may seem impossible to a first-time mother. Care should be taken to assist the mother not only with the positioning of her infant relative to her breast but also with understanding the importance of putting the nipple and areola into the infant's mouth when it is open. The suck-swallow pattern should be evaluated while the infant is breastfeeding. Proper latch-on is evident by the infant's suckling and then swallowing. One can hear an infant's feeding rhythm, which produces a characteristic sound. During the early postpartum period, the mother typically reports that she feels her uterus contracting while her infant is breastfeeding.

Feedback from the mother during the breastfeeding process

Simply asking a mother if breastfeeding is going well is not enough. Many women report that everything is fine, but when further questioned about nipple pain, hearing the infant suckle, or the frequency of breastfeeding, problems often surface. The best way to know if breastfeeding is going well is to observe the mother-infant dyad. This observation allows the staff to assist the mother with immediate feedback and corrective measures when necessary. The observation checklist that Lawrence and Lawrence proposed in 1999 is adapted below.

Key observation checkpoints of the breastfeeding mother-infant dyad

- Observe the position of the mother, her body language, and her level of tension. Offer pillows to support the mother's arm or the infant. Help reposition the mother if necessary.
- Observe the position of the infant. The mother and infant should be positioned ventral surface to ventral surface (ie, stomach to stomach). The infant's lower arm, if not swaddled, should be around the mother's thorax. The infant cannot swallow if he or she has to turn to face the breast because the infant's grasp of the areola is poor in this position. The infant's head should be in crook of the mother's arm and moved toward the breast by the mother's arm movement.
- Observe the position of the mother's hand on the breast and ensure that it is not impeding proper grasping by the infant.

- Observe the position of the infant's lips on the areola. Typically, the lips should be 1-1.5 inches (2.5-3.8 cm) beyond the base of the nipple.
- Observe the lower lip. If folded in, suckling does not occur. The lips should be flanged.
- Observe the presentation of breast to the infant and the mother's assisting the infant to latch-on.
- Observe the response of the infant to lower lip stimulus. The infant should open his or her mouth wide to allow the insertion of the nipple and areola.
- Observe the motion of the masseter muscle during suckling, and listen for sounds of swallowing.
- Observe the mother's comfort level, and ensure that she is not having breast pain.

One should reinforce a mother's own physiologic cues during breastfeeding. A mother's letdown is the interplay of her physiologic response to suckling and her emotional state. Prolactin, the hormone responsible for letdown, is inhibited by stress (mediated by dopamine, norepinephrine, and epinephrine). The mother's relaxation ensures adequate letdown and the continued adequacy of breastfeeding.

Putting the infant to breast 8-12 times a day during the first 4-5 days after birth ensures the creation of an adequate milk supply, which the infant's use later regulates. A mother who responds to her infant's cry with letdown and who breastfeeds her infant on demand (ie, unrestricted breastfeeding) is more successful with continued lactation than the mother who breastfeeds according to the clock. The recommendation for mothers to use systematic or controlled timed feedings to help regulate the baby's cycles is fraught with misinformation. A mother should be empowered to follow the internal schedule that is appropriate for her and her baby.

FACTORS AFFECTING THE MATERNAL MILK SUPPLY	Section 5 of 11

True difficulties in the supplying of milk are most commonly related to the irregular or incomplete removal of milk. In the human mammary gland, lactation is under autocrine control in which the frequency and degree of milk removal appears to regulate an inhibitory peptide present in the milk. In other words, if the milk is not removed, this inhibitory peptide accumulates and subsequently decreases the synthesis of milk. If the milk is removed frequently, this inhibitory peptide does not accumulate, and milk synthesis increases.

Although most women are capable of producing more milk than their infants require, more than half of breastfeeding mothers perceive that their milk supply as inadequate. A mother may state that her milk is not in and that her infant is not getting enough milk. This misperception is most common during the immediate postpartum period. The neonate's requirements for fluid gradually increase over the first few days; ideally, the neonate frequently ingests milk in small volumes. As the baby's GI tract becomes more regulated and functional and as the stomach volume increases, the baby's milk intake increases.

The composition changes of the milk from colostrum to mature milk, which has a higher energy density (ie, caloric density) because of its higher fat content. Mothers should be encouraged to breastfeed at least 8-12 times during the immediate postpartum period to increase their milk supply. If a mother breastfeeds only 4-5 times during those early days, her milk production is delayed. Infrequent breastfeeding is associated with neonatal jaundice (referred to as breastfeeding jaundice or dehydration jaundice) and the early cessation of breastfeeding. Another perception of inadequate milk supply is related to the infant's growth spurts. During periods of enhanced growth, the infant may be more irritable and may seek the breast more often. These growth spurts usually resolve in about 1 week. Growth spurts should be explained to the mother to prevent undue stress or interruptions in breastfeeding.

Because the milk supply is directly related to its removal and ongoing synthesis, factors that hinder milk removal affect milk production. Factors that could disrupt the complete removal of milk are numerous (see Recognition and Management of Common Breastfeeding Problems). For example,

stress and fatigue in both parents may have an impact on the mother's milk production. Evaluating for these risk factors in the mother-infant dyad is essential to ensure that the milk supply is sufficient and that breastfeeding difficulties are not perpetuated.

If an infant is ill, a mother typically uses a breast pump to remove and store her milk. Premature infants who are first learning to breastfeed may be ineffective at milk removal. Some infants have neurologic disabilities or suck-swallow incoordination (common among premature infants born at <33 wk of gestation). In those situations, a mother may need to pump her breasts after breastfeeding to maintain adequate lactation while her infant learns to breastfeed more effectively. By facilitating complete removal of the milk by using a pump, the mother's supply remains abundant and thus easier for the infant to consume. Marianne Neifert, MD, uses this simile: "With an increase in a mother's milk supply, feeding is like drinking from a fire hydrant; the infant cannot miss."

In summary, factors affecting maternal milk supply include the following: (1) irregular or incomplete milk removal, (2) growth spurts (The infant's demand and maternal supply can change. The milk supply should normalize within 1-2 days.), (3) maternal fatigue and stress, and (4) the infant's medical condition (eg, prematurity, neurologic injury).

EARLY FOLLOW-UP OF THE BREASTFEEDING MOTHER AND HER INFANT

In accordance with recommendations from the American Academy of Pediatrics, breastfed neonates should be evaluated for breastfeeding performance within 24-48 hours after delivery and again at 48-72 hours after they are discharged from the hospital. At this follow-up visit, the newborn's weight and general health assessment are determined. The assessment of breastfeeding performance includes a direct observation of the baby latching on and suckling. The neonate should be evaluated for jaundice, adequate hydration, and age-appropriate elimination patterns when he or she is aged 5-7 days. .

Follow-up of breastfeeding infants

- Evaluate the infant's breastfeeding performance in the hospital within 24-28 hours after delivery, before he or she is discharged.
- Follow-up with telephone contact or an office visit 48-72 hours after the neonate is discharged from the hospital.
    - Check the baby's weight.
    - Assess the neonate's general health status.
    - Ask the mother if latch-on and suckling at breast are good.
    - Ask the mother if she has sore or painful nipples.
    - Ask the mother about support or help at home.
- Follow-up with an office or clinic visit when the neonate is aged 5-7 days.
    - Evaluate baby for jaundice, adequate hydration, and age-appropriate elimination patterns.
    - Assess maternal well-being. For example, evaluate for fatigue, stress, postpartum depression, sore nipples, and engorgement.

The options for early follow-up assessment of the breastfeeding mother-infant dyad are numerous and can include a home health visit, a consultation with a lactation specialist, a hospital follow-up program, or an appointment at a doctor's office or clinic. Telephone counseling should be viewed as an additional support, but it should not replace a visit in person.

This degree of follow-up may seem excessive, but ensuring the well-being of the breastfeeding mother-infant dyad is imperative. Such follow-up helps eliminate the rare but tragic cases of death caused by dehydration secondary to inadequate breastfeeding. Most morbidity associated with poor breastfeeding, such as failure to thrive, hypernatremic dehydration, and jaundice, can be prevented with early follow-up and an assessment of maternal and neonate risk factors for inadequate feeding.

What are the warning signs of ineffective breastfeeding in the infant? For example, if milk production is inadequate secondary to poor latch-on or infrequent breastfeeding, the infant may become dehydrated with a concurrent increase in his or her sodium level. Prolonged hyperbilirubinemia may accompany the dehydration. Dehydration occurs over days to weeks, depending on the milk supply and the frequency of breastfeeding. In rare cases, the sodium concentration may be as high as 180 mmol/L. Nothing may be inherently wrong with the mother's milk, but if it is not adequately removed from her breasts, either by suckling or by pumping, the milk becomes weaning milk with a higher sodium concentration.

The main reason that the sodium level increases in the infant, however, is volume contraction secondary to dehydration and insufficient water in the milk. Human milk is 87% water, but its composition changes if an insufficient amount of milk is removed from the breast. The treatment of an infant with hypernatremic dehydration is to replace the free water losses slowly, because an abrupt decrease in the sodium level can trigger seizures secondary to cerebral edema and the rapid flux of sodium concentrations. This treatment involves giving the infant intravenous fluid with decremental concentrations of sodium to achieve a normal serum sodium level.

Another warning sign of ineffective breastfeeding is failure to thrive in the breastfeeding infant, which also results from an insufficient milk supply. An infant can have both hypernatremic dehydration and failure to thrive. These disorders occur along a spectrum depending on whether the milk produced is adequate to maintain the infant's hydration state but insufficient to allow adequate growth. The primary care provider must assess the growth of the breastfeeding infant over time. Neonates typically regain their birth weight by 2 weeks of age, and their weight should increase by 50% at age 6-8 weeks. At 4-5 months of age, the baby's weight should be double his or her birth weight. Also, the infant's head circumference and length should be assessed. The monitoring of subcutaneous fat deposition also aids the clinician in assessing the adequacy of growth. An infant's growth should follow the growth curve.

Failure to thrive in an infant should not be attributed to breastfeeding without an exploration of other differential diagnoses. The mother whose infant is failing to thrive should be encouraged to breastfeed with close assistance and, possibly, short-term supplementation. Daily visits for weight checks and overall health assessments are often necessary. In rare cases, hospitalization may be indicated.

The assessment of the breastfed infant includes an evaluation of its voiding and elimination patterns; feeding routines; jaundice; and, most importantly, weight. In addition, the mother should be examined for pain or irritation of her breast and nipples and for signs and symptoms of undue stress or fatigue.

Healthy breastfed neonates should not lose more than 10% of their birth weight, and they should regain birth weight by the time they are aged 10-14 days. Newborns should have a minimum average weight gain of 20 g/d between ages 14 and 42 days. The average weight gain during this time is 34 g/d for girls and 40 g/d for boys. In addition, breastfed neonates tend to gain weight faster than formula-fed neonates for the first 2-3 months, and the rate begins to slow at 6-12 months. Breastfed infants also tend to have leaner bodies than those of formula-fed infants.

In the first 48 hours after birth, the neonate may void as infrequently as a couple times a day. Once the mother's milk supply is established, the baby voids after most feedings, usually 6-8 times a day.

As the mother's milk supply is established, the infant's stool changes from green-black meconium to yellow yogurtlike stools with seedy curds. This transition usually occurs by the infant's fifth day of life. Compared with formula-fed infants, breastfed infants tend to have more frequent and higher-volume bowel movements during their first 2 months of life. At weeks 4-6, an infant should pass at least 3 yellow stools of sufficient volume per day. If he or she doesn't, the possibility of inadequate milk intake must be considered. The number of stools gradually decreases after this time; by 2-3 months, several days or a week may pass before an infant has a stool.

As discussed in [Factors Affecting the Maternal Milk Supply](), incomplete breast emptying frequently causes insufficient milk production. An inadequate frequency or duration of breastfeeding is a common preventable cause of decreased milk production and thus intake. The expected frequency of breastfeeding in newborns is once every 2-3 hours. Breastfeeding should last approximately 10-15 minutes per breast and should include active suckling with short pauses and frequent audible swallows.

Essentials of early follow-up

Early follow-up of the mother-infant dyad supports breastfeeding and the continued good health of the neonate. Although assessing the infant's weight and state of hydration (skin turgor, capillary refill, hydration of mucous membranes) is vitally important, the interaction between infant and mother must also be assessed. Early breastfeeding is fatiguing and possibly overwhelming, especially for the primiparous mother. In addition to the physiologic assessment of the infant, the staff should encourage the mother and discuss ways to decrease her fatigue (eg, napping when the infant is napping, waking the infant during the day if its day-night cycle is switched, taking walks, talking with other mothers and friends). Postpartum depression may occur in the early postpartum period. Early recognition is essential for appropriate treatment. Women often do not see their obstetricians until 6 weeks after delivery; therefore, the physician who is caring for the infant and mother becomes an important link in the care of the infant and mother. A mother who has depression often has difficulties with her daily activities, including breastfeeding. The early follow-up visit helps with the early identification of problems and with the initiation of appropriate intervention.

Hyperbilirubinemia occurs in nearly all newborns and can be classified in several categories, including pathologic jaundice, physiologic jaundice of the newborn, breastfeeding jaundice, and breast milk jaundice.

Pathologic jaundice: Jaundice in the first 24 hours after birth is not normal, and causes such as sepsis and blood type incompatibility should be sought.

Physiologic jaundice: Physiologic jaundice is due to a higher erythrocyte circulating volume, a larger amount of precursors that undergo early degeneration, and a shorter life span of the newborn's erythrocytes. In addition to these physiologic considerations, the newborn hepatic uptake and conjugation of bilirubin are reduced, and the reabsorption of bilirubin is relatively enhanced due to a process called enterohepatic recirculation. These factors can lead to an early elevation in unconjugated bilirubin levels, which typically become normal adult values when the neonate is aged 2-3 weeks.

Breastfeeding jaundice: In addition to physiologic jaundice, breastfeeding jaundice or dehydration jaundice may develop in infants who breastfeed. Breastfeeding jaundice is due to inadequate milk intake, regardless of the cause. This condition occurs in the neonate's second or third day of life, usually before the mother's milk supply is in. The treatment is to put the infant to the breast more frequently, and the mother-infant dyad should be observed for proper latch-on. Maternal pumping with supplementation should be considered only if increasing the breastfeeding frequency does not lead to an increased milk supply. Evaluation of the overall nutritional status and breastfeeding technique of the mother-infant dyad is essential for successful lactation and the resolution of breastfeeding jaundice.

Breast milk jaundice is different from breastfeeding jaundice in that unconjugated bilirubin levels in the serum continue to increase during the first 2 weeks. With breast milk jaundice, the unconjugated bilirubin level typically peaks between days 5 and 15 after birth, and they usually return normal levels by the end of the third week. However, elevated levels that persist into the third month are not uncommon.

Interrupting breastfeeding in an otherwise healthy infant is not recommended unless the serum bilirubin concentration exceeds 20-22 mg/dL. The cause of breast milk jaundice is still not clear, an inhibitor of hepatic glucuronyl transferase is thought or exists, and/or the enterohepatic circulation of bilirubin increases. Other more rare forms of unconjugated hyperbilirubinemia, such as Crigler-Najjar syndrome (ie, glucuronyl transferase deficiency), should be considered if the bilirubin level remains elevated after the infant's first month of life.

RECOGNITION AND MANAGEMENT OF COMMON BREASTFEEDING PROBLEMS	Section 9 of 11

Risk factors for breastfeeding difficulties

Mother-infant pairs who are at risk for breastfeeding difficulties should have closer follow-up care. Risk factors in the mother include a history of poor breastfeeding with a previous newborn, flat or inverted nipples, abnormal breast appearance, previous breast surgery, previous breast abscess, extremely sore nipples, minimal prenatal breast enlargement, failure of the milk to come in abundantly after delivery, and chronic or severe medical problems. Breastfeeding risk factors in the infant include small size or prematurity, poor sucking, any oral abnormality, multiple gestation, medical problems, or neurologic or muscle-tone problems.

Common breastfeeding problems and solutions

Common breastfeeding problems and their solutions include the following:

- Engorgement: The treatment is prevention with frequent breastfeeding.
- Areolar engorgement: Treatment involves the manual expression or pumping of milk to soften the areola and allow better latch-on
- Mammary vascular engorgement: Treatment involves frequent breastfeeding around the clock, the application of cabbage leaves, and manual or electric pumping.
- Sore nipple: This problem is commonly associated with improper latch-on. Help the mother with positioning and encourage her to insert the areola and nipple into the infant's open mouth.
- Cracked nipple: The mother should begin the breastfeeding session on the less-affected side. Placing a drop of milk on each nipple and allowing this to air dry after breastfeeding may help. The use of high-grade lanolin or nipple shields should be considered if bleeding occurs.
- Mastitis: This problem is more common in engorged breasts. The mother should continue to breastfeed while taking antibiotics. Frequent emptying of the breast is essential for relief and recovery. The mother may also take acetaminophen or ibuprofen for relief.
- Abscess: This problem typically requires surgical incision and drainage, as well as antibiotics. The mother should continue to breastfeed on the unaffected side and pump the affected side to relieve pressure and facilitate recovery. The infant may be breastfed on the affected side when the breast is no longer painful to touch. Analgesia is essential for mother's comfort.
- Yeast infection of the breast: *Candida albicans,* which causes thrush in infants, may infect the nipple and intraductal system. Complaints of the mother include pain during breastfeeding or a diminution of her milk supply. Culture samples obtained from the skin. Treatment may begin with topical nystatin, but systematic therapy may be required for eradication.

Engorgement

Engorgement is a common breastfeeding problem, and its prevention is important. A mother should be encouraged to breastfeed several times a day to establish her milk supply and to ensure relief after her milk has come in. If a mother's breasts are so distended that the nipple is obscured, the infant may have difficulty in latching on. A mother may manually express or pump her milk to relieve the tension and distortion of the breast, which makes the nipple to be available for suckling by the infant. The mother should continue this cycle frequently as her breasts regulate to the requirements of her infant.

Cabbage leaves, either whole or as a minced paste, have been shown to relieve the swelling and pain of engorgement within 12-24 hours of application. The use of lanolin is not helpful in engorgement. Recommending that the mother discontinue breastfeeding is not appropriate because breast milk is the preferred source of nutrition for the infant and because the mother has shown that she desires to breastfeed with her action of initiating breastfeeding.

Insufficient milk supply

The misperception of an insufficient milk supply is common, particularly with first-time mothers. A mother who plans to breastfeed should undergo a prenatal assessment to evaluate her breast development during pregnancy and the condition of her nipples (eg, Are they inverted?) and to discuss strategies to achieve successful lactation. These strategies include frequent breastfeeding every 1.5-2 hours during the first few days. If a mother does not breastfeed frequently enough, her milk production is delayed.

The first-line treatment for an insufficient milk supply is to have the mother breastfeed frequently because any milk removed is quickly replaced. If a mother has been too ill to breastfeed or pump her milk or if her infant is too ill to breastfeed, the mother may have an insufficient milk supply. Again, the mother should be encouraged to breastfeed, if her infant is able, or to pump her breasts to stimulate milk production.

Galactagogues

Galactagogues or milk production enhancers may facilitate milk production. Probably the best known agent with the fewest adverse effects is fenugreek, an herb used in Indian curries and cooking. It is well-tolerated by most women. It can be taken as a tea (2-3 cups of tea per day) or as a capsule (two 500-mg caps tid for a total of 6 caps per day). Milk production should increase within 48-72 hours.

Other herbal remedies include fennel seeds brewed as a tea (1 tsp boiled in water and steeped for 10 min, served 2-3 times per day), milk thistle, and goat's rue. Contraindications to these herbal remedies include the current use of antiepileptic agents, coumadin, or heparin because the herbs may affect drug levels or clotting parameters.

Medical therapy

Metoclopramide (*Reglan*) acts as a potent stimulator of prolactin release and has been used to treat lactation insufficiency. Although the US Food and Drug Administration (FDA) has not approved metoclopramide for this indication, a dose of 10 mg PO tid has been shown to increase milk production. An increase of milk letdown response was experienced by as many as 60% of women within 3-5 days. Limit use to a maximum of 10-14 days. Coadministration of opioid analgesics with metoclopramide may increase CNS toxicity.

Large trials of galactagogues are lacking. Available data come from small studies and case reports.

Picture 1. When breastfeeding begins, the nipple, surrounding areola, and underlying breast tissue are brought deeply into the mouth of the infant, whose lips and cheeks form a seal.

Complete suck cycle. The baby is shown in medial section.
The baby exhibits good feeding technique: the nipple is drawn well into the mouth, extending back to the junction of the hard and soft palate (the lactiferous sinuses are depicted within the teat, although these cannot be visualized on exam.)

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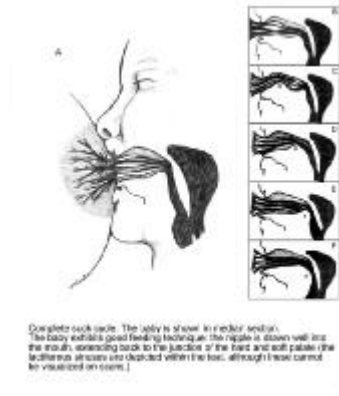
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Counseling the Breastfeeding Mother excerpt

Ethical Issues in Neonatal Care

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INTRODUCTION	Section 2 of 8

Background

As neonatal medicine has developed in the United States, clinical ethics (ie, bioethics, medical ethics, healthcare ethics) also have become increasingly present in the healthcare environment. For more than 30 years, neonatal medicine has been practiced to provide specialized and intensive care measures aimed at improving the health and survival of premature and critically ill newborns.

Throughout this period, great strides have been made in improving the technical capabilities that allow more rapid and precise diagnoses, effective monitoring, and specific therapy. The availability of special-care nursery beds has increased dramatically. The number of trained professionals and specialists also has risen.

The results of these progresses are mixed. A substantial reduction in the mortality of premature infants has occurred. Furthermore, the rate of handicap or significant morbidity appears to have remained steady or declined in survivors of the neonatal intensive care unit (NICU) of nearly all gestational ages and weights. Despite these facts, the rate of prematurity has not declined in the United States, nor has the rate of low birth weights. Also, the rate of birth defects remains relatively constant, and infant mortality, though diminished over the past decade, remains higher in the United States than in many developed nations. Finally, the discrepancy between black and Caucasian infant mortality remains a concern.

ETHICAL QUESTIONS	Section 3 of 8

Questions about the current state of practice in neonatal medicine are as follows:

- "Who deserves access to prenatal and neonatal specialty care?"
- "Who pays for this care?"
- "How can this care be assured and equitably distributed?"
- "Are some babies too sick or too premature for newborn intensive care?"
- "Who decides whether an infant receives care?"
- "How are these decisions made?"

These particular questions are at the root of what many healthcare professionals see as the dilemmas in providing neonatal intensive care. These questions often are raised at bedside while providing care, during teaching rounds, and during special ethics rounds held in the NICU.

However, these questions usually are asked in a more obscure manner, and the sequence of questions is typically in the reverse order of their annotation above. Healthcare professionals often hear, "Are we doing the right thing for this baby?" "What else can we do for this patient?" "Would the infant be a candidate for this therapy or a different one?"

Amidst the flurry of activity in stabilizing the health of an infant or working through his or her resuscitation, professionals from all disciplines involved in the care of a critically ill newborn may wonder, "Why is this procedure being performed?" "Should this procedure stop?" "What do the parents want?" "Does a better or more standard way of providing this care exist?"

Often, after hours or days of exhaustive efforts that still may result in neonatal death, clinicians may wonder, "Why are we here?" "Did we make a difference?" "What are we trying to accomplish with these efforts?"

These questions broach issues that are central to the clinician's perception of being a valued person in the NICU environment while trying to serve patients, families, and a broader society. In part, these questions reflect the values of the healthcare professions, the values of individuals, and the values of patients and families. To ignore these questions is to fail to recognize the significant influence these values have had in shaping individual professional lives and human interactions.

Beyond that, failing to answer these questions perpetuates an inability or unwillingness to responsibly address the value-laden charge that comes with professing to be willing and able to help a newborn who is vulnerable and sick, which is the charge to practice the art of medicine with scientific rigor, technologic skill, and human caring, even in the face of medical uncertainty. Ignoring these questions leads to moral uncertainty and, quite possibly, moral distress or angst stemming from doing things against one's own better judgment. This article considers 3 questions that pertain to some of the ethical issues raised in neonatal medicine. In the course of answering these 3 questions and discussing clinical ethics, ethics are defined as the applied philosophical study of right actions or how healthcare professionals may struggle to do what is right or good for their patients. These questions aim to address the ethical concerns raised by caring for critically ill newborns.

"What are the goals of neonatal intensive care?"

As in other clinical paradigms, neonatal medicine requires a defined end or objective, which may be presumed to be treating the newborn who is ill and/or curing any acute disease process that impedes the normal physiologic transition toward healthy extrauterine life. But what are the more global goals? Or, when the curative model is inadequate, what do the goals become?

"What place do guidelines have in the ethical practice of neonatal medicine and how should they be developed?"

As neonatal medicine has been practiced in the United States and around the world, a number of guidelines have emerged. The roles of authoritative statements, professional policies, and recommendations lead to this question.

"What is good for critically ill newborns and who determines this?"

The presence of numerous voices in deliberations about newborn patient care presses this question.

Overview

Healthcare professionals may experience frustration at the lack of specific resource material that provides a ready answer to these questions. If such material were available and agreed upon, the vexing nature of these questions may have long since passed. Although a difference of opinion in material authored by philosophers, clergy, lawyers, administrators, healthcare professionals, and parents is expected, one may think that some hint about the goals of neonatal intensive care could be found. This is not necessarily true.

After reviewing major textbooks and the medical literature, as well as attending local, regional, and national meetings for years, this writer scarcely has found or heard the goals of neonatal intensive care publicly stated. This is the basis of the problem encountered when working through ethically challenging situations. Involved professionals and parents first must come together and decide what neonatology is about. Neither the simply stated goal "to save all babies" nor "to reduce infant mortality" says enough.

In addressing ethical issues in the NICU, at all times consider the goals of specific monitoring, diagnostic tests, therapies, or research protocols that are administered. Center the goals of care on the patient and the family. The patient is treated, but the family must live with the long-term consequences of the daily decisions made in caring for the baby.

Essential Components

Skilled professional care

Goals include more than the simple application of critical care technology, such as ventilators, monitors, medications, invasive devices, and a multiplicity of laboratory measurements, to sick and premature newborn patients.

The goals of neonatal intensive care include the provision of skilled professional care. This requires trained professionals of many disciplines to create an effective team of providers who render neonatal intensive care; no single professional can do this alone.

Physical constraints

Care is extended over a necessarily limited period of time. The simple physical constraints of a nursery environment make evident the unsuitable nature of the NICU for older infants and children. The developmental needs of growing newborns and young infants are difficult to meet in the NICU environment from the standpoint of staffing, time utilization, and patient access and interaction (with family or staff) throughout the passing months.

Conclusion of care

The ends to which care is provided include initial stabilization of the newborn and, ultimately, facilitation of the transition to normal, extrauterine, neonatal physiology. This transition takes longer for some infants and may require significant intervention and support. The reversal of acute disease processes, such as infection and respiratory distress, is a recognized end.

Iatrogenic effects

Minimizing chronic or debilitating outcomes, including iatrogenic sequelae of applied neonatal intensive care, falls within these goals. The potential for negative iatrogenic effects in much of what is performed in neonatal practice must be recognized. Such effects may result from the following:

- Environment in which the baby is managed
- Mode of ventilation
- Types, doses, and results of medications used
- Short-term and long-term effects of certain procedures
- Foreign bodies or devices used
- How the baby's nutritional needs are met

Expected outcomes

Provide care with a reasonable expectation of steady improvement. Care should proceed with the absence of unnecessary pain and avoidable suffering. Develop care toward a capacity for the newborn to enjoy and participate in the human experience over a life prolonged beyond infancy.

Parents

Goals seek to maintain a focus upon the best interests of the child. In determining the best interests of the child, the parents generally are considered to be the spokespersons; hence, seek their opinions, discern their values, and consider their goals.

Decision-making Methods

Shared decision making should be the commonly employed process, requiring shared information among relevant care providers and a willingness and capability to communicate effectively with parents.

This process also suggests the need for outcome data. Such data should be relevant to the population seeking care at a given institution. Relying on national or other reported regional or institutional data from outside a particular practice setting is not always valid, because data from different practice settings likely are neither constituted nor controlled in the same fashion. The provision of care, which is decided on by local clinical and population data, and the determination of best interests, or what can be viewed as either effective, beneficial, and appropriate care versus ineffective, burdensome or inappropriate care, demand the availability of data from which to make these determinations with parents. Until such data are available, healthcare professionals should be frank in recognizing and communicating some uncertainty in their decisional process with parents.

Overview

NICU guidelines are developed to relate professional medical consensus. Institutional, regional, or societal goals can establish norms and provide a reference point to assist healthcare professionals and parents as they make decisions. Clinical practice guidelines have gained broad acceptance by healthcare managers and many clinicians over recent years.

Existing Guidelines

Medical futility or futile care

Several US regions are developing clinical ethics guidelines to address this issue, including Houston, Texas; Charleston, South Carolina; Denver, Colorado; Sacramento, California; and the state of Georgia.

Do not resuscitate orders

Guidelines for the use of do not resuscitate (DNR) orders developed and promulgated by professional societies and ethicists have assisted in the day-to-day management of numerous difficult issues, including determining brain death and the withdrawal or withholding of life-sustaining therapy.

Other guidelines of ethical import

- Report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 1983
- "Guidelines on the termination of life-sustaining treatment and the care of the dying." The Hastings Center, 1987
- American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG) Guidelines for Perinatal Care, now in its fourth edition
- Canadian Pediatric Society and Society of Obstetricians and Gynecologists of Canada statement "Management of the woman with threatened birth of extremely low gestational age." 1994
- AAP Committee on Fetus and Newborn and ACOG Committee on Obstetric statement entitled "Perinatal care at the threshold of viability." 1995
- AAP Committee on Bioethics statement "Ethics and the care of critically ill infants and children." 1996

When applying these technologies, consider guidelines such as Dr John Tyson and colleagues' 1996 evaluation of criteria for considering risk-benefit ratios in providing intensive care interventions (eg, mechanical ventilation to extremely low birth weight infants).

Institution-specific guidelines, such as those developed at the Medical College of Georgia for hospice care of newborns with life-limiting conditions, also have a place in clinical practice. The process of their development may prove beneficial to staffs and families and may serve newborn patient interests.

Communication process

In the attempt to derive guidelines at any level, give attention to the processes of communication and decision making. This process may be more important than the actual product, the specific guideline itself. If both professional and community consensus building can work toward deriving guidelines that address the needs of the community, then such work is beneficial.

Often, the initial communication is the most difficult. Even if the parents know what their wishes are and can communicate them, the timing of premature deliveries unfortunately may not afford the luxury of ascertaining parental wishes prior to birth. The aim of guidelines should not be to dictate medical care but to facilitate decision making and perhaps give consistency to the process in which difficult decision making takes place. An end result may be that families are empowered in decision making; however, certainly all parties involved in these decisions for critically ill newborns should benefit from enhanced communication and clearly defined goals.

Using a cautious approach

Three reasons to consider a more cautious approach to the use of neonatal intensive care than simply providing it to every patient at all times are as follows:

- Guidelines for the appropriate application of neonatal intensive care may help healthcare professionals as they consider the possibility that the provision of every imaginable resource to the smallest, most ill, and most vulnerable infants may compromise the outcomes of other patients (eg, larger infants who have better prognoses).
- Allocating scarce resources to provide for the needs of all babies is difficult; often, the very low birth weight infants garner all of the attention, perhaps to the detriment of larger babies. Clearly, what is used for one patient is unavailable to others.
- Given the limited availability of follow-up data, the generally poor tracking of patients after discharge, and the failure of many practitioners to listen to parents' wishes and concerns, unrestrained interventions actually may provide patients or their families a disservice.

Expertise

Guidelines reflect thoughtful consideration by experts. While they do not necessarily provide the absolute answer, they provide a possible answer and, generally, more than just a starting point. Knowing that a group of concerned professionals have addressed a problem, considered multiple perspectives, and examined options and outcomes to the best of their abilities is reassuring. When confronted with weighty problems, it helps to not feel alone and to be able to rely on the experience and expertise of others.

Enabling

Guidelines enable professionals who previously have been constrained by lack of policy or clear direction regarding certain problems. If a hospital has never addressed withholding certain life-sustaining care, making such decisions or seeing them implemented may become difficult. If a new technology is offered without guidelines for indicated or appropriate use, be it clinical or research, using that technology reliably or responsibly may prove difficult. Guidelines in such cases enable staffs and institutions to make responsible decisions with their patients' best interests at heart.

Empowering

Guidelines empower the team of healthcare professionals and parents involved in a particular case. Guidelines typically identify responsible decision makers and provide a voice to those whose perspectives should be considered.

Encouraging

The process of deriving guidelines encourages teamwork, communication, and confronting (rather than avoiding) issues. When facing difficult issues, many staff members need encouragement. Professional staff members feel a sense of accomplishment upon the completion of a guideline, and they are encouraged to face a new or different problem needing similar attention in the future.

Education

Guidelines, and the process by which they are developed, are educational for all involved and provide a format for educating the staff and community. Contributing to the process of developing a guideline, at the institutional, community, or professional society level, is an educational experience. Once derived, communicating these guidelines to the community of interested persons (patients, staffs, professionals, the public) involves ongoing education. The disclosure or dissemination of guidelines may provide a springboard for additional educational endeavors.

Potential negative aspects of guidelines in healthcare decision making exist. The most obvious of these is the fact that guidelines are, of necessity, incomplete. Not all healthcare cases fall under the general guideline parameters. Some cases test the system or do not represent the norm; hence, consistency may not result in every case, even with the best-intended guidelines. Guidelines are recognized as imperfect because they are imperfect. However, as previously stated, guidelines represent more than a simple starting place and reflect considerable expertise and judgment. The exceptional case does not negate the value of the guideline any more than the guideline reflects simple anecdotal experience. The value lies in the broader applicability of the guideline to most cases.

In view of these potential shortcomings, guidelines do not please everyone. Some practitioners see them as an intrusion into what they believe to be private decision making, others view them as medicine by committee, and still others view guidelines as unwarranted bureaucratic oversight.

In some situations, tragic situations leave only tragic options. Guidelines cannot resolve the hurt associated with the emotional investment made toward patient care when outcomes are dismal. Following a guideline does not necessarily make a dismal outcome easier to bear.

Basis on fact: Guidelines need to be based on fact. The use of data is fundamental to the credibility of guidelines. Such data should be more than anecdotal and ideally should reflect local institutional or regional experience rather than national data, which may represent a significantly dissimilar population that undergoes vastly different experiences over remote points of time. Data should be current, complete, and comprehensive.

Currency of guidelines: Guidelines should be kept current. When conditions in place at the time a guideline was developed change (eg, local population; availability of healthcare technology; social, political, or fiscal influences), evaluate the guidelines and, if necessary, change them to reflect the new paradigm.

Responsibility for public disclosure: Responsibility for public disclosure exists within any institution that develops or uses guidelines. Patients who are subject to care under certain guidelines have a right to know how they are affected by them, and healthcare professionals have a duty to inform patients of these guidelines. This responsibility stems from the principles of respect for persons, patient autonomy, avoidance of harm, and maximizing benefit. This is the nature of fiduciary, or trust-based, relationships between healthcare professionals and their patients. Only in this way can such professionals truly be advocates for their patients. Advocacy begins with staff involvement in the development of guidelines, but it realizes itself in the conveying of information to patients and families to facilitate their understanding of why care proceeds along certain lines and how they can contribute to it.

ACHIEVING THE GOOD	Section 6 of 8

In addressing the third question, doing what is good for critically ill newborns, the concept of doing good is worthy of some attention. Doing good appeals to people of sound moral character and is assumed practically in all who have pursued professions in the healing arts. Healthcare professionals are healers. They are people who look out for the well being of their patients. They act positively to accomplish good health and to avoid perceived harms that would be contrary to their patients' good health. Traditionally, communities or populations who share moral traditions have subscribed to a concept of the good. These communities and populations may include the following:

- Communities of faith
- Communities with a shared ethnic or social heritage
- Perhaps, a perceived image of health that is shared

Recent reflection makes it clear that a great deal of diversity exists in the moral concepts of what is the good to which individuals should aspire. Given the many diverse communities across the United States, that they do not universally share the very idea of good health is not surprising. Perhaps the peculiar American emphasis on individuality and independence has disrupted previously shared values of what good health is within traditional moral or faith communities.

Even in the NICU environment, where shared professional training, avowed determination to work for their patient's best interests, and experiences that would appear commonplace to all are present, a diversity in the concept of the good exists. This leads to instances in which no universal agreement occurs as to which of many alternatives is the right good or even whether the good that is pursued is worthwhile. How, then, is "the good" defined?

In many specific healthcare environments, a concept of the good must be refined to reflect the peculiarities of the patients, their conditions, the available treatment alternatives, the values placed upon those alternatives by relevant parties, the likely outcomes of treatment or nontreatment, and the

influences of external considerations. In the NICU, as elsewhere, goods that are pursued include health, prevention or elimination of disease or morbidity (including iatrogenic sequelae of treatment), relief of unnecessary pain or suffering, and the prolongation of life.

Joy Penticuff, a nurse writing in the text *Ethics and Perinatology,* states that the goods desired for infant patients in the NICU include comfort, opportunities for affectionate parental interaction that promotes infant-parent emotional bonding, and protection and nurturance of the infant's future emotional, cognitive, and physical development. While these and others are desired goods for neonatal patients, they may not be easy to accomplish. At times, barriers to the accomplishment of these desired goods seemingly are present.

Consider the following barriers to achieving the good:

- Lack of knowledge: Healthcare professionals may need larger amounts and more diverse types of information.
- Lack of sufficient time: Healthcare professionals may need to act immediately and may not have the luxury of contemplation.
- Lack of interest: Some members of the healthcare team, perhaps someone known well, may not be interested in achieving the good.
- Emotional barriers: These may be present in the individual healthcare provider, colleagues, parents, and others.
- Past experiences: Experiences in similar cases or with similarly charged emotions may exist.
- Intimidation: Healthcare providers with real or perceived power may intimidate others.
- Lack of perceived power or a poor team concept: Lack of being valued as a contributor to the treatment team can provide a barrier.
- Lack of policies or guidelines: Policies or guidelines may not exist to facilitate action or an organized approach to a problem.
- Lack of a concept of goals for this patient
- Lack of resources: Monetary, equipment, personnel, or other lack of resources can provide barriers to achieving the good.

CONCLUSION	Section 7 of 8

Perhaps the final consideration in answering these questions is that each day, healthcare professionals must work within the realities of the cases before them. Each patient has a unique set of problems that prompt action, moral reflection, and re-evaluation. Each family brings with it the awareness that the prevailing (or traditional) concept of family must be adjusted to what comprises the group of nurturing interested persons for this baby. Each diagnosis challenges the collective knowledge and notion of effective care of a healthcare team. Each healthcare dilemma reminds caregivers of their limitations, including uncertainty, the human predicament, lack of knowledge, and decision-making abilities. All of these are tempered by the moral constraints under which they act.

Healthcare professionals must, at times, accept the reality that tragic cases have tragic outcomes; the healthcare professional may not always rest easy with decisions wherein the pursuit of some good yields only emptiness. As John Dewey stated, "All the serious perplexities of life come back to the genuine difficulty of forming a judgment as to the values of a situation; they come back to a conflict of goods." In summary, the reader and practitioner are asked to not only inquire "What good are we doing here?" but also to move toward defining goals, perhaps for the specialty, but more realistically, for the individual patient. Base each patient's care on goals of care that are consonant with professional goals, societal norms, institutional mission, and mutually derived goals with parents or families. This requires time and thoughtful reflection while communicating with families and advocating for the patient's benefit. Consider the potential value of guidelines in the process of working through common or recurring problems, ethical or otherwise, in the nursery and hospital. In so doing, the good that individual healthcare professionals perform may become more evident to themselves, their colleagues, and their patients.

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Extremely Low Birth Weight Infant

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INTRODUCTION	Section 2 of 7

Extremely low birth weight (ELBW) is defined as a birth weight less than 1000 g (2 lb, 3 oz). ELBW infants also represent the youngest of premature newborns, born at 27 weeks' gestational age or younger. Nearly 1 in 10 infants with low birth weight (<2500 g) are ELBW infants (27,988 births in the United States in 1997). ELBW survival has improved with the widespread use of surfactant agents and maternal steroids, treatments that have lowered the minimum age of viability to as young as 23 weeks.

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Survivability correlates with gestational age (11.6% for birth weights <500 g, 50.7% for birth weights of 500-749 g, 83.9% for birth weights of 750-1000 g). Although black infants comprise 15.5% of live births in the United States, they account for 36.8% of babies with birth weights less than 1000 g. ELBW infants are more susceptible to all of the possible complications of premature birth, both in the immediate neonatal period and after discharge from the nursery. Although the mortality rate has diminished with the use of surfactants, the proportion of surviving infants with severe sequelae, such as mental retardation, cerebral palsy, and deafness, has not.

Thermoregulation

As a result of a high body surface area–to–body weight ratio, decreased brown fat stores, and decreased glycogen supply, ELBW infants are particularly susceptible to heat loss immediately after birth. Hypothermia may result in hypoglycemia, apnea, and metabolic acidosis. ELBW infants can lose heat in 4 ways, namely, via radiation, conduction, convection, and evaporation. Radiation occurs when the infant loses heat to a colder object, conduction occurs when the infant loses heat through contact with a surface, convection occurs when the infant loses heat to the surrounding air, and evaporation occurs when heat is lost through water dissipation.

Temperature control is paramount to survival and typically is achieved with use of radiant warmers or double-walled incubators. Immediately after birth, the infant should be dried and placed on a radiant warmer and a hat or another covering should be placed on its head. Hypothermia (<35°C) has been associated with poor outcome, including chronic oxygen dependency.

During transport from the delivery room to the neonatal intensive care unit, care should be taken to cover the baby, either with warmed blankets or with cellophane wrap, to help the infant retain body heat. The infant should be placed in a double-walled heated incubator during transport. The delivery room and the neonatal intensive care unit also should be kept warm to prevent hypothermia in the infant. Future architectural designs should facilitate adjacent location of delivery rooms and neonatal intensive care units or at least provide separately heated resuscitation rooms.

Hypoglycemia

Fetal euglycemia is maintained during pregnancy by the mother via the placenta. However, ELBW infants have difficulty maintaining glucose levels within reference range after birth, at which time the maternal source of glucose is lost. In addition, ELBW infants are usually under stress and have insufficient levels of glycogen stores. In the preterm infant, hypoglycemia usually is diagnosed when whole blood glucose levels are lower than 20-40 mg/dL. In a recent review, Cornblath et al also recommended that a glucose concentration of less than 45 mg/dL be used as a screening or treating level in preterms infants. Symptoms may be present but may not be as obvious as those in a more mature infant (seizures, jitteriness, lethargy, apnea, poor feeding). Thus, hypoglycemia often may be discovered only after routine serum dextrose sampling. One form of accepted treatment consists of an immediate intravenous glucose infusion of 2 mL/kg of 10% dextrose-in-water solution (200 mg/kg) followed by a continuous infusion of dextrose at 6-8 mg/kg/min to maintain a constant supply of glucose for metabolic needs and to avoid hypoglycemia.

Fluids and electrolytes

Fluid and electrolyte management must be closely controlled because disturbances may result in or exacerbate morbidities, such as patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), and chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD). Compared to full-term newborns, ELBW infants have proportionally more fluid in the extracellular fluid compartment than the intracellular compartment. They also have a larger proportion of total body weight composed of water. During the early days after birth, diuresis may result in a 10-20% weight loss, which can be exacerbated by iatrogenic causes, such as radiant warmers and phototherapy.

ELBW infants also have compromised renal function stemming from a decreased glomerular filtration rate; a decreased ability to reabsorb bicarbonate, secrete potassium, and other ions; and a relative inability to concentrate urine. In addition, they reabsorb creatinine via the tubules following birth and, thus, serum creatinine levels are elevated for at least the first 48 hours of life, especially in ELBW infants, and do not reflect renal function for the first few days following birth. Fluid status is commonly monitored with daily (or sometimes twice daily) body weights and strict recording of fluid intake and output.

Electrolytes are monitored frequently to maintain homeostasis. ELBW infants are prone to nonoliguric hyperkalemia, defined as a serum potassium level greater than 6.5 mmol/L, which has been associated with cardiac arrhythmias and death. Omar et al concluded that prenatal administration of steroids prevented nonoliguric hyperkalemia in ELBW infants, and they speculated that prenatal use of steroids induced up-regulation of cell membrane sodium-potassium-ATP activity in the fetus.

Nutrition

Initiating and maintaining growth of ELBW infants is a continuing challenge. Infants commonly are weighed daily, and body length and head circumference usually are measured weekly to track growth. The growth rate often lags because of complications such as hypoxia and sepsis. Concern that early feeding may be a risk factor for necrotizing enterocolitis (NEC) often deters initiation of enteral feeding. Parenteral nutrition may provide the greater source of energy in ELBW infants in the first few weeks after birth.

ELBW infants have high energy requirements because of their greater growth rate. Heat loss from the skin also raises energy needs. ELBW infants expend 60-75 kcal/kg/d and need at least 120 kcal/kg/d to achieve the desired growth rate of 15 g/kg/d. Current common practice in the early days after birth calls for most energy to be provided in the form of parenteral glucose and lipids. ELBW infants may tolerate a glucose infusion rate of 6-8 mg/kg/min, but hyperglycemia may be a common and serious complication early after birth.

Lipid intake may vary from 1-4 g/kg/d of 20% lipid emulsion, as tolerated. Since ELBW infants lose at least 1.2 g/kg/d of endogenous protein, they require at least that amount of amino acids and 30 kcal/kg/d to maintain protein homeostasis. They also need such essential amino acids as cysteine and may require glutamine, found in human breast milk but not always present in parenteral nutrition mixtures. Trace minerals, such as iron, iodine, zinc, copper, selenium, and fluorine, are beneficial as well. Early evidence suggests that chromium, molybdenum, manganese, and cobalt may need to be added to the nutritional regimen, especially in ELBW infants who require long-term parenteral nutrition.

Enteral feeding often is begun when the infant is medically stable, using small-volume trophic feeding (approximately 10 mL/kg/d) to stimulate the gastrointestinal tract and prevent mucosal atrophy. Prolonged use of parenteral nutrition may result in cholestasis and elevated triglyceride levels. To reduce these complications, weekly laboratory tests usually are obtained to evaluate liver function, alkaline phosphatase, and triglyceride levels. Bolus feedings every 2-4 hours may begin as early as day 1. If tolerated, as evidenced by minimal gastric residuals and clinical stability, feeding may increase to 10-20 mL/kg/d, although feeding practices vary widely. Although bolus feeding may appear to be more physiologically appropriate, infants who do not tolerate the volume of the bolus may be fed continuously.

Breast milk is considered by some to be the best choice for enteral feeding and has been suggested to have protective effects against NEC. Breast milk must be fortified with calcium and phosphorus to promote proper bone growth. Low birth weight infants have a high need for macronutrients and micronutrients that approaches intrauterine needs; at the same time, the functionally immature gastrointestinal tract precludes adequate enteral intake. Despite its many immunologic and nutritional advantages, an exclusive diet of unsupplemented breast milk may provide insufficient quantities of energy, protein, calcium, and phosphorous to support the goals of intrauterine bone mineralization and growth rates in small premature infants.

Human milk may be supplemented by adding liquid or powder commercially available fortifiers, premature infant formulas, modular supplements, or vitamin/mineral supplements. Commercially available multinutrient fortifiers include Enfamil Human Milk Fortifier (Mead Johnson Nutritionals; Evansville, Indiana) or Similac Human Milk Fortifier (Ross Products, Abbott Laboratories; Columbus, Ohio), both of which are powders. Similac Natural Care Liquid Fortifier (Ross Products), which is a liquid, is also available.

Comparisons of the nutrient content and source of macronutrients of these fortifiers have been published. Potential complications of human milk fortifiers include nutrient imbalance, increased osmolarity, and bacterial contamination. A number of specially formulated preterm formulas are available that have been shown to promote proper growth, as well. Caloric density usually is increased when a full feeding volume is achieved and the infant is no longer on intravenous supplementation.

Hyperbilirubinemia

Most ELBW infants develop clinically significant typically unconjugated or indirect hyperbilirubinemia requiring treatment. Hyperbilirubinemia develops as a result of increased red blood cell turnover and destruction, an immature liver that is impaired during conjugation and elimination of bilirubin, and reduced bowel motility, which delays elimination of bilirubin-containing meconium. These manifestations of extreme prematurity in addition to typical conditions that cause jaundice (eg, ABO incompatibility, Rh disease, sepsis, inherited diseases) place these infants at higher risk for kernicterus at levels of bilirubin far below those in more mature infants. Kernicterus occurs when unconjugated bilirubin crosses the blood-brain barrier and stains the basal ganglia, pons, and cerebellum. Infants with kernicterus who do not die may have sequelae such as deafness, mental retardation, and cerebral palsy.

Phototherapy is used to decrease bilirubin levels to prevent the elevation of unconjugated bilirubin to levels that cause kernicterus. Phototherapy, which uses special blue lamps with wavelengths of 420-475 nm, breaks down unconjugated bilirubin to a more water-soluble product via photoisomerization and photooxidation through the skin. Then, this product can be eliminated in bile and urine. The fluorescent bulbs are positioned at 50 cm above the infant with a resulting intensity of 6-12 $\mu W/cm^2$. Tan has shown that the rate of bilirubin reduction is proportional to the light intensity. Phototherapy causes an increase in insensible water loss, so the amount of fluid intake typically should be increased. The infant's eyes are covered with patches to avoid exposure to blue light.

While phototherapy is initiated at birth of ELBW infants at some institutions, others start phototherapy when the bilirubin value approaches 50% of the birth weight value (eg, 4 mg/dL in an 800-g infant). If the level of bilirubin does not decrease satisfactorily with phototherapy, exchange transfusion is another option. If the level of bilirubin approaches 10 mg/dL (or 10 mg/dL/kg), exchange transfusion can begin to be considered in ELBW infants. In otherwise healthy term infants, exchange transfusion is not considered until the bilirubin level approaches 25 mg/dL.

In exchange transfusions, almost 90% of the infant's blood is replaced with donor blood, and the bilirubin level falls to 50-60% of the preexchange level. Complications include electrolyte abnormalities (hypocalcemia, hyperkalemia), acidosis, thrombosis, sepsis, and bleeding.

Respiratory distress syndrome

An early complication of extreme prematurity is respiratory distress syndrome (RDS), which is caused by surfactant deficiency. Clinical signs include tachypnea (>60 breaths/min), cyanosis, chest retractions, nasal flaring, and grunting. Untreated RDS results in increased difficulty in breathing and an increased oxygen requirement over the first 24-72 hours of life. Chest radiographs reveal a uniform reticulogranular pattern with air bronchograms. Since the incidence of RDS correlates with the degree of prematurity, most ELBW infants are affected. As a result of surfactant deficiency, the alveoli collapse, causing a worsening of atelectasis, edema, and decreased total lung capacity. Surfactants decrease the surface tension of the smaller airways so that the alveoli or the terminal air sacs do not collapse, which results in less need for supplemental oxygen and ventilatory support.

Common complications include air leak syndromes, CLD, and retinopathy of prematurity (ROP). Surfactant agents may be administered as prevention or prophylactic treatment or as rescue intervention after hyaline membrane disease (HMD) is established. Synthetic surfactants lack the proteins found in animal-derived surfactants and may not be as effective as the latter.

Available evidence based on cost analysis and clinical outcome suggests that surfactants should be administered routinely as prophylaxis in infants younger than 30 weeks' gestation. When used as prophylactic treatment, surfactants should be administered as soon after birth as possible. When administered as rescue treatment, a reasonable guideline is to administer surfactants when the infant reaches an arterial-to-alveolar (a/A) oxygen ratio of 0.22 or less. Typically, this is seen in an infant who requires greater than 35% oxygen to maintain a PaO_2 of 50-80 mm Hg.

A major morbidity of premature birth is CLD, which is defined as receiving supplemental oxygen at 36 weeks' postmenstrual age, which has become more frequently accepted than the former definition of oxygen dependence beyond age of 28 days. BPD is included in the spectrum of CLD and was originally described by Northway et al in 1967 as the clinical sequelae of prolonged ventilation associated with radiographic and pathologic findings.

Lemons et al looked at the outcomes of 4438 infants in the National Institutes of Child Health and Human Development Neonatal Research Network (NICHD) registry with birth weights between 501-1500 g born from 1995-1996. They found that 52% of the infants in the 501- to 750-g group had CLD and 34% of the infants in the 751- to 1000-g group also were affected. Hack et al, looking at 333 ELBW infants born from 1992-1995 also found that of the 241 infants who survived to 20 months' corrected age, 40% (89) had CLD. CLD is also a risk factor for poor neurodevelopmental outcome. The exact reason is not clear but appears to be related to poor growth and prolonged episodes of hypoxia, which may contribute to neuronal injury.

Apnea of prematurity (AOP) is common in ELBW infants and is defined as cessation of breathing, typically lasting 15-20 seconds, with or without bradycardia or cyanosis. The incidence is inversely correlated with gestational age and weight. As many as 90% of infants weighing less than 1000 g at birth have AOP. Apnea can be caused by decreased central respiratory drive, which causes what is termed central apnea. Apnea also can be caused by an obstruction in which no nasal airflow occurs despite initiation of respiration, by a combination of central and obstructive apnea, or by mixed apnea, in which a lack of central respiratory stimulation is followed by airway obstruction.

In addition, apnea can be caused by hypoxia, sepsis, hypoglycemia, neurologic lesions, seizures, and temperature irregularities. Apnea is diagnosed clinically and can be detected via use of cardiorespiratory monitors and pulse oximetry. A pneumogram can be used to illustrate the number and severity of the apneic episodes, with or without bradycardia, in conjunction with a continuous electrocardiogram reading. Treatment of AOP includes nasal continuous positive airway pressure (CPAP) and use of pharmacologic agents, such as theophylline and caffeine citrate. Caffeine appears to be more effective in stimulating the central nervous system and has a wider therapeutic range than theophylline, and caffeine causes less tachycardia than theophylline. Theophylline is more efficacious than caffeine as a bronchodilator and diuretic.

Premature infants who are believed to have AOP at the time of discharge may be sent home with an apnea monitor. In one study, as many as 40% of babies born weighing less than 750 g went home with a monitor; however, the use of home apnea monitors remains controversial. AOP often persists beyond 40 weeks' corrected age, which is longer than was previously believed. AOP does not appear to be related to an increased incidence of sudden infant death syndrome.

Patent ductus arteriosus

In the fetus, the ductus arteriosus is a conduit between the left pulmonary artery and the aorta that results in shunting of blood past the lungs. In full-term newborns, the PDA typically closes within 48 hours of birth because of oxygen-induced prostaglandin production, which constricts the ductus. However, as many as 80% of ELBW infants have a clinically significant PDA, resulting in a left-to-right shunt that causes a variety of symptoms, including a loud systolic murmur, widened pulse pressures, bounding pulses, hyperactive precordium, increased effort to breathe, and, because of a net decrease in systemic cardiac output due to left-to-right shunting, decreased urine output, feeding intolerance, and hypotension. Diagnosis typically is confirmed using echocardiography, and treatment includes decrease of fluid intake, indomethacin administration, and surgical ligation, if necessary.

Indomethacin is used prophylactically at some institutions and is administered in the first 24 hours of life to close a PDA in anticipation of the deleterious effects of a continued PDA in an ELBW infant. Some evidence suggests that prophylactic use of indomethacin has led to decreased symptomatic PDAs and PDA ligations in ELBW infants. Concerns regarding indomethacin and its effects on cerebral and renal blood flow have led to the investigation of the role of intravenous ibuprofen as an agent to close a PDA in preterm infants.

Infection

Infection remains a major contributing factor to the morbidity and mortality of ELBW infants and can present at any point in the clinical course. Early infection that occurs during the first 3-4 days of life is believed to result from maternal factors, particularly if chorioamnionitis was diagnosed prenatally. Late nosocomial infections typically occur after the first week of life and result from endogenous hospital flora. Signs of infection are myriad, may be nonspecific, and include temperature instability (hypothermia or hyperthermia), tachycardia, decreased activity, poor perfusion, apnea, bradycardia, feeding intolerance, increased need for oxygen or higher ventilatory settings, and metabolic acidosis. Laboratory studies may include complete blood count with differential, blood culture, cerebrospinal fluid culture, urine culture, and cultures from indwelling foreign bodies, such as central lines or endotracheal tubes.

The most common causes of early sepsis in the immediate newborn period are group B streptococci (GBS), *Escherichia coli,* and *Listeria monocytogenes*. Nosocomial sources of infection include coagulase-negative staphylococci (CoNS), and *Klebsiella* and *Pseudomonas* species, which may necessitate a different antibiotic regimen than antibiotics typically started after birth for suspected sepsis. CoNS and fungi, most commonly *Candida albicans,* are causes of late-onset sepsis and may manifest with the above-mentioned symptoms and with thrombocytopenia. Importantly, fulminant late-onset clinical sepsis rarely is caused by CoNS and is more commonly secondary to gram-negative organisms. Late-onset sepsis is especially common in ELBW infants who have indwelling catheters, and it may occur in as many as 40% of these infants.

In most institutions, first-line therapy in infants with early sepsis is with ampicillin and gentamicin or a third-generation cephalosporin. Vancomycin should be reserved for proven CoNS infections and organisms resistant to other agents to prevent the emergence of resistant organisms. Vancomycin and a third-generation cephalosporin often are used to treat late-onset sepsis. Therapy with amphotericin commonly is initiated in infants with fungal infections. Cultures should dictate antibiotic management whenever possible.

Necrotizing enterocolitis

NEC is a disease of the premature gastrointestinal tract that represents injury to the intestinal mucosa and vasculature. Incidence of NEC is associated with decreasing gestational age, and it is a dreaded complication of premature birth. NEC accounts for 7.5% of all neonatal deaths. Risk factors include asphyxia or any ischemic insult to the gastrointestinal blood supply. The role of enteral feeding is controversial. Breast milk may have a protective effect but has not been shown to prevent NEC.

Presenting symptoms may be vague and include apnea, bradycardia, and abdominal distention. These symptoms can quickly progress to indicators of increasing sepsis, such as large gastric residuals, metabolic acidosis, and lethargy. Radiographic findings include stacked bowel loops, pneumatosis intestinalis (presence of gas in the bowel wall), portal venous gas, and free air, which indicates perforation of the bowel and is an ominous sign of impending deterioration. NEC usually presents close to the time that the infant is taking full enteral feedings, usually between the second and third weeks of life.

NEC is commonly managed with antibiotics, elimination of oral intake, gastric decompression by nasogastric tube, and supportive measures to correct complications such as metabolic acidosis, thrombocytopenia, and hypotension. Surgical intervention may be necessary if evidence of perforation exists (presence of free air on radiographs) or medical treatment fails. Long-term complications include those related to bowel resection (short gut syndrome), bowel strictures, and risk of abdominal adhesions.

Spontaneous bowel perforation often occurs in the first week of life, presenting earlier than a typical case of NEC. Stark et al showed a strong interaction between postnatal use of dexamethasone and indomethacin on incidence of perforation (19%) in ELBW infants in a trial designed to determine if a 10-day course of postnatal dexamethasone would reduce the risk of CLD or death.

Intraventricular hemorrhage

A hemorrhage in the brain that begins in the periventricular subependymal germinal matrix can progress into the ventricular system. Both incidence and severity of IVH are inversely related to gestational age. ELBW babies are at particular risk for IVH because development of the germinal matrix typically is incomplete. Any event that results in disruption of vascular autoregulation can cause IVH, including hypoxia, ischemia, rapid fluid changes, and pneumothorax. Presentation can be asymptomatic or catastrophic, depending on the degree of the hemorrhage. Symptoms include apnea, hypertension or hypotension, sudden anemia, acidosis, changes in muscular tone, and seizures. One commonly used system classifies IVH into 4 grades, as follows:

- Grade I - Germinal matrix hemorrhage
- Grade II - IVH without ventricular dilatation
- Grade III - IVH with ventricular dilatation
- Grade IV - IVH with extension into the parenchyma

IVH is diagnosed using cranial ultrasound, which usually is performed on ELBW infants during the first week after birth, since most IVHs occur within 72 hours of delivery. Use of antenatal steroids decreases incidence of IVH, and treatment consists of supportive care. Early administration of indomethacin also reduces the risk of IVH when used prophylactically in ELBW infants but may affect urine output and platelet function adversely. Prognosis is correlated with the grade of IVH. The outcome in infants with grades I and II is good; as many as 40% of infants with grade III IVH have significant cognitive impairment, and as many as 90% of infants with grade IV IVH have major neurologic sequelae.

The recent Trial of Indomethacin Prophylaxis in Prematurity (TIPP) demonstrated a decrease in the incidence of severe grades of IVH but no difference in neurodevelopmental outcomes at age 18-24 months. Thus, the question of using such an approach remains unanswered. The use of antenatal steroids has been associated with a decreased incidence of IVH in ELBW infants.

Periventricular leukomalacia

Periventricular leukomalacia (PVL) is defined as damage to white matter that results in severe motor and cognitive deficits in ELBW infants who survive. PVL occurs most often at the site of the occipital radiation at the trigone of the lateral ventricles and around the foramen of Monro. The origin of PVL is believed to be multifactorial; the injury possibly results from episodes of fluctuating cerebral blood flow, which are caused by prolonged episodes of systemic hypertension or hypotension. PVL has been linked to periods of hypocarbic alkalosis. Recently, PVL also has been associated with chorioamnionitis. PVL is diagnosed using brain ultrasound in patients aged 4-6 weeks, and it occurs in 10-15% of ELBW infants. The presence of PVL, particularly cystic PVL, is associated with an increased risk of cerebral palsy; spastic diplegia is the most common outcome.

Nearly all ELBW infants require neurodevelopmental follow-up monitoring to track their progress and to identify disorders that were not apparent during the hospital stay. These infants typically have complicated medical courses and often go home with multiple treatments and medications. In addition to monitoring their immediate medical needs upon discharge, evaluation of cognitive development, vision and hearing ability, and neurodevelopmental progress is important.

As many as 48% of ELBW infants have some type of major neurosensory or neurodevelopmental impairment. Infants with grade III or IV IVH or infants with PVL (cysts in brain parenchyma, typically seen on routine brain ultrasound images in infants aged 4-6 wk) are at the greatest risk for mental retardation. Other risk factors for developmental disabilities include meningitis, asphyxia, delayed head growth, and CLD.

Saigal et al investigated the long-term academic and social outcomes of ELBW infants born from 1977-1982 in Ontario, Canada. ELBW infants performed more poorly at psychometric testing at age 8 years and continued to do so into their adolescence. When the birth weights were stratified, the cohort with birth weights less than 750 g performed worse than the heavier ELBW cohort (750-1000 g), but both groups still required more remedial resources than the control group of term children. However, although this group of children were reported by their parents to have more frequent and more complex limitations to daily functioning, the children and their parents rated the quality of life of the children to be fairly high.

Vision

Retinopathy of prematurity (ROP) is a disease of a premature retina that has not yet fully vascularized. Changes in oxygen exposure have been postulated to cause a disruption in the natural course of vascularization and may result in abnormal growth of blood vessels, which can result in retinal detachment and blindness. All infants with birth weights less than 1000 g should undergo an eye examination by an experienced pediatric ophthalmologist at age 4-6 weeks and, depending on the results, at least every 2 weeks thereafter until the retina is fully vascularized.

If ROP is present, its stage and location dictate management, which can range from repeat examinations 1 week later to laser surgery or cryotherapy. The presence of plus disease, or tortuosity of the retinal vessels, is a poor prognostic sign and requires immediate treatment. Infants with ROP are also at greater risk for sequelae, such as myopia, strabismus, and amblyopia. ELBW infants without ROP should have a follow-up eye examination at age 6 months.

Hearing

All infants should undergo hearing examinations prior to discharge, using either evoked otoacoustic emissions or brainstem auditory evoked potentials. ELBW infants are at higher risk for hearing impairment because of their low birth weights. Other risk factors include meningitis, asphyxia, exchange transfusions, and administration of ototoxic drugs such as gentamicin. In addition, ELBW infants should undergo repeat hearing examinations at age 6 months.

Other therapy

For problems with cognitive and neurodevelopmental development, physical and occupational therapy and early intervention development programs should be some of the options available. Such programs should be coordinated with the infant's pediatrician and with the follow-up care clinic. As an increasing number of babies are born and continue to survive with birth weights less than 1000 g; optimizing their chances for a healthy productive life is important.

As the number of ELBW infants increased in the postsurfactant era, so did questions regarding ethical, economic, and legal dilemmas surrounding the care of the infants. The United States is no longer alone in confronting neonatal-perinatal medical, legal, and ethical issues.

Management of anticipated delivery of an ELBW infant and subsequent care require the clinician to make decisions "in the moment of clinical truth." Pellegrino successfully argues that morally defensible difficult decisions must be made with available information and focus on "the morally right and good thing to do in this patient." Information regarding mortality, morbidity, and prognosis changes with time. Using the best information available, the clinician should manage the situation while taking into account the family's wishes and "what is in the best interest of the patient." When resolving bioethical dilemmas facing families and clinicians, the physician must address issues of futility, extension of the dying process, respect for the dignity of life, and pain and suffering. From a legal standpoint in the United States, government regulations exist based on child abuse laws enforced by individual states.

The question of what to do in the case of extreme prematurity (<23 wk) is a difficult one. Gestational age, which typically is based on the mother's recount of her last menstrual period, can differ from the actual gestational age by as much as 2 weeks, even when the latest ultrasound technology is used. Most centers do not have minimum birth weight criteria for resuscitation, and often a "trial of life" may be discussed with the parents before the birth so that the infant can be resuscitated and evaluated for viability after birth. Discussions about treatment or withdrawal of support are often necessary when the family and medical team agree that continuation of medical treatment is not in the infant's best interest.

Naturally, these circumstances raise numerous ethical, moral, and legal issues and sometimes generate more questions than answers. Bioethics consultants and multidisciplinary ethics committees discuss such issues and arrive at recommendations for clinicians and families.

A 1987 California study calculated that the average cost per first-year survivor in infants in neonatal intensive care units with birth weights less than 750 g was $273,900; for those who weighed 750-999 g, average cost was $138,800. However, the overall percentage of costs for infants who died, usually within the first 3 days of life, was small. Hospital bills continue to rise as a result of advancing technology and may rise even higher if the child needs any type of rehabilitation or follow-up care. The infant's family undergoes severe emotional and financial stress with the birth of an extremely premature infant, and they often are confused, angry, and frustrated by resulting issues. In addition, society in general is affected by these infants, some of whom are significantly cognitively or physically impaired and require lifelong public assistance.

Since no single rule has been written regarding what to do in the impending birth of an extremely premature infant, both the obstetrician and the neonatologist must talk with the parents regarding what can be expected after delivery. The role of the medical team is (1) to fully inform the parents, based on the expected gestational age and any other pertinent prenatal data, of the most recent local and national statistics describing morbidity and mortality; (2) to describe procedures that may occur after the infant is delivered; and (3) to answer any questions the parents may have regarding the infant's care. Remember that opportunities to discuss management options will be available after the infant is born, allowing better evaluation of the infant and time for the family to fully comprehend the situation.

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Extremely Low Birth Weight Infant excerpt

Fluid, Electrolyte, and Nutrition Management of the Newborn

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INTRODUCTION	Section 2 of 11

This article describes important principles and specific methods of fluid, electrolyte, and nutrition (FEN) management in newborns, particularly infants requiring special attention, including premature, very low birth weight (VLBW), and extremely low birth weight (ELBW) neonates. FEN management in the context of acid-base disorders (eg, acidosis, alkalosis, metabolic, respiratory, mixed disorders), hypercalcemia, magnesium disorders, metabolic disorders, and complications of total parenteral nutrition (TPN) are not discussed in this article.

FEN management is important because most infants in a neonatal intensive care unit (NICU) require IV fluids. If inappropriate fluids are administered, serious morbidity can result from fluid and electrolyte imbalances.

FLUID AND ELECTROLYTE PRINCIPLES	Section 3 of 11

The principles of fluid and electrolyte balancing include the following points:

- Total body water (TBW) equals intracellular fluid (ICF) plus extracellular fluid (ECF).
- ECF equals ICF (plasma and lymph in the vessels) plus interstitial fluid (between cells).
- Characteristics of fluid changes
  - Neonates are born with an excess of TBW, primarily ECF, which needs to be removed.
  - Adult bodies are 60% water (20% ECF, 40% ICF).
  - Term neonate bodies are 75% water (40% ECF, 35% ICF), and term neonates usually lose 5-10% of their weight in the first week.
  - Preterm neonates have more water (at 23 weeks' gestation, 90% water composed of 60% ECF and 30% ICF), and they may lose 5-15% of their weight in the first week.

- Characteristics of insensible water loss
  - Insensible water loss (IWL) is water loss that is not readily measured, and IWL is water lost via evaporation through the skin (two thirds) or respiratory tract (one third).
  - IWL depends on gestational age; the earlier the gestational age of the preterm infant, the greater the IWL.
  - The magnitude of IWL also depends on the postnatal age. Since skin thickens with age, the IWL decreases as neonates age.
  - All other measurable sources of fluid and electrolyte losses need to be considered as well. Sources include stool (eg, diarrhea and ostomy), nasogastric (NG) or orogastric (OG) drainage, and cerebrospinal fluid (CSF), including ventricular drainage.
- Renal function changes: Neonates have a decreased capacity to concentrate or dilute urine in response to changes in intravascular fluid status, and they are at risk for dehydration or fluid overload. The normal maturation of renal function that occurs with increasing gestational and postnatal age also plays a role in determining fluid requirements.

A number of conditions can impact neonatal renal function adversely. The presence of several of these can be suspected on the basis of information found in the prenatal and neonatal history.

Maternal history

- A newborn's fluid and electrolyte (FE) status partially reflects the mother's FE status. For example, excessive administration of oxytocin or hypotonic intravenous fluid (IVF) to the mother can cause hyponatremia in the neonate at birth.
- Placental dysfunction (eg, from hypertension in pregnancy) can affect intrauterine growth adversely. Infants who are growth retarded at birth (<10th percentile for gestational age) tend to grow poorly despite adequate nutrition after birth.
- Poorly controlled maternal diabetes may be associated with renal vein thrombosis. This can affect an infant's renal function adversely.
- Maternal use of angiotensin-converting enzyme (ACE) inhibitors, such as captopril, during pregnancy can lead to acute renal failure in infants. Other medications administered to the mother, including indomethacin, furosemide, and aminoglycoside, also may affect renal function in the neonate.
- Antenatal steroids may increase skin maturation, thereby decreasing IWL and the risk of hyperkalemia (Omar, 1999; Omar, 2000).

Newborn history

- The presence of polyhydramnios or oligohydramnios can be associated with either congenital nephrotic syndrome or congenital renal dysfunction.
- Severe in utero hypoxemia or birth asphyxia may lead to acute tubular necrosis.
- Posterior urethral valves can be suspected when weak urinary stream and dribbling are present.
- The environment in which an infant is cared for also affects fluid loss. An environment with high ambient humidity decreases IWL, while the use of a radiant warmer or phototherapy may significantly increase an infant's IWL.

Clinical evaluation

- Weight factors
  - Sudden changes in an infant's weight do not necessarily correlate with changes in intravascular volume. An infant's weight rises significantly for a number of reasons while intravascular volume has decreased. Examples include the long-term use of paralytic agents and peritonitis, both of which can lead to increased interstitial fluid volume and increased body weight but decreased intravascular volume.
  - While growth charts are valuable in following growth parameters and nutritional status over time, they play little role in the daily management of fluid and electrolyte balances.
- Skin and mucosa manifestations: Altered skin turgor, a sunken anterior fontanelle (AF), and dry mucous membranes are not sensitive indicators of dehydration in babies. Remembering that premature infants have poorly keratinized skin that leads to a marked elevation in IWL is important.
- Cardiovascular signs
  - Tachycardia can result either from too much ECF (as can be seen in congestive heart failure [CHF]) or from too little ECF (as can be seen in hypovolemia).
  - Although delayed capillary refill occurs in low cardiac output states, it also can be seen in infants with peripheral vasoconstriction resulting from cold stress.
  - Hepatomegaly can occur in neonates with ECF excess, especially in CHF.
  - As a result of an infant's compensatory mechanisms, blood pressure (BP) readings usually are normal, with mild or moderate hypovolemia. With severe hypovolemia, hypotension is present almost invariably.

Laboratory evaluation

Depending on the clinical situation and the suspected etiology of fluid and electrolyte derangements, some or all of the following tests may be warranted:

- Serum electrolyte, urea nitrogen, creatinine, and plasma osmolarity levels: Keep in mind that over the first 12-24 hours, results of these tests may still reflect maternal values.
- Accurate total urine output and total fluid intake
- Urine electrolytes and specific gravity: If the infant is being treated with diuretics, such as furosemide, results of these tests are difficult to interpret.
- Calculation of the fractional urinary excretion of sodium in relation to creatinine (FENa)
- Blood gas analysis: Metabolic acidosis may be a marker of inadequate tissue perfusion.

FLUID AND ELECTROLYTE MANAGEMENT	Section 5 of 11

Management goals

FE management is a balancing act between intake and output. Primary goals are to maintain the appropriate ECF volume, ECF and ICF osmolality, and ionic concentrations.

Allow the initial loss of ECF over the first week, as reflected by weight loss, while maintaining normal intravascular volume and tonicity, as reflected by heart rate, urine output, and electrolyte and pH values. Subsequently, maintain water and electrolytes while supplying requirements for body growth. Individualize the approach rather than relying on a cookbook formula.

Total fluid equals maintenance requirements (IWL plus urine plus stool water) plus growth requirements. In the first few days, IWL is the largest component of lost fluids. Later, as the renal solute load increases, the amount of water the kidneys need to excrete this load increases (80-120 cal/kg/d equals 15-20 mOsm/kg/d, which means that 60-80 mL/kg/d is needed to excrete wastes). Stool requirement usually is 5-10 mL/kg/d. As infants add tissue, they also need to add water to maintain normal ECF and ICF volumes. Since weight gain is 70% water, an infant growing 30-40 g/d requires 20-25 mL/kg/d of water.

Factors modifying fluid requirements

As the skin matures postnatally, the IWL decreases. Elevated body and environmental temperatures increase IWL. Radiant warmers increase IWL by 50%, phototherapy increases IWL by 50%, and the use of a plastic heat shield reduces IWL by 10-30%. Environmental humidification decreases IWL from the skin and respiratory mucosa by up to 30%. Skin breakdown and skin defects (eg, omphalocele) increase IWL proportionally to the area affected.

Electrolyte requirements

- For the first 12-24 hours, sodium, potassium, and chloride usually are not required.
- Later in the first week, needs are 1-2 mEq/kg/d for potassium and 2-4 mEq/kg/d for sodium and chloride.
- During the active growth period after the first week, needs for potassium increase to 2-3 mEq/kg/d, and for sodium and chloride to 3-5 mEq/kg/d.
- Some of the smallest preterm infants have sodium requirements as high as 6-8 mEq/kg/d because of the decreased capacity of the kidneys to retain sodium.

Fluids and electrolytes in common neonatal conditions

- Respiratory distress syndrome (RDS): Infants with RDS need appropriate fluid replacement. Administration of excessive fluid can lead to hyponatremia and volume overload, worsening the pulmonary condition and increasing the risk of developing bronchopulmonary dysplasia (BPD). Inadequate fluid administration leads to hypernatremia and dehydration
- Bronchopulmonary dysplasia: As a result of an increased work of breathing, infants with BPD have higher energy requirements. Diuretics often are prescribed in these infants, which can lead to electrolyte disturbances.
- Patent ductus arteriosus (PDA): Avoiding volume overloading is critical in infants with a PDA, since this often significantly worsens their respiratory status. This is especially important when indomethacin is prescribed to treat PDA, since indomethacin can decrease urine output significantly.
- Perinatal asphyxia: Infants who have experienced perinatal asphyxia usual have involvement of multiple organ systems. They are prone to acute tubular necrosis and significant oliguria, and the degree of CNS injury may produce the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Restricting fluid intake to minimize the risk of volume overload often is necessary.

Common electrolyte problems

- Sodium (Na)
  - Hyponatremia is defined as a serum sodium level less than 130 mEq/L. Usually, this is not a cause for concern until the serum sodium has dropped to less than 125 mEq/L. Remember that hyponatremia usually results from excessive free water intake. However, especially in the extremely premature infant or infants with increased sodium losses, inadequate sodium intake can contribute to the development of hyponatremia.

- o Hypernatremia is defined as a serum sodium level greater than 150 mEq/L. Usually, this is not a cause for concern until the serum sodium level has risen to greater than 150-155 mEq/L. Hypernatremia typically is seen in the first few days of life in ELBW micropremies and is most often the result of inadequate free water intake to compensate for very high IWLs. Very rarely, hypernatremia is the result of excessive administration of sodium in either the diet or intravenous fluids. The usual causes of excessive administration of sodium are administration of sodium bicarbonate to infants with pulmonary hypertension or metabolic acidosis in an effort to increase pH levels.
- Potassium (K)
  - o Remember that most of the potassium in the body is contained in the intracellular compartment; therefore, serum potassium levels often do not indicate total-body potassium stores accurately.
  - o Serum potassium levels also depend on blood pH levels, since pH affects the distribution of potassium between ICF and ECF compartments. A handy rule is that each 0.1 unit of pH change results in a 0.3-0.6 mEq/L change in the serum potassium level. The potassium level rises with acidosis, while it drops with alkalosis.
  - o Hypokalemia is defined as a serum potassium level less than 3.5 mEq/L. Unless the patient is receiving digoxin therapy, hypokalemia is rarely cause for concern until the serum potassium level is less than 3.0 mEq/L. Hypokalemia often results from chronic diuretic use and unreplaced electrolyte loss from NG drainage. ECG manifestations of hypokalemia include a flattened T wave, prolongation of the QT interval, or the appearance of U waves. Severe hypokalemia can produce cardiac arrhythmias, ileus, and lethargy. When significant, this condition is treated by slowly replacing potassium either intravenously or orally.
  - o Hyperkalemia is defined as a serum potassium level greater than 6 mEq/L, measured in a nonhemolyzed specimen. Hyperkalemia is of far more concern than hypokalemia, especially when serum potassium levels exceed 6.5 mEq/L or if ECG changes have developed. ECG manifestations of hyperkalemia are a progression from peaked T waves, as the earliest sign, to a widened QRS configuration, bradycardia, tachycardia, supraventricular tachycardia (SVT), ventricular tachycardia, and ventricular fibrillation. Causes of hyperkalemia include potassium release from damaged cells following intraventricular hemorrhage (IVH), trauma, and intravenous hemolysis. In addition, severe acidosis and decreased urinary potassium excretion contribute to elevations in serum potassium. Finally, hyperkalemia may be one of the earliest manifestations of congenital adrenal hyperplasia.
  - o Management of significant hyperkalemia may include the following:
    - All administration of potassium is discontinued.
    - Calcium gluconate 100-200 mg/kg (1-2 mL/kg of 10% solution) is administered as a slow IV infusion over 5-10 minutes.
    - Alkalinization is performed, either with hyperventilation or sodium bicarbonate 1-2 mEq/kg IV.
    - Insulin is administered to assist in driving potassium into the ICF compartment. Insulin must be administered with glucose as a combined infusion to avoid producing hypoglycemia.
    - Medications are administered to enhance potassium excretion, including furosemide 1 mg/kg IV or sodium polystyrene sulfonate (Kayexalate) 1 g/kg PR (do not use sorbitol-containing products and do not administer orally). Several hours must pass before any effect is observed with either of these medications.
    - Dialysis or exchange transfusion may be used to assist in more rapidly removing potassium from the body.
- Calcium (Ca)
  - o Total serum calcium levels in term infants decline from values of 10-11 mg/dL at birth to 7.5-8.5 mg/dL over the first 2-3 days of life. Approximately 50% of the total calcium is in the ionized form and is the only biologically available form of calcium. Ionized calcium values, rather than total values, correlate better with calcium functions, such as cardiac contractility. Therefore, many centers currently rely exclusively on measurements of ionized calcium.

- o Calcium concentrations can be reported either in milligrams per deciliter (mg/dL) or in millimolar units (mmol/L). Conversion between the two methods is accomplished easily by dividing by 4 (eg, 4 mg/dL of ionized calcium equals 1 mmol/L)
- o Hypercalcemia is rarely observed in neonates and is defined as a total serum calcium concentration higher than 11 mg/dL or an ionized calcium concentration higher than 5 mg/dL (1.25 mmol/L).
- o Hypocalcemia occurs more commonly and is defined as a total serum calcium concentration less than 7 mg/dL or an ionized calcium concentration less than 4 mg/dL (1 mmol/L).
- o Early-onset hypocalcemia may occur within the first 3 days in premature infants born to mothers with poorly controlled diabetes or in infants who experienced perinatal asphyxia. If the infant is asymptomatic and has a total serum calcium level higher than 6.5 mg/dL or an ionized calcium level higher than 0.8-0.9 mmol/L, close observation alone is appropriate. Calcium supplementation should be provided if the total serum calcium level is less than 6.5 mg/dL or if the ionized level is less than 0.8-0.9 mmol/L.
- o Late-onset hypocalcemia develops after the first week of life and usually is associated with conditions with high serum phosphate levels, including hypoparathyroidism, maternal anticonvulsant use, and vitamin D deficiency. Vitamin D deficiency usually resolves with reduction of the renal phosphate load or vitamin D supplementation.

Common fluid problems

Oliguria is defined as a urine output less than 1 mL/kg/h. Oliguria can be caused by a variety of conditions that can be classified as prerenal, renal, or postrenal problems. Urine output often is less than 1 mL/kg/h during the first 12-18 hours after birth. Most healthy term babies urinate within the first 12 hours; however, a small number of healthy infants may not urinate until 24-36 hours after birth. Persistent oliguria beyond 36 hours should be evaluated in an otherwise healthy infant.

NUTRITION PRINCIPLES	Section 6 of 11

Nutrient requirements

- Energy, measured as cal/kg/d
- Carbohydrates
- Water
- Minerals and trace elements
- Protein
- Vitamins
- Fat

Energy needs

- The exact energy needs of a given neonate depend upon several factors, including postnatal age, weight, gest age, route of energy intake, growth rate, activity, and thermal environment.
- Infants who are ill or experiencing stressful situations (sepsis, surgery, BPD) have higher energy requirements.
- Infants receiving parenteral nutrition need less energy for adequate growth. Since they do not need to absorb the provided nutrients, they have no fecal losses. As a result, 70-90 cal/kg/d with 2.4-2.8 g/kg/d of protein may be adequate for growth.
- Protein is not an ideal source of energy; rather, it is provided as a building block for new tissue. If adequate nonprotein calories are provided, the nitrogen balance in the infant is positive, and the protein provided is used to build new tissue. Therefore, even if energy

intake from protein is included in calculations of total energy intake, not all the protein-derived calories are available for energy expenditure.

- The ideal energy ratio is to provide 65% of the energy as carbohydrates and 35% as lipids. Providing more than 165-180 cal/kg/d is of no benefit.
- As an example, the total energy needs of a growing enterally fed premature infant without any acute illness are listed as follows:
  - Resting expenditure: 50 cal/kg/d
  - Minimal activity: 4-5 cal/kg/d
  - Occasional cold stress: 10 cal/kg/d
  - Fecal loss (10-15% of intake): 15 cal/kg/d
  - Growth (4.5 cal/g of growth): 45 cal/kg/d
  - Total required to produce a 10 g/d weight gain: 125 cal/kg/d

Goals for nutrition management

The primary goal is to provide energy and nutrients in sufficient quantities to allow normal growth and development. Although the goal is to have growth rates that follow either the intrauterine growth curve for premature infants or the postnatal growth curve for term infants, this is rarely achieved during the acute phase of an infant's illness.

Calculations

When calculating FEN requirements, most practitioners use an infant's birth weight until the infant has regained the birth weight. Thereafter, daily weight is used in calculations. Total parenteral nutrition (TPN) can be started on the first or second day of life in infants who are not likely to achieve total enteral nutrition within the first week of life. Especially in infants who are ill, protein is required to decrease or prevent catabolism, and starting TPN on the first day is important. The goal for TPN is to provide 90-100 kcal/kg/d with 2.5-3 g/kg/d protein.

- Fluid requirement: Calculate the infant's daily fluid (water) requirement. Then, determine the delivery method, either parenteral (IV) or enteral (OG/PO).
- Energy requirement: Calculate the amount of energy required.
  - Determine the specific amounts and sources of carbohydrates and lipids.
  - Determine the amount of protein to deliver based on the total number of calories to be provided. Keep in mind that an infant needs an adequate number of nonprotein calories (150-200 kcal/g nitrogen) to have a positive balance of nitrogen. Most practitioners start at 1.5 g/kg/d of protein on the first or second day and increase daily by 0.5-1.0 g/kg/d, as tolerated. Various amino acid preparations are commercially available for use in the neonate (eg, TrophAmine).
- Determine the amounts of vitamins and trace elements to deliver.

Carbohydrate

IV dextrose provides most of the energy in TPN. The caloric content of aqueous dextrose is 3.4 kcal/g glucose, which is equal to 34 kcal/100 mL of D10W. As a result of the high osmolarity of concentrated dextrose solutions, the maximum dextrose concentration that can be delivered safely through a peripheral vein is 12.5%. Even with central venous access, a dextrose concentration exceeding 25% usually is not required.

A glucose infusion rate expressed in mg glucose/kg/min is the most appropriate way to express glucose administration, since the rate accounts for both the glucose concentration and rate of infusion. Very small premature infants weighing less than 1500 g demonstrate impaired glucose tolerance. For this reason, in infants weighing less than 1 kg, start at an infusion rate of 6 mg/kg/min. In infants weighing 1-1.5 kg, start at 8 mg/kg/min. If the glucose infusion rate is

excessive, hyperglycemia develops. If blood glucose levels are greater than 150-180 mg/dL, glucosuria occurs, producing an osmotic diuresis and dehydration. This can be controlled either by decreasing the glucose infusion rate or by treating the infant with insulin.

Fat

At least 3% of the total energy should be supplied as essential fatty acids (EFA). This can be accomplished by providing Intralipid 0.5 g/kg/d 3 times per week. Parenteral fat usually is provided as a 20% lipid emulsion made from soybeans (eg, Intralipid). Intralipid is a concentrated source of energy with a caloric density of 2 kcal/mL (for 20% Intralipid). Most practitioners start with 0.5-1.5 g/kg/d on the first day and increase steadily to 3-3.5 g/kg/d. Limiting Intralipid infusions in infants with sepsis and severe lung disease is generally recommended.

Neonates with hyperbilirubinemia who are on phototherapy often have Intralipid intake restricted to less than 2 g/kg/d (especially if bilirubin levels are rising while on phototherapy) because some evidence exists that high lipid-emulsion intake may decrease bilirubin binding (Spear, 1985). Many practitioners monitor triglyceride levels and adjust infusion rates to maintain triglyceride levels of less than 150 mg/dL.

Protein

Term infants need 1.8-2.2 g/kg/d along with adequate nonprotein energy for growth. Preterm VLBW infants need 3-3.5 g/kg/d along with adequate nonprotein energy for growth. Usually, providing more than 4 g/kg/d of protein is not advisable. Infants under stress or who have cholestasis usually are limited to 2.5 g/kg/d of protein because it has been observed that the severity of TPN-induced cholestasis may depend on the duration of TPN and the amount of amino acids infused (Sankaran, 1985; Yip, 1990).

Protein supplementation should be started early, as soon as FE requirements have stabilized. Very high protein intake, at greater than 5-6 g/kg/d, may be dangerous. Maintain a nonprotein-to-protein calorie ratio of at least 25-30:1. The current role of supplements, such as additional glutamine, inositol, and carnitine, is under investigation. Although a physiologic rationale exists for their use, they have not yet been shown to be of benefit in large randomized controlled trials; however, to date, small clinical trials are promising.

Minerals (other than sodium, potassium, chloride)

- Calcium and phosphorus (Ca and P): Once protein intake has been started, calcium and phosphorous should be added to the TPN. Take care to ensure that solubility is not exceeded. If this happens, calcium and phosphorous may precipitate spontaneously.
- Magnesium (Mg): Supplemental Mg should be added to TPN once protein has been added.

Vitamins and trace elements

- Vitamins A, D, E, and K are fat soluble.
- Vitamins B-1, B-2, B-6, B-12, C, biotin, niacin, pantothenate, and folic acid are water soluble.
- Vitamin supplementation should be started as soon as protein is added to the TPN. The addition of a commercially available neonatal vitamin preparation provides appropriate quantities of all vitamins, except possibly vitamin A. Evidence exists that therapeutic doses of vitamin A (5000 IU administered IM 3 times/wk) may reduce the incidence of chronic lung disease and other long-term adverse outcomes in ELBW infants.
- The trace elements zinc, copper, selenium, chromium, manganese, molybdenum, and iodine also should be added to TPN once protein is started. This can be easily accomplished by the addition of a commercially available solution containing trace elements.

Energy

- With enteral nutrition, human milk and standard infant formulas (20 cal/oz) provide 67 cal/100 mL. In general, human milk is the preferred source of enteral nutrition because of its trophic and immunologic properties. Evidence is substantial that necrotizing enterocolitis is lower in preterm infants fed with breast milk.
- Higher caloric densities include 22 cal/oz and 24 cal/oz formulas. Formulas with caloric densities higher than 24 cal/oz should be used with caution, as they often have a very high renal solute load and can lead to dehydration.

Carbohydrate

- Lactose is the carbohydrate source in human milk and in most standard formulas given to term infants. Lactose provides 40-45% of the energy.
- In preterm infant formulas, lactose provides 50% of the carbohydrates and glucose polymers provide 50%. This is because of the lower intestinal lactase levels and relatively higher intestinal glycosidase levels in premature infants. The use of glucose polymers (rather than monosaccharides or disaccharides) also helps maintain a lower osmolality.
- Soy and lactose-free formulas use sucrose, maltodextrins, and glucose polymers as the carbohydrate sources.

Fat

- With enteral nutrition, approximately 50% of the energy is derived from fat. If more than 60% of the energy is derived from fat, risk of ketosis is increased.
- Medium-chain triglycerides can be absorbed without pancreatic lipase or bile salt emulsification. As a result, preterm infant formulas have a higher percentage of fat supplied as medium-chain triglycerides.

Protein

- Protein requirements of 1.8-2.2 g/kg/d are readily provided to term infants by human milk and standard infant formulas.
- Preterm infant formulas have a higher protein content to allow delivery of the necessary 3-3.5 g/kg/d.

Minerals, vitamins, and trace elements

- Calcium, phosphorous, and magnesium
  - During the third trimester, accretion rates for calcium (120-150 mg/kg/d) and phosphorous (75-85 mg/kg/d) are higher than rates that can be provided in premature infants receiving human milk. As a result, a human milk fortifier is essential, and premature infants fed human milk must receive supplementation to minimize the risk of osteopenia of prematurity.
  - Premature infant formulas have a much higher concentration of these minerals, which helps approximate the third trimester accretion rates in infants receiving these formulas.
  - Human milk and term and premature infant formulas all provide amounts of magnesium adequate to meeting an infant's nutritional requirements if the infant is receiving at least 100 cal/kg/d.

- Iron
  - To minimize the risk of iron deficiency anemia, all formula-fed term infants should receive iron fortified formulas. Breastfed term infants should receive supplemental iron beginning at age several months.
  - Premature infants should be started on supplemental iron once they are receiving full enteral feedings regardless of whether they are fed human milk or premature infant formula.
- Vitamins and trace elements
  - Full-term infants fed standard infant formula do not routinely require vitamin supplements, since adequate quantities of all of the vitamins are present in the formula.
  - Full-term infants fed human milk should receive supplemental vitamin D to minimize the risk of osteopenia and rickets.
  - Premature infants fed human milk without human milk fortifier should be started on a multivitamin supplement as soon as they are receiving full enteral nutrition.
  - Premature infants receiving human milk with human milk fortifier or standard premature infant formulas should not routinely require additional vitamin supplements.

Special formulas

A number of special infant formulas are available to meet the very specific dietary needs of small groups of patients who cannot be maintained on standard term or premature infant formulas. These formulas include soy-based formulas, elemental formulas, and formulas with unique protein, fat, and carbohydrate content.

As a result of the low calcium and phosphorous contents of soy-based formulas, they are not appropriate for premature infants. Specialty formulas are available for infants with galactosemia, phenylketonuria, short gut syndrome, and protein allergy, as well as many other conditions.

ENTERAL FEEDING METHODS	Section 9 of 11

Premature infants in the NICU usually are fed by OG or NG tube until they are sufficiently mature to coordinate sucking, swallowing, and breathing. Then, the transition is made gradually to feeding by mouth (PO) at the breast or bottle. Staff at many NICUs encourage nonnutritive sucking, which may facilitate the tube-to-oral (bottle/breast) feeding transition.

- Initiation and advancement of feedings: Variation between NICUs and, sometimes, between neonatologists at a single unit is marked regarding when feedings are commonly initiated. Currently, some evidence exists that trophic or minimal enteral feedings are safe and well tolerated. In this technique, small volumes are fed to infants for a few days without significant increments. Many neonatologists start feedings within the first week of life and advance the feedings at a rate dependent on gestational age, degree of illness, and other clinical factors. Although some retrospective studies suggested that a rapid increase in feedings may predispose infants to necrotizing enterocolitis, prospective studies have not confirmed this. In general, most neonatologists advance feedings over a period ranging from 5-15 days in ELBW infants and over 4-10 days in neonates weighing 1000-1500 g.
- OG feedings: Conventionally, infants receive intermittent bolus gavage feedings over 10-20 minutes (by gravity) every 2-3 hours. Feedings also may be administered continuously using an infusion pump. Currently, no evidence strongly indicates that one method of feeding is superior to the other.
- Transpyloric feedings: These feedings initially were believed to reduce the risk of gastroesophageal reflux. However, studies have shown a high rate of complications using the transpyloric route, with no additional benefits; hence, it is not often used unless feeding intolerance using NG or OG tubes is marked (Macdonald, 1992).
- Fortification: Infants on breast milk commonly are fed fortified breast milk, which increases energy and mineral intake. That infants fed fortified breast milk have improved short-term

growth and bone mineral content has been documented; however, evidence of long-term benefit is insufficient. At present, whether breast milk feeding (with or without fortification) improves long-term neurodevelopment compared to preterm formula is controversial.

- Supplementation: Supplementation with long-chain polyunsaturated fatty acids (LCPUFAs), such as docosahexaenoic acid (DHA) and arachidonic acid (AA), has been recommended for preterm infants on physiologic grounds. Although visual maturation may possibly be somewhat accelerated, no long-term benefits have been demonstrated yet.
- Feedings at discharge: At discharge, premature infants usually are fed either breast milk or formula (22 cal/oz or 20 cal/oz). Some evidence exists that 22-cal/oz formula may lead to slightly better nutritional outcomes, probably because of its higher energy, calcium, and phosphate content.

PICTURES	**Section 10 of 11**

Picture 1. Fluid, electrolyte, and nutrition management of the newborn. This patient is an ill preterm infant, a common situation requiring fluid, electrolyte, and nutrition management in a neonatal intensive care unit.

Picture 2. Fluid, electrolyte, and nutrition management of the newborn. Radiograph depicts necrotizing enterocolitis in a preterm infant. Note the extensive pneumatosis intestinalis and the portal venous air. This situation often requires long-term administration of total parenteral nutrition.
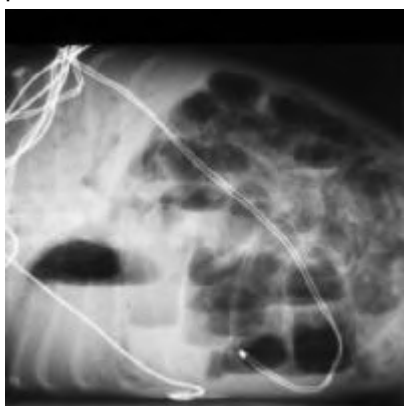
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Fluid, Electrolyte, and Nutrition Management of the Newborn excerpt

Hemolytic Disease of Newborn

Last Updated: March 14, 2003

Synonyms and related keywords: HDN, erythroblastosis fetalis, transplacental hemorrhage, fetomaternal hemorrhage, alloimmunization, hemolysis, hyperbilirubinemia, jaundice, kernicterus, nonimmune hydrops fetalis

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INTRODUCTION	Section 2 of 11

Background: A French midwife was the first to report hemolytic disease of the newborn (HDN) in a set of twins in 1609. In 1932, Diamond and colleagues described the relationship of fetal hydrops, jaundice, anemia, and erythroblasts in the circulation, a condition later called erythroblastosis fetalis. Levine later determined the cause after Landsteiner and Weiner discovered the Rh blood group system in 1940. In 1953, Chown subsequently confirmed the pathogenesis of Rh alloimmunization to be the result of passage of Rh-positive fetal red blood cells after transplacental hemorrhage into maternal circulation that lacked this antigen.

Pathophysiology: Although the Rh antibody was and still is the most common cause of severe HDN, other alloimmune antibodies belonging to Kell (K and k), Duffy (Fya), Kidd (Jka and Jkb), and MNSs (M, N, S, and s) systems do cause severe HDN. Rh blood group antigens are determined by at least 2 homologous but distinct membrane-associated proteins. Two separate genes located on chromosome 1 encode Rh proteins. Rh-negative phenotype represents absence of D protein on RBCs and results from deletion of the *RHD* gene on both chromosomes. Rh antigens exist in 3 loci: Cc, Dd, and Ee. Expression is limited to RBCs, with an increasing density during their maturation, unlike the ABH system, which exists in a wide variety of tissues. Rh antigen is not expressed on RBC progenitors. Of individuals who are Rh positive, 45% are homozygous and 55% are heterozygous.

Frequency of Rh negativity is higher in whites (15%) than in blacks (5%), and it is rare in Asians. The paternal heterozygosity determines the likelihood of an Rh-positive child being born to an Rh-negative mother. The Kleihauer-Betke acid elution technique that determines the proportion of fetal RBCs in maternal circulation has shown the incidence of fetomaternal hemorrhage to be 75% of all pregnancies. Incidence and degree of such hemorrhage appears to increase with gestation. Risk is also increased in pregnancies complicated by placental abruption, spontaneous or therapeutic abortion, and toxemia, as well as after cesarean delivery and ectopic pregnancy.

Procedures such as amniocentesis, chorionic villus sampling, and cordocentesis also increase the risk of alloimmunization. Because in most pregnancies the transplacental hemorrhage is less than 0.1 mL, most women are sensitized as a result of small undetectable fetomaternal hemorrhage.

After the initial exposure to a foreign antigen, the maternal immune system produces antibodies of the immunoglobulin M (IgM) isotype that do not cross the placenta, and later it produces antibodies of the IgG isotype that traverse the placental barrier. This is termed the primary response, and it is dose dependent (documented in 15% of pregnancies with 1 mL of Rh-positive cells in an Rh-negative individual versus 70% of pregnancies after 250 mL). A repeat exposure to the same antigen rapidly induces the production of IgG. This secondary immune response can be induced with as little as 0.03 mL of Rh-positive RBCs.

Risk of Rh immunization after delivery of the first child to a nulliparous Rh-negative mother is 16% if the Rh-positive fetus is ABO compatible with its mother, 2% if ABO incompatible, and 2-5% after an abortion. The ABO-incompatible RBCs are rapidly destroyed in the maternal circulation, reducing the likelihood of exposure to the immune system. The degree of Rh sensitization of the mother is directly related to the amount of fetomaternal hemorrhage (ie, 3% with <0.1 mL versus 22% with >0.1 mL).

After sensitization, maternal anti-D antibodies cross the placenta into fetal circulation and attach to Rh antigen on fetal RBCs, which form rosettes on macrophages in the reticuloendothelial system, especially in the spleen. These antibody-coated RBCs are lysed by lysosomal enzymes released by macrophages and natural killer lymphocytes, and they are independent of the activation of the complement system.

Prolonged hemolysis leads to severe anemia, which stimulates fetal erythropoiesis in liver, spleen, bone marrow, and extramedullary sites, such as skin and placenta. In severe cases, this can lead to displacement and destruction of hepatic parenchyma by erythroid cells, resulting in dysfunction and hypoproteinemia. Destruction of RBCs releases heme that is converted to unconjugated bilirubin. Hyperbilirubinemia becomes apparent only in the delivered newborn because the placenta effectively metabolizes bilirubin. HDN due to Kell sensitization results in hemolysis and suppression of erythropoiesis because the Kell antigen is expressed on the surface of erythroid progenitors.

Hemolysis associated with ABO incompatibility is limited to type O mothers with fetuses who have type A or B blood. In mothers with type A and B blood, naturally occurring antibodies are of IgM class, which do not cross the placenta, whereas in type O mothers, the antibodies are predominantly IgG in nature. Because A and B antigens are widely expressed in a variety of tissues besides RBCs, only small portion of antibodies crossing the placenta is available to bind to fetal RBCs. In addition, fetal RBCs appear to have less surface expression of A or B antigen, resulting in few reactive sites—hence the low incidence of significant hemolysis in affected neonates.

Frequency: **In the US:** Before the establishment of modern therapy, 1% of all pregnant women developed Rh alloimmunization. Since the advent of routine prophylaxis of at-risk women, incidence of Rh sensitization is reduced to 11 cases per 10,000 births with less than 10% requiring intrauterine transfusion. Alloimmunization due to Kell antigen accounts for 10% of severely affected fetuses. ABO incompatibility frequently occurs during the first pregnancy and is present in approximately 12% of pregnancies, with evidence of fetal sensitization in 3% of live births. Fewer than 1% of births are associated with significant hemolysis.

Mortality/Morbidity: Nearly 50% of the affected newborns do not require treatment. Approximately 25% are born near term but become extremely jaundiced without treatment and either die (90%) or become severely affected by kernicterus (10%). The remaining 25% of affected newborns are severely affected in utero and become hydropic; about half of newborns are affected before 34 weeks' gestation, and the other half are affected between 34 weeks' gestation and term. Before any interventions were available, the perinatal mortality rate was 50%. Wallerstein introduced exchange transfusion in 1945 and reduced the perinatal mortality rate to 25%. Later, Chown suggested the early delivery of those severely affected nonhydropic fetuses by 34 weeks' gestation followed by prompt exchange transfusion, and the mortality rate was further reduced to the current rate of 16%.

History: Women at risk for alloimmunization should undergo an indirect Coombs test and titers at their first prenatal visit. If positive, obtain a paternal blood type and genotype. Obtain serial maternal titers if the father is homozygous. If the father is heterozygous, determine fetal blood type by using polymerase chain reaction testing of fetal cells in amniotic fluid or maternal circulation or by performing cordocentesis. Indicators for severe HDN are previous children with hemolytic disease, rising maternal antibody titers, rising amniotic fluid bilirubin concentration, and ultrasonographic evidence of fetal hydrops (eg, ascites, edema, pleural and pericardial effusions, worsening biophysical profile, decreasing hemoglobin [Hb]).

The major advance in predicting the severity of hemolytic disease was the delta-OD 450 reported by Liley in 1961. The serial values of deviation from baseline at 450 nm and the wavelength at which bilirubin absorbs light are plotted on a Liley curve (see Image 1) against the gestational weeks. The values above 65% on zone 2 are indication of direct fetal monitoring by cordocentesis, and hematocrit (Hct) below 30% or a single value in zone 3 is an indication for intrauterine transfusion. The modified Liley curve (see Image 2) is used to correct for gestation less than 24 weeks because bilirubin levels normally peak at 23-25 weeks' gestation for unaffected fetuses.

Physical: The infant born to an alloimmunized mother shows clinical signs based on severity of the disease. The typical diagnostic findings are jaundice, pallor, hepatosplenomegaly, and hydrops fetalis in severe cases. The jaundice typically manifests at birth or in the first 24 hours after birth with rapidly rising unconjugated bilirubin level. Occasionally, conjugated hyperbilirubinemia is present because of placental or hepatic dysfunction in those infants with severe hemolytic disease. Anemia is most often due to destruction of antibody-coated RBCs by the reticuloendothelial system, and in some infants, anemia is due to intravascular destruction. The suppression of erythropoiesis by intravascular transfusion of adult Hb to an anemic fetus can also cause anemia. Hepatosplenomegaly results from extramedullary hematopoiesis and leads to portal hypertension, contributing to ascites. Anemia is not the only cause of hydrops. Excessive hepatic extramedullary hematopoiesis causes portal and umbilical venous obstruction and diminished placental perfusion because of edema. Increased placental weight and edema of chorionic villi interfere with placental transport. Hydrops fetalis results from fetal hypoxia, anemia, congestive cardiac failure, and hypoproteinemia secondary to hepatic dysfunction. Commonly, hydrops is not observed until Hb drops below approximately 4 g/dL (Hct <15%). Clinically significant jaundice occurs in up to 20% of ABO-incompatible infants.

Causes: In the absence of a positive direct Coombs test result, other causes of pathologic jaundice should be considered, including intrauterine congenital infections; erythrocyte membrane defects; RBC enzyme deficiencies; and nonhemolytic causes, such as enclosed hemorrhages, hypothyroidism, gastrointestinal obstruction, and metabolic diseases. Similarly, hydrops can occur from nonimmune hematologic disorders causing anemia, cardiac failure from dysrhythmia, congenital heart defects, and infections (eg, syphilis, cytomegalovirus [CMV], Parvovirus).

- Common causes for HDN

    - Rh system antibodies
    - ABO system antibodies

- Uncommon causes - Kell system antibodies
- Rare causes

    - Duffy system antibodies
    - MNS and s system antibodies

- No occurrence in HDN : Lewis system antibodies and P system antibodies

Anemia, Acute
Atrial Flutter
Cardiac Tumors
Cytomegalovirus Infection
Galactose-1-Phosphate Uridyltransferase Deficiency (Galactosemia)
Hydrops Fetalis
Hypothyroidism
Parvovirus B19 Infection
Syphilis
Toxoplasmosis
Tyrosinemia

Other Problems to be Considered:

In short, all causes of pathologic jaundice and nonimmune hydrops fetalis should be considered in the differential diagnosis.

WORKUP	Section 5 of 11

Lab Studies:

- CBC: The severity of hematologic abnormalities is directly proportional to the severity of hemolysis and extent of hematopoiesis. The following abnormalities are observed:

  - Anemia: Measurements are more accurate using central venous or arterial samples rather than capillary blood.
  - Increased nucleated RBCs, reticulocytosis, polychromasia, anisocytosis, spherocytes, and cell fragmentation: The reticulocyte count can be as high as 40% in patients without intrauterine intervention. The nucleated RBC count is elevated and falsely elevates the leukocyte count, reflecting a state of erythropoiesis. Spherocytes (<40%) are more commonly observed in cases of ABO incompatibility. Glucose does not correct the autohemolysis in ABO incompatibility unlike hereditary spherocytosis. In severe hemolytic disease, schistocytes and burr cells may be observed, reflecting ongoing disseminated intravascular coagulation. A low reticulocyte count is observed in fetuses provided with intravascular transfusion in utero and with Kell alloimmunization.
  - Neutropenia: This condition seems to be secondary to stimulation of erythropoiesis in favor of myelopoiesis. However, neutrophilia can be observed after intrauterine transfusion because of an increase in circulating cytokines (granulocyte-macrophage colony-stimulating factor).
  - Thrombocytopenia: This condition is common, especially after intrauterine or exchange transfusions because of platelet-poor blood product and suppression of platelet production in favor of erythropoiesis.

- Metabolic abnormality: Hypoglycemia is common and is due to islet cell hyperplasia and hyperinsulinism. The abnormality is thought to be secondary to release of metabolic byproducts such as glutathione from lysed RBCs. Hypokalemia, hyperkalemia, and hypocalcemia are commonly observed during and after exchange transfusion.

- Serologic tests

    o Indirect Coombs test and direct antibody test (DAT) results are positive in the mother and affected newborn. The maternal titers are the highest dilution of maternal serum at which a positive agglutination test result is obtained. Unlike Rh alloimmunization, DAT results are positive in only 20-40% of infants with ABO incompatibility. This is because fetal RBCs have less surface expression of type-specific antigen compared to adult cells.
    o Although the indirect antiglobulin test result (neonate's serum with adult A or B RBCs) more commonly is positive in neonates with ABO incompatibility, it has poor predictive value for hemolysis. This is because of the differences in binding of IgG subtypes to the Fc receptor of phagocytic cells and, in turn, in their ability to cause hemolysis.
    o IgG2 is more commonly found in maternal serum but has weak lytic activity, which leads to the observation of little or no hemolysis with a positive DAT result. On the other hand, significant hemolysis is associated with a negative DAT result when IgG1 and IgG3 are predominant antibodies, which are in low concentration but have strong lytic activity, crossing to neonatal circulation.

Table 1. Comparison of Rh and ABO Incompatibility

Characteristics		Rh	ABO
Clinical aspects	First born	5%	50%
	Later pregnancies	More severe	No increased severity
	Stillborn/hydrops	Frequent	Rare
	Severe anemia	Frequent	Rare
	Jaundice	Moderate to severe, frequent	Mild
	Late anemia	Frequent	Rare
Laboratory findings	DAT	Positive	Weakly positive
	Indirect Coombs test	Positive	Usually positive
	Spherocytosis	Rare	Frequent

- Perinatal ultrasonography: High-resolution ultrasonography has been a major advance in detection of early hydrops, and it has also reduced the fetal trauma and morbidity rate to less than 2% during percutaneous umbilical blood sampling (PUBS) and placental trauma during amniocentesis. High-resolution ultrasonography has been extremely helpful in directing the needle with intraperitoneal transfusion (IPT) and intravascular transfusion (IVT) in fetal location.

Medical Care:

Management of maternal alloimmunization

Initial attempts to suppress Rh antibody production with Rh hapten, Rh-positive RBC stroma, and administration of promethazine were unsuccessful. Extensive plasmapheresis with partial replacement using 5% albumin and intravenous immunoglobulin (IVIG) or the administration of IVIG 1 g/kg body weight weekly has been shown to be moderately effective. The mechanism of action appears to be blockage of Fc receptors on phagocytes in the fetal reticuloendothelial system. However, these techniques only postpone the need for PUBS and IVT until 20-22 weeks' gestation, when these procedures can be performed with acceptable risk.

As a rule, serial maternal antibody titers are monitored until a titer of 1:16, which indicates that a high risk of fetal hydrops is reached. For Kell alloimmunization, hydrops can occur at low maternal titers because of suppressed erythropoiesis, and thus, delta-OD 450 values also are unreliable in predicting disease severity. Amniocentesis is then performed to assess the severity, and serial delta-OD 450 values are plotted on the Liley chart to evaluate the risk of hydrops. Frequent ultrasonographic monitoring is also performed to assess fetal well-being and detect early signs of hydrops.

During the period when intrauterine peritoneal transfusion was the only means of treatment, newborns were routinely delivered at 32 weeks' gestation. This approach resulted in a high incidence of hyaline membrane disease and exchange transfusions. With the advent of IVT in utero, the general approach to the severely affected fetus is to perform IVT as required until 35 weeks' gestation, with delivery planned at term. Establishment of lung maturity is difficult in these fetuses because of contamination of amniotic fluid with residual blood during transfusion.

Liley first described IPT in 1963. A Tuohy needle is introduced into the fetal peritoneal cavity under ultrasonographic guidance. An epidural catheter is threaded through the needle. A radiopaque medium is injected into the fetal peritoneum. The proper placement is confirmed by delineation outside of bowel or under the diaphragm or by diffusion in fetal ascites. Packed RBCs that are CMV negative and irradiated, less than 4 days old, group O, Rh negative, Kell negative, and cross matched with maternal serum are injected in 10-mL aliquots to a volume calculated by the following formula:

IPT volume = (gestation in wk - 20) X 10 mL

Residual Hb in the fetus is estimated to allow for proper spacing of IPT and selection of gestation of delivery by the following formula:

Hb g/dL = 0.85/125 X a/b X 120 - c/120

In the formula, a is the amount of donor RBC Hb transfused, b is the estimated fetal body weight, and c is the interval in days from the time of transfusion to the time of donor Hb estimation.

IPT is repeated when the donor Hb is estimated to have dropped to 10 g/dL. Usually, a second IPT is performed 10 days after the first transfusion in order to raise the Hb above 10 g/dL. Then another transfusion is performed every 4 weeks until the time of planned delivery at 34-35 weeks' gestation. Fetal diaphragmatic movements are necessary in order for absorption of RBC to occur. This approach is of no value for a moribund nonbreathing fetus. Maternal complications include infection and transplacental hemorrhage, while fetal complications are overtransfusion, exsanguination, cardiac tamponade, infection, preterm labor, and graft versus host disease. Survival rates after IPT approached approximately 75% with the help of ultrasonography.

Direct IVT has become a preferred route of fetal intervention because of the higher rate of complications and limited effectiveness of IPT in a hydropic fetus. Rodeck first successfully performed

IVT in 1981. With ultrasonographic guidance, a needle is introduced into an umbilical vessel, and a fetal blood sample is obtained. The blood sample is confirmed to be of fetal origin by rapid alkaline denaturation test. All the relevant fetal tests (eg, Hb, Hct, blood type, DAT, reticulocyte count, platelet count, serum albumin, erythropoietin level) are sent. If the Hb is below 11 g/dL, an IVT is started. The position of the needle is confirmed by noting the turbulence in the fetal vessel on injection of saline. The fetus is frequently paralyzed with pancuronium in order to prevent the displacement of the needle by fetal movements.

The transfusion is performed in 10-mL aliquots to a volume of 50 mL/kg estimated body weight or until Hct of 60% is reached. The procedure is discontinued promptly if cardiac decompensation is noted on ultrasonography. In addition to all the complications of IPT, umbilical vein compression has also been noted during IVT. However, IVT has many advantages, such as immediate correction of anemia and resolution of fetal hydrops, reduced rate of hemolysis and subsequent hyperinsulinemia, and acceleration of fetal growth for nonhydropic fetuses who often are growth retarded. IVT also is the only intervention available for moribund hydropic fetuses and those with anterior placenta. The risk of fetal loss is about 0.8% with IVT versus 3.5% per procedure for IPT, and the overall survival rate is 88%.

Management of the sensitized neonate

Mild hemolytic disease accounts for 50% of newborns with positive DAT results. Most of these newborns have no anemia (cord Hb >14 g/dL) and minimal hemolysis (cord bilirubin <4 mg/dL). Apart from early phototherapy, they require no transfusions. However, these newborns are at risk of developing severe late anemia with low reticulocyte count by 3-6 weeks of life. Therefore, monitoring their Hb levels after hospital discharge is important.

Moderate hemolytic disease accounts for approximately 25% of affected neonates. Moderate HDN is characterized by moderate anemia and increased cord bilirubin levels. These infants clinically are not jaundiced at birth but develop rapid unconjugated hyperbilirubinemia in the first 24 hours of life. Peripheral smear shows numerous nucleated RBCs, decreased platelets, and, occasionally, a large number of immature granulocytes. These newborns often have hepatosplenomegaly and are at risk of developing bilirubin encephalopathy without adequate treatment. Early exchange transfusion with type-O Rh-negative fresh RBCs with intensive phototherapy is usually required. These newborns also are at risk of developing late hyporegenerative anemia of infancy at 6 weeks of life.

Severe hemolytic disease accounts for the remaining 25% of the alloimmunized newborns who are either stillborn or hydropic at birth. The hydrops fetalis is predominantly caused by a capillary leak syndrome due to tissue hypoxia, hypoalbuminemia secondary to hepatic dysfunction, and high-output cardiac failure from anemia. About half of these fetuses become hydropic before 34 weeks' gestation and need intensive monitoring and management of alloimmunized gestation as described earlier. A previous history of neonatal hemolytic disease and rising maternal titers prompts a fetal blood sampling to establish the fetal blood type by direct cordocentesis (PUBS). Alternatively, Rh genotype can be determined by polymerase chain reaction technique using amniocytes or chorionic villus samples. No further monitoring is necessary if the fetus is Rh negative.

Management of ABO incompatibility

Management of hyperbilirubinemia is a major concern in newborns with ABO incompatibility. The criteria for exchange transfusion and phototherapy are similar to those used in Rh alloimmunization. Tin (Sn) porphyrin a potent inhibitor of heme oxygenase, the enzyme that catalyzes the rate-limiting step in the production of bilirubin from heme, has been shown to reduce the production of bilirubin and reduce the need for exchange transfusion and the duration of phototherapy in neonates with ABO incompatibility.

Tin or zinc protoporphyrin or mesoporphyrins have been studied in newborns. They must be administered intramuscularly in a dose based on body weight, and their effectiveness appears to be dose related in all gestations. Their possible toxic effects include skin photosensitization, iron deficiency, and possible inhibition of carbon monoxide production. Their use in Rh HDN has not been reported. Their routine use cannot be recommended yet because of lack of long-term safety data.

Drug Category: *Immunomodulators* -- Normalize the antibody level in patients with primary defective antibody synthesis. Prevent and treat certain bacterial and viral infections. Reduce the immune-mediated hemolysis and phagocytosis.

Drug Name	Intravenous immunoglobulin (Gamimune, Gammagard, Sandoglobulin, Gammar-P) -- Several studies have reported success in minimizing the need for exchange transfusion in severe HDN with IVIG. It is an effective adjunct to phototherapy. The mechanism of action appears to be related to blockage of Fc receptors in the neonatal reticuloendothelial system. Studies have also documented decreased hemolysis after administration of IVIG using carboxyhemoglobin levels. Administration of IVIG in doses of 500-1000 mg/kg in the first few hours of life to a newborn with severe hemolysis should be considered. Its efficacy, however, depends on timing of administration, duration of treatment, and severity of hemolysis.
Adult Dose	1 g/kg IV qwk for maternal alloimmunization
Pediatric Dose	0.5-1 g/kg IV in first few h following birth for severe hemolysis in newborn; start infusion at rate of 0.01 mL/kg/min for 30 min, then increase q15-30min; not to exceed rate of 0.06 mL/kg/min; if adverse reactions occur, reduce rate to a previously well-tolerated rate
Contraindications	Documented hypersensitivity; IgA deficiency; anti-IgE/IgG antibodies
Interactions	Globulin preparation may interfere with immune response to live virus vaccine (MMR) and reduce efficacy (do not administer within 3 mo of vaccine)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Ensure that patient is not volume depleted before initiation of therapy; periodic monitoring of renal function and urine output should be undertaken in those at increased risk for developing acute renal failure (eg, preexisting renal insufficiency, diabetes mellitus, age >65 y, hypovolemia, sepsis, paraproteinemia, those on nephrotoxic drugs); in such patients, reduce rate of infusion and discontinue if renal function deteriorates; patients with agammaglobulinemia or extreme hypogammaglobulinemia who have never received IVIG before or have not received IVIG within preceding 8 wk are at increased risk of developing inflammatory reaction after IVIG infusion (these reactions are manifested by fever, chills, nausea, and vomiting and appear to be related to rate of infusion)

Further Inpatient Care:

- The stabilization of a hydropic newborn requires a high level of intensive coordinated management by a neonatal team well prepared for the possibly affected infant. In general, immediate intubation followed by draining of pleural effusions and ascites results in immediate improvement in respiratory gas exchange. A cautious correction of anemia with packed RBCs or by exchange transfusion is necessary to prevent circulatory overload. These neonates have normal blood volume but elevated central venous pressure. A close monitoring of metabolic

status (eg, watching for hypoglycemia, hypocalcemia, hyperkalemia, acidosis, hyponatremia, renal failure) is absolutely essential to achieve a successful outcome.

- In spite of the first use of phototherapy by Cremer and associates more than 40 years ago, no standard method for delivering phototherapy yet exists.

  - Phototherapy units differ widely with respect to the type and size of lamps used. The efficacy of phototherapy depends on the spectrum of light delivered, the blue-green region of visible light being the most effective; irradiance (μW/cm^2/nm); and surface area of the infant exposed. High-intensity phototherapy first described by Tan in 1977 uses irradiance greater than 25 μW/cm^2/nm up to 40 μW/cm^2/nm when a dose-response relationship to bilirubin degradation reaches a plateau. Nonpolar bilirubin is converted into 2 types of water-soluble photoisomers as a result of phototherapy. The initial and most rapidly formed configurational isomer 4z, 15e bilirubin accounts for 20% of total serum bilirubin level in newborns undergoing phototherapy and is produced maximally at conventional levels of irradiance (6-9 μW/cm^2/nm).
  - The structural isomer lumirubin is formed slowly, and its formation is irreversible and is directly proportional to the irradiance of phototherapy on skin. Lumirubin is the predominant isomer formed during high-intensity phototherapy. Decrease in bilirubin is mainly the result of excretion of these photoproducts in bile and removal via stool. In the absence of conjugation, these photoisomers can be reabsorbed by way of the enterohepatic circulation and diminish the effectiveness of phototherapy.

    Table 2. Indications for Phototherapy in the Term Infant with Hemolytic Disease of the Newborn

Age	Serum Bilirubin, g/dL
Unborn (cord blood)	>3.5
<12 h	>10
<18 h	>12
<24 h	>14
2-3 d	>15

- Exchange transfusion removes circulating bilirubin and antibody-coated RBCs, replacing them with RBCs compatible with maternal serum and providing albumin with new bilirubin binding sites.

  - The process is time consuming and labor intensive, but it remains the ultimate treatment to prevent kernicterus. The process involves the placement of a catheter via the umbilical vein into the inferior vena cava and removal and replacement of 5- to 10-mL aliquots of blood sequentially, until about twice the volume of the neonate's circulating blood volume is reached (ie, double-volume exchange).
  - This process removes approximately 70-90% of fetal RBCs. The amount of bilirubin removed varies directly with the pretransfusion bilirubin level and amount of blood exchanged. Because most of the bilirubin is in the extravascular space, only about 25% of the total bilirubin is removed by an exchange transfusion. A rapid rebound of serum bilirubin level is common after equilibration and frequently requires additional exchange transfusions.
  - The indications for exchange transfusion are controversial, except for the fact that severe anemia and the presence of a rapidly worsening jaundice despite optimal phototherapy in the first 12 hours of life indicate the need for exchange transfusion. In addition, the presence of conditions that increase the risk of bilirubin encephalopathy lowers the threshold of safe bilirubin levels.

Indirect Bilirubin Level, mg/dL	Weight, g
>20	Healthy, >2500
>18	Septic, >2500
>17	2000-2499
>15	1500-1999
>13	1250-1499
>9-12	<1250

- o The following are requirements for exchange transfusion
    1. Severe anemia (Hb <10 g/dL)
    2. Rate of bilirubin rises more than 0.5 mg/dL despite optimal phototherapy
    3. Hyperbilirubinemia

- o Exchange transfusion is not free of risk, with the estimated morbidity rate at 5% and the mortality rate as high as 0.5% from the procedure. Apnea, bradycardia, cyanosis, vasospasm, and hypothermia with metabolic abnormalities (eg, hypoglycemia, hypocalcemia) are the most common adverse effects.

Deterrence/Prevention:

- Prevention of Rh hemolytic disease

    - o Rh immunoglobulin (RhIG) was licensed in 1968 in North America after several studies demonstrated its effectiveness in preventing Rh alloimmunization when administered to the mother within 72 hours of delivery. The current standard is to administer RhIG to all unsensitized Rh-negative women at 28 weeks' gestation with an additional dose administered soon after birth if the infant is Rh-positive, irrespective of the ABO status of the baby.
    - o The standard dose of RhIG is 300 mcg and is increased (300 mcg for every 25 mL of fetal blood in maternal circulation) based on the amount of fetomaternal hemorrhage, which can be quantified using the Kleihauer-Betke technique. Because the time required for the Kleihauer-Betke test usually is longer, most physicians resort to the indirect Coombs test in the mother to assess the adequacy of RhIG dose in a woman with significant fetomaternal hemorrhage. The indirect Coombs test result should become positive in a woman with a prior negative test result, suggesting the presence of excess antibody in circulation. Also administer RhIG to unsensitized Rh-negative women after any event known to be associated with transplacental hemorrhage. The current incidence of Rh immunization stands at 0.1% with the above recommendations.

Complications:

- The 2 major complications of HDN are bilirubin encephalopathy (kernicterus) and late anemia of infancy.

    - o Bilirubin encephalopathy
        - Before the advent of exchange transfusion, kernicterus affected 15% of infants born with erythroblastosis. Approximately 75% of these neonates died within 1 week of life, and a small remainder died during the first year of life. Survivors had permanent neurologic sequelae and were thought to have accounted for 10% of all patients with cerebral palsy (CP) .

- The mechanism by which unconjugated bilirubin enters the brain and damages it is unclear. Bilirubin enters the brain as lipophilic free bilirubin unbound to albumin, as supersaturated bilirubin acid that precipitates on lipid membrane in low pH, or as a bilirubin-albumin complex that transfers bilirubin to tissue by direct contact with cellular surface. A damaged blood-brain barrier enhances the entry of all forms of bilirubin into the brain, which is especially important in preterm neonates with respiratory acidosis and vascular injury.
- Bilirubin has been postulated to cause neurotoxicity via 4 distinct mechanisms: (1) interruption of normal neurotransmission (inhibits phosphorylation of enzymes critical in release of neurotransmitters), (2) mitochondrial dysfunction, (3) cellular and intracellular membrane impairment (bilirubin acid affects membrane ion channels and precipitates on phospholipid membranes of mitochondria), and (4) interference with enzyme activity (binds to specific bilirubin receptor sites on enzymes).
- The pathologic findings include characteristic staining and neuronal necrosis in basal ganglia, hippocampal cortex, subthalamic nuclei, and cerebellum. The cerebral cortex is s generally pared. About half of these neonates also have extraneuronal lesions, such as necrosis of renal tubular, intestinal mucosal, and pancreatic cells.
- Clinical signs of bilirubin encephalopathy typically evolve in 3 phases. Phase 1 is marked by poor suck, hypotonia, and depressed sensorium. Fever and hypertonia are observed in phase 2, and at times, the condition progresses to opisthotonus. Phase 3 is characterized by high-pitched cry, hearing and visual abnormalities, poor feeding, and athetosis. The long-term sequelae include choreoathetoid CP, upward gaze palsy, sensorineural hearing loss, and, less often, mental retardation.
- Currently, the mortality rate stands at 50% in term newborns, but mortality is nearly universal in the preterm population who may simply appear ill without signs specific for kernicterus. Lately, research has indicated that bilirubin production rates may be the critical piece of information identifying jaundiced infants at risk of neurotoxicity. A high bilirubin production rate is thought to result in rapid transfer of bilirubin to tissue, causing high tissue load, in which case any small further increase has great potential to enter the brain. Because the total serum bilirubin represents not only bilirubin production but also distribution and elimination, it is not an absolute indicator of risk of kernicterus. Techniques have been developed to measure the bilirubin production rates accurately and noninvasively using end-tidal carbon monoxide measurement and percutaneous measurement of carboxyhemoglobin.

- Late anemia of infancy
  - Infants with significant hemolytic disease often develop anemia in the first few months of life and frequently require packed RBC transfusion. The etiology of anemia appears to be diminished hypoxic stimulus from transfusion of adult Hb during intrauterine or exchange transfusion, resulting in low erythropoietin levels and reticulocyte count.
  - Continued destruction of neonatal RBCs by high titers of circulating maternal antibodies often contributes to low reticulocyte count and anemia. Administration of recombinant human erythropoietin (rh-EPO) has been shown to minimize the need for transfusion in these newborns.

- Potential complications of exchange transfusion include the following:

  - Cardiac - Arrhythmia, volume overload, congestive failure, and arrest
  - Hematologic - Overheparinization, neutropenia, thrombocytopenia, and graft versus host disease
  - Infectious - Bacterial, viral (CMV, HIV, hepatitis), and malarial
  - Metabolic - Acidosis, hypocalcemia, hypoglycemia, hyperkalemia, and hypernatremia
  - Vascular - Embolization, thrombosis, necrotizing enterocolitis, and perforation of umbilical vessel
  - Systemic - Hypothermia

Prognosis:

- Most survivors of alloimmunized gestation are intact neurologically. However, Janssens and colleagues have reported neurologic abnormality to be closely associated with severity of anemia and perinatal asphyxia.

Medical/Legal Pitfalls:

- Failure to provide RhIG therapy to an Rh-negative woman resulting in maternal alloimmunization and affecting the outcome of her future offspring has a very high potential for medicolegal litigation. This warrants that significant attention should be paid to blood type and Rh status of every pregnant woman beginning at the first prenatal visit.

- Explain in detail to every parent the risk of adverse outcome of an alloimmunized gestation irrespective of its severity, including fetal loss, prematurity, brain injury, risk of bilirubin encephalopathy, and subsequent CP.

Picture 1. Hemolytic disease of newborn. Liley curve. This graph illustrates an example of amniotic fluid spectrophotometric reading of 0.206, which when plotted at 35 weeks' gestation falls into zone 3, indicating severe hemolytic disease.
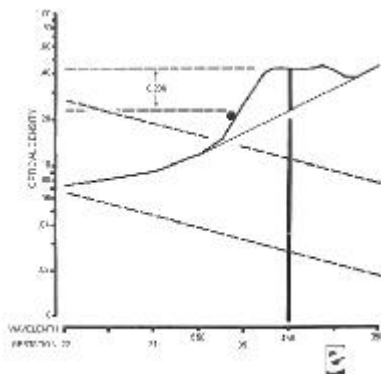
Picture 2. Hemolytic disease of newborn. Modified Liley curve for gestation of less than 24 weeks showing that bilirubin levels in amniotic fluid peak at 23-24 weeks' gestation.
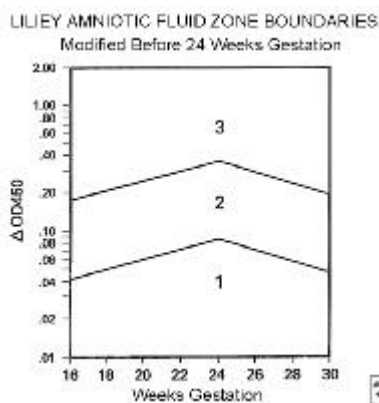
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Hemolytic Disease of Newborn excerpt

Hemorrhagic Disease of Newborn

Last Updated: April 29, 2005

Synonyms and related keywords: HDN, vitamin K deficiency bleeding, VKDB, coagulopathy, intracranial hemorrhage, ICH, late-onset VKDB, early-onset VKDB, classic VKDB

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INTRODUCTION	Section 2 of 10

Background: The more appropriate term for hemorrhagic disease of newborn is vitamin K deficiency bleeding (VKDB). Historically, all bleeding disorders in the newborn were grouped together under the diagnosis of hemorrhagic disease of the newborn (HDN). With methods available today for the accurate diagnosis of other factor deficiency states and immune thrombocytopenias, VKDB can be distinguished from other disorders by exclusion.

Pathophysiology: Newborns are relatively vitamin K deficient for a variety of reasons. Factors that can contribute to this deficiency include low vitamin K stores at birth, poor placental transfer of vitamin K, low levels of vitamin K in breast milk, and sterility of the gut. Because standard commercial infant formulas contain supplemental vitamin K, VKDB is almost exclusively a problem of breastfed infants. Infants with inadequate intake are at higher risk.

The most common sites of bleeding are the umbilicus, mucous membranes, GI tract, circumcision, and venipunctures. Hematomas at sites of trauma, such as large cephalohematomas and bruising, are also common findings. Intracranial bleeding can occur and is the main cause of mortality and long-term morbidity.

Frequency:

- **In the US:** The frequency of VKDB is variably reported from 0.25-1.7%. The frequency in a given US population depends upon the frequency of breastfeeding.
- **Internationally:** The frequency of VKDB in countries outside the United States varies with the use of vitamin K prophylaxis, the efficacy of prophylaxis programs, frequency of breastfeeding, and the content of locally available formulas.

Mortality/Morbidity: Intracranial hemorrhage (ICH) is uncommon in classic VKDB but can be observed in more than 50% of infants with late-onset VKDB. ICH is responsible for nearly all mortality and all long-term sequelae resulting from VKDB.

No racial predilection exists, but breastfeeding practices can result in apparent racial disparities.

Sex: No apparent sex predilection exists.

Age: VKDB can occur in 3 general time frames.

- Early onset, at less than 24 hours after birth, rarely occurs and is almost always associated with maternal medications that interfere with vitamin K, such as anticonvulsants, anticoagulants, and antibiotics. Postnatal administration of vitamin K has no effect in preventing early-onset disease. Maternal vitamin K supplementation that is administered prenatally may prevent this form of VKDB.
- The classic onset of VKDB is 2-7 days after birth in breastfed infants.
- Late-onset VKDB occurs after 2 weeks of life. In addition to breastfeeding, risk factors include diarrhea, hepatitis, cystic fibrosis (CF), celiac disease, and alpha1-antitrypin deficiency. Late-onset VKDB tends to be more severe than early-onset or classic disease and has a high frequency of ICH.

CLINICAL	**Section 3 of 10**

Physical: The findings from the physical examination are normal except for findings at the sites of bleeding.

Causes: Vitamin K deficiency in the newborn, which can be present for a variety of reasons, causes VKDB (see Pathophysiology).

- Maternal medications that interfere with vitamin K stores or function, such as carbamazepine, phenytoin, barbiturates, some cephalosporins, rifampin, isoniazid, and warfarin, can result in VKDB in the infant.
- In addition to breastfeeding, risk factors for late-onset VKDB include the following:

    o Diarrhea
    o Hepatitis
    o Cystic fibrosis
    o Celiac disease
    o Alpha1-antitrypin deficiency

DIFFERENTIALS	**Section 4 of 10**

Consumption Coagulopathy
Von Willebrand Disease

Other Problems to be Considered:

Maternal isoimmune thrombocytopenia
Alloimmune thrombocytopenia
Hepatobiliary disease
Uncommon coagulopathies

Lab Studies:

- Include prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels, and a platelet count in the initial workup for bleeding in a newborn. A thrombin clotting time (TCT) is optional.
    - A prolonged PT usually is the first laboratory test result to be abnormal in VKDB; however, no laboratory test can confirm the diagnosis of VKDB.
    - Vitamin K direct assay is not useful because levels normally are low in newborns.
    - Levels of protein induced by vitamin K antagonism (PIVKA) II are increased in VKDB, but this test generally is not available outside of research laboratories.
    - Infants with VKDB typically have a prolonged PT with reference range platelet counts and fibrinogen levels. Thrombocytopenia or a prolonged aPTT should prompt workup for other causes of bleeding.
- The diagnosis of VKDB is confirmed if administration of vitamin K brings a halt to the bleeding and reduces the PT value.

Imaging Studies:

- Intracranial bleeding is rare and usually associated with other causes of bleeding, particularly the thrombocytopenias; however, ICH has been reported in VKDB and can be fatal. Investigate any neurologic symptoms with a CT scan.

Medical Care:

- Immediately administer a vitamin K SC dose for any infant in whom VKDB is suggested or with any sort of bleeding.
    - IM administration can result in a hematoma because of the coagulopathy.
    - IV administration of vitamin K has been associated with anaphylactoid reactions.
- Fresh frozen plasma may be considered for moderate-to-severe bleeding.
    - Life-threatening bleeding may also be treated with prothrombin complex concentrates (PCC).
    - Because the bleeding in classic VKDB usually is not life threatening, a single dose of parenteral vitamin K is sufficient to stop the bleeding and return PT values to the reference range.
- In the early 1990s, an association between parenteral vitamin K and the later occurrence of childhood cancer was reported; however, a large cohort study and a large retrospective analysis of a database in the United States could not confirm this association. Because this association is weak at best, routine vitamin K prophylaxis is recommended and supported by the American Academy of Pediatrics.

Vitamin K is essential in the treatment of VKDB. Other coagulation factors rarely are needed. Severe bleeding may warrant the use of fresh frozen plasma. No other drugs or treatments are acceptable substitutes for prompt vitamin K dosing.

Drug Category: *Vitamins* -- Vitamin K is required to correct the deficiency that defines VKDB.

Drug Name	Phytonadione (Phytomenadione, AquaMEPHYTON) -- Vitamin K, a fat-soluble vitamin that is a cofactor in the synthesis of clotting factors. May be ineffective if liver disease is severe. Coagulation factors should increase in 6-12 h after PO dosing and in 1-2 h after parenteral administration. Monitor efficacy with PT.
Pediatric Dose	Aqueous (for injection): 2 mg/mL and 10 mg/mL diluted in 5-10 mL D5W or NS; maximum concentration 10 mg/mL; infuse over 15-30 min; maximum rate of infusion 1 mg/min Prophylaxis: 0.5-1 mg SC/IM Treatment: 1 mg SC or 1-10 mg IV Note: Use IM or IV administration routes only when SC is not feasible and condition justifies risk
Contraindications	Documented hypersensitivity
Interactions	Incompatible with phenytoin; antagonizes actions of warfarin; mineral oil decreases enteral absorption
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	IV administration rate should not exceed 1 mg/min because of reported anaphylactoid reactions; IM administration can result in hematomas, particularly in infants with evidence of bleeding; hemolytic anemia and hyperbilirubinemia rarely occur with larger doses (10-20 mg)

Further Outpatient Care: Follow-up interval after discharge depends on the nature and severity of bleeding, hematocrit at discharge, and any neurologic complications. Mild VKDB that has been treated successfully can be monitored at routine newborn visits.

Transfer: Infants with evidence of intracranial bleeding may require transfer to a level III nursery after stabilization with SC or IV vitamin K.

Deterrence/Prevention:

- IM vitamin K prophylaxis at birth is the standard of care in the United States.

- Commercial infant formulas in the United States contain supplemental vitamin K.

- These measures have served to make VKDB a rarity. However, parental refusal of prophylaxis and an increasing frequency of breastfeeding may cause a resurgence of VKDB in developed countries.

Complications:

- ICH is the primary serious complication of VKDB.

- Complications of treatment include anaphylactoid reactions to IV vitamin K, hyperbilirubinemia or hemolytic anemia after high-dose vitamin K, and hematomas at the site of injection if administered IM.

Prognosis: In the absence of ICH, the prognosis for VKDB in an otherwise healthy infant is excellent. Prognosis after ICH depends on the extent and location of the hemorrhage. Long-term sequelae of ICH may include motor and intellectual deficits.

Medical/Legal Pitfalls:

- Most hospital nurseries include vitamin K administration in standing admission orders. A newborn's hospital chart should have a specific place for documentation of dose and administration. Failure to provide vitamin K at birth and subsequent bleeding presents a legal liability for physicians and hospitals. If parents refuse prophylaxis, document the discussion of the risks and benefits along with the parents' refusal in the chart.

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Hemorrhagic Disease of Newborn excerpt

Human Milk and Lactation

Last Updated: August 7, 2004

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INTRODUCTION	Section 2 of 11

Breast milk is commonly known as the best form of nutrition for neonates and infants. Human milk has bioactive properties that facilitate the transition of life from in utero to ex utero. This dynamic fluid provides a diverse array of bioactive substances to the developing infant during critical periods of brain, immune, and gut development. The clinician must be familiar with how human milk is manufactured by the mammary gland and with the properties of human milk that render it nourishing and protective of the breastfeeding infant.

Clinicians play a crucial role in a mother's decision to breastfeed and can facilitate her success in lactation. Although a mother may not be aware of the evidence indicating that breast milk contributes to her baby's short- and long-term well-being, she has certain attitudes and cultural beliefs about breastfeeding. The issue of bonding between mother and newborn may be a strong factor; however, stronger cultural or societal barriers may be present that result in formula feeding. Such issues must be understood for successful counseling. The mother makes her decision regarding breastfeeding prior to delivery in more than 90% of cases; therefore, a discussion regarding her choice of infant nutrition after delivery should take place beginning in the second trimester and as part of an ongoing dialogue during each obstetric visit.

This article reviews the development of the mammary gland (mammogenesis), the process by which the mammary gland develops the capacity to secrete milk (lactogenesis), the process of milk production (lactation), and the specific properties of human milk that make it unique and appropriate for human infants. In a related article entitled Counseling the Breastfeeding Mother, the mechanics of breastfeeding and how to evaluate the breastfeeding mother-infant dyad are discussed. These articles are intended to be overviews. For a more in depth treatise, please refer to textbooks by Lawrence and Lawrence (1999) and Riordan and Auerbach (1998).

The breast must undergo many years of development for proper breastfeeding to occur. A bulb-shaped mammary bud can be discerned in the fetus at 18-19 weeks' gestation. Inside the bud, a rudimentary mammary ductal system is formed, which is present at birth. After birth, growth of the gland parallels that of the child until puberty. The normal anatomy of the mammary gland following pubertal development is shown in Images 1-2. The basic unit of the mammary gland is the alveolus or acini cell that connects to a ductule. Each ductule independently drains to a duct that in turn empties to the lactiferous sinuses. In the nipple, 15-25 openings allow milk to flow to the recipient infant.

At puberty, released estrogen stimulates breast tissue to increase in size through growth of mammary ducts into the preexisting mammary fat pad. Progesterone, secreted in the second half of the menstrual cycle, causes limited lobuloalveolar development. The effects of estrogen and progesterone facilitate the formation of the characteristic structure of the adult breast, which is the terminal duct lobular unit. Full alveolar development and maturation of epithelium, however, requires the hormones of pregnancy.

Lactogenesis is the process by which the mammary gland develops the capacity to secrete milk. It includes all processes necessary to transform the mammary gland from its undifferentiated state in early pregnancy to its fully differentiated state sometime after pregnancy. It is this fully differentiated state that allows full lactation. The 2 stages of lactogenesis are discussed below.

Lactogenesis has been divided into 2 stages. Stage 1 occurs by mid pregnancy. It is the process whereby the mammary gland becomes competent to secrete milk. During stage 1, lactose, total protein, and immunoglobulin concentrations increase within the secreted glandular fluid, sodium and chloride concentrations decrease. The gland is now sufficiently differentiated to secrete milk, as evidenced by the fact that women often describe drops of colostrum on their nipples in the second or third trimester. The secretion of milk, however, is held in check by high circulating levels of progesterone and estrogen.

Stage 2 of lactogenesis occurs around the time of delivery. It is defined as the onset of copious milk secretion. In stage 2, blood flow, oxygen, and glucose uptake increase, and the citrate concentration increases sharply. This increase of citrate is considered a reliable marker for lactogenesis stage 2. Progesterone plays a key role in this stage. Removal of the placenta (ie, the source of progesterone during pregnancy) is necessary for the initiation of milk secretion; however, the placenta does not inhibit established lactation. Work by Haslam and Shyamala reveals that this noninhibition occurs because progesterone receptors are lost in lactating mammary tissues. In addition, maternal secretion of insulin, growth hormone (GH), cortisol, and parathyroid hormone (PTH) facilitates the mobilization of nutrients and minerals that are required for lactation.

The stages of lactation can be summarized as follows (adapted from Riordan and Auerbach, 1998):

- Mammogenesis: Mammary (breast) growth occurs. The size and weight of the breast increase.
- Lactogenesis
  - Stage 1 (late pregnancy): Alveolar cells are differentiated from secretory cells.
  - Stage 2 (day 2 or 3 to day 8 after birth): The tight junction in the alveolar cell closes. Copious milk secretion begins. Breasts are full and warm. Endocrine control switches to autocrine (supply-demand) control.
- Galactopoiesis (later than day 9 after birth to beginning of involution): Established secretion is maintained. Autocrine system control continues.
- Involution (average 40 days after last breastfeeding): Regular supplementation is added. Milk secretion decreases from the buildup of inhibiting peptides.

Two essential hormones - prolactin and oxytocin

During the second stage of lactogenesis, the breast becomes capable of milk production. For the ongoing synthesis and secretion of human milk, hormonal signals must be received by the mammary gland continually. These signals are in direct response to stimulation of the nipple and areola (mammae) and are then relayed to the central nervous system. This cyclical process of milk synthesis and secretion is termed lactation. Lactation occurs with the help of 2 hormones, prolactin and oxytocin. While prolactin and oxytocin act independently on different cellular receptors, their combined actions are essential for successful lactation.

Prolactin

Milk synthesis occurs in the mammary gland epithelial cells in response to prolactin activation of epithelial cell prolactin receptors. Prolactin, a hormone synthesized by the anterior pituitary, is structurally similar to GH. It stimulates mammary glandular ductal growth and epithelial cell proliferation and induces milk protein synthesis. The significance of prolactin can be seen in the inhibition of lactogenesis using bromocriptine and other dopamine analogues, which are prolactin inhibitors.

Oxytocin

The other important hormone involved in the milk ejection or letdown reflex is oxytocin. When the neonate is placed at the breast and begins suckling, oxytocin is released. The suckling infant causes stimulation of the touch receptors that are densely located around the nipple and areola. The tactile sensations create impulses that, in turn, activate the dorsal root ganglia via the intercostals nerves (4, 5, and 6). These impulses ascend the spinal cord, creating an afferent neuronal pathway to both the paraventricular nuclei of the hypothalamus where oxytocin is synthesized and secreted and the pituitary gland. The stimulation of the nuclei causes the release of oxytocin down the pituitary stalk and into the posterior pituitary gland, where oxytocin is stored.

Once the posterior pituitary gland is stimulated by the afferent impulses created by the infant's suckling, oxytocin is released in a pulsatile fashion to adjacent capillaries, traveling to the mammary myoepithelial cell receptors that in turn stimulate the cells to contract. Oxytocin causes the contraction of the myoepithelial cells that line the ducts of the breast. These smooth muscle–like cells, when stimulated, expel milk from alveoli into ducts and subareolar sinuses that empty through a nipple pore.

Milk secretion and synthesis - directly correlated

The regulation of milk synthesis is quite efficient. Milk synthesis is remarkably constant, at around 800 mL/d. The actual volume of milk secreted, however, may be adjusted to the requirement of the infant by feedback inhibitor of lactation, a local factor secreted into the milk; therefore, the rate of synthesis of milk is related to the degree of emptiness or fullness of the breast. The emptier breast produces milk faster than the fuller one.

Human milk is a unique, species-specific, complex nutritive fluid with immunologic- and growth-promoting properties. This unique fluid actually evolves to meet the changing needs of the baby during growth and maturation. The synthesis and secretion of milk by the mammary gland involve numerous cellular pathways and processes (summarized in Image 4). The processing and packaging of nutrients within human milk changes over time as the recipient infant matures. For example, early milk or colostrum has lower concentrations of fat than mature milk but higher concentrations of protein and minerals (see Image 5). This relationship reverses as the infant matures.

Fore and hind milk - important differences

In addition to the changes from colostrum to mature milk that mirror the needs of the developing neonate, variation exists within a given breastfeeding session. The milk first ingested by the infant (fore milk) has a lower fat content. As the infant continues to breastfeed over the next several minutes, the fat content increases (hind milk), which is thought to facilitate satiety in the infant. Finally, diurnal variations in breast milk exist, which reflect maternal diet and daily hormonal fluctuations.

Specific enzymes to aid neonatal digestion

Various enzymes are components of human milk, some specific for the biosynthesis of milk components in the mammary gland (eg, lactose synthetase, fatty acid synthetase, thioesterase) and others specific for the digestion of proteins, fats, and carbohydrates that facilitate food breakdown and absorption of human milk by the infant. Certain enzymes also serve as transport moieties for other substances such as zinc, selenium, and magnesium.

Three-dimensional structure of human milk

Under a microscope, the appearance of human milk is truly amazing. While a fluid, human milk has substantial structure in the form of compartmentation. Within the various compartments of human milk, nutrients and bioactive substances are sequestered. The most elegant example of this structure involves lipids. Lipids are enveloped at the time of secretion from the apical mammary epithelial cell within its plasma membrane, becoming the milk-fat globule. Certain proteins, growth factors, and vitamins also become sequestered within this milk-fat globule and are embedded within the membrane itself.

The membrane acts as a stabilizing interface between the aqueous milk components and compartmentalized fat. This interface allows controlled release of the products of lipolysis and transfer of polar materials into milk serum (aqueous phase). The bipolar characteristics of the membrane are also necessary for the emulsion stability of the globules themselves; thus, the structure of human milk provides readily available fatty acids and cholesterol for micellar absorption in the small intestine.

Proteins, carbohydrates, and designer fats for optimal brain development

Human milk provides appropriate amounts of proteins (the major components of which are alpha-lactalbumin and whey), carbohydrates (lactose), minerals, vitamins, and fats for the growing term infant. The fats are comprised of cholesterol, triglycerides, short-chain fatty acids, and long-chain polyunsaturated (LCP) fatty acids. The LCP fatty acids (18- to 22-carbon length) are needed for brain and retinal development. Large amounts of omega-6 and omega-3 LCP fatty acids, predominately the 20-carbon arachidonic acid (AA) and the 22-carbon docosahexaenoic acids (DHAs), are deposited in the developing brain and retina during prenatal and early postnatal growth.

An infant, particularly a preterm infant, may have a limited ability to synthesize optimal levels of AA and DHA from linoleic and linolenic acid. These 2 fatty acids may be essential. Recently, some infant formulas in the United States have added AA or DHA. Increasing evidence suggests that breastfed infants have better visual acuity at 4 months and slightly enhanced cognitive development than formula-fed infants, even when socioeconomic factors are taken into account. These differences are more pronounced in premature infants. Rather than causing better vision or greater intelligence, breast milk may somehow protect the developing neonatal brain from injury or less optimal development by providing necessary building materials and growth factors.

Human milk immunoglobulins

Human milk contains all of the different antibodies (M, A, D, G, E), but secretory immunoglobulin A (sIgA) is the most abundant. Milk-derived sIgA is a significant source of passively acquired immunity for the infant during the weeks before the endogenous production of sIgA occurs. During this time of reduced neonatal gut immune function, the infant has limited defense against ingested pathogens that are enhanced by ingested breast milk.

Assuming that the mother and her infant, who are closely associated, share common flora, the antigenic specificity of the mother's milk sIgA will be directed against the same antigens in the neonate. Maternal immunoglobulin A (IgA) antibodies derived from the gut and respiratory immune surveillance systems are transported via blood and lymphatic circulations to the mammary gland, to be finally extruded into her milk as sIgA. The packaging of IgA with a secretory component unique to the mammary gland affords the sIgA protection from stomach acids to later reach the small intestine intact.

Other immunological properties of human milk

In addition to antibodies, human milk also has numerous factors that can affect the intestinal microflora of the baby by enhancing the colonization of some bacteria while inhibiting the colonization by others. These immunologic components include lactoferrin, which binds to iron making it unavailable to pathogenic bacteria; lysozyme, which enhances sIgA bactericidal activity against gram-negative organisms; oligosaccharides, which intercept bacteria forming harmless compounds that the baby excretes; milk lipids, which damage membranes of enveloped viruses; and mucins, which present on the milk-fat globule membrane. Mucins adhere to bacteria and viruses and help eliminate them from the body. Interferon and fibronectin have antiviral activities and enhance lytic properties of milk leukocytes.

Human milk leukocytes

Macrophages comprise 40-60% of the cells in colostrum, with the remainder of cells consisting primarily of lymphocytes and polymorphonucleocytes. Extruded into the milk are rare mammary epithelial cells and the plasma membrane-bound lipid droplets referred to as milk-fat globules. By 7-10 days postpartum, with the transition from colostrum to mature milk, the percentage of macrophages then increases to 80-90% at a concentration of 10^4-10^5 human milk macrophages per milliliter of milk. Milk leukocytes can tolerate extremes in pH, temperature, and osmolality, and they have been shown to survive during the first postnatal week in baboons and lambs.

Passive immunity from mother to her recipient breastfeeding infant

While awaiting endogenous maturation of the baby's own immunologic systems, a variety of immunologic and bioactive milk components act synergistically to provide a passive immunological support system extending from the mother to her infant in the first days to months after birth. The neonate becomes passively immunized through ingested milk. This scenario and its clinical benefit are clearly documented by numerous studies that demonstrate a decreased risk to gastrointestinal and respiratory infections, particularly during the first year of life.

Evidence is increasing that these immune and bioactive substances prime the neonatal gastrointestinal and immune systems in their selective recognition of antigens and development of cellular signaling. This premise may explain the decreased risk of intestinal and respiratory allergy in children who have been breastfed and the lower-than-predicted risk of autoimmune diseases in the breastfed population. Direct effects are difficult to prove given the multifactorial nature of such diseases; however, when taken together, the data support the beneficial nature of human milk for the developing infant.

Human milk also contains growth modulators such as epidermal growth factor (EGF), nerve growth factor (NGF), insulinlike growth factors (IGFs), and interleukins. Transforming growth factor (TGF)–alpha, TGF-beta, and granulocyte colony-stimulating factor (G-CSF) are also identified in human milk. These growth modulators are produced either by the epithelial cells of the mammary gland or by activated macrophages, lymphocytes (mainly T cells), or neutrophils in the milk.

Neonatal gut maturation and growth appear to be influenced by certain bioactive substances and live cells in milk through their transfer of developmental information to the newborn. While most of these biosubstances have been identified in mother's milk in quantities that exceed maternal serum levels, their exact role in newborns is unknown as most current information is from animal models whose development may differ significantly.

Human milk, in addition to its numerous nutrients ideal for the growing term infant, is a bioactive fluid that evolves as the infant matures, from colostrum to mature milk. This bioactive fluid contains numerous factors and live cells that in concert promote the growth and well-being of the breastfeeding infant. Oliver Wendell Holmes said it best when he said, "A pair of substantial mammary glands has the advantage over the two hemispheres of the most learned professor's brain, in the art of compounding a nutritious fluid for infants." With the ever-expanding knowledge resulting from current research, it should be evident that human milk is not reproducible.

Picture 1. Human milk and lactation. Schematic diagram of the breast.
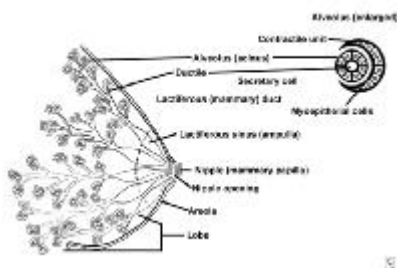
Picture 2. Human milk and lactation. Frontal view of lactating breast.
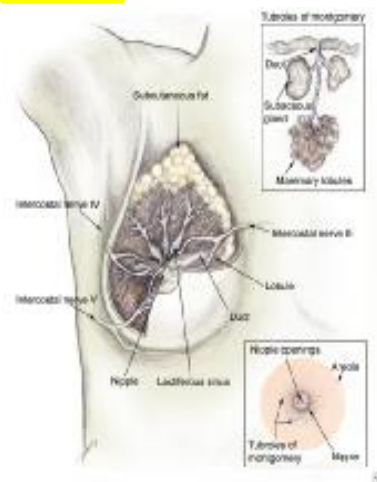
Human milk and lactation. Myoepithelial cells, open and contracting.
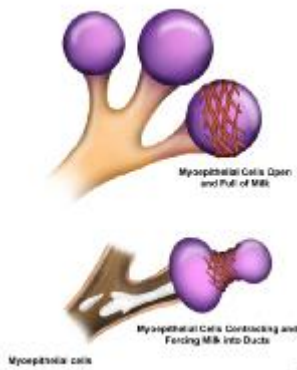

Picture 4. Human milk and lactation. The pathways for milk secretion and synthesis by the mammary epithelial cell. I - exocytosis of milk protein, lactose, and other components of the aqueous phase in Golgi-derived secretory vesicles. II - Milk fat secretion by way of the milk fat globule. III - Direct movement of monovalent ions, water and glucose across the apical membrane of the cell. IV - Transcytosis of components of the interstitial space. V - The paracellular pathway for plasma components and leukocytes. Pathway V is open only during pregnancy, involution, and in inflammatory states such as mastitis. SV - secretory vessicle; RER - rough endoplasmic reticulum; BM - basement membrane; MFG - milk fat globule; CLD - cytoplasmic lipid droplet; N - nucleus; PC - plasma cell; FDA - fat depleted adipocyte; TJ - tight junction; GJ - gap junction; D - desmosome; ME - myoepithelial cell.
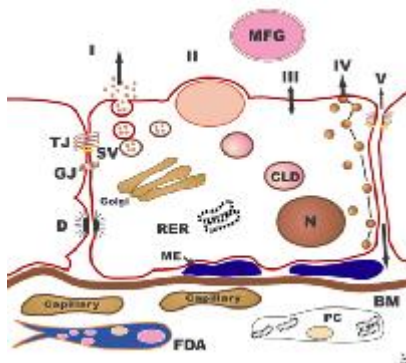
Picture 5. Human milk and lactation. Lactose, protein, and total lipid concentrations in human milk.
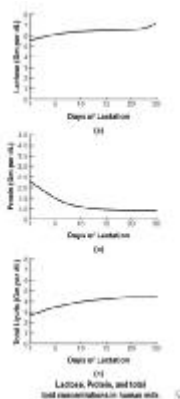
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Human Milk and Lactation excerpt

Hydrops Fetalis

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<mark>**Synonyms and related keywords:**</mark> hydrops foetalis, nonimmune hydrops, fetal edema, fetal subcutaneous tissue edema, placental edema, hydramnios, maternal-fetal blood group incompatibilities, maternal isoimmunization to fetal blood group antigens, isoimmune hemolytic disease, immune hydrops, homozygous alpha-thalassemia, Bart hydrops, congenital malformations, premature delivery, fetal fluid accumulations, fetal thoracentesis, fetal paracentesis, fetal surgical procedures, maternal ABO-factor isoimmunization, Rh D hemolytic disease, drug use, collagen disease, thyroid disease, diabetes, organ transplant, blunt abdominal trauma, coagulopathy, use of teratogenic drugs, sexually transmitted diseases, hemoglobinopathy, viral illness, fetomaternal transfusion, herpetic lesions, chancre, hemolytic disease of newborn, erythroblastosis, glucose phosphate isomerase deficiency, pyruvate kinase deficiency, G-6-PD deficiency, congenital dyserythropoietic anemia, Diamond-Blackfan syndrome, lethal hereditary spherocytosis, spectrin synthesis defects, congenital erythropoietic porphyria, Günther disease, leukemia with Down syndrome, leukemia with Noonan syndrome, Bart hemoglobinopathy, Parvovirus B19, B19V, intracranial hemorrhage, intraventricular hemorrhage, hepatic laceration, placental subchorial hemorrhage, sacrococcygeal teratoma, fetomaternal hemorrhage, twin-to-twin transfusion, isoimmune fetal thrombocytopenia, fetal anemia, fetal aplastic anemia, malformation syndromes, fetal hemorrhage, placental choriocarcinoma, placental chorangioma, partial placental abruption, reduced fetal body movements, sinusoidal fetal heart rate patterns, fetal acardia, fetus papyraceous, stuck twin, vanishing twin, velamentous cord insertion, atrial natruretic factor, fetal meconium peritonitis, lysosomal storage disorders, cystic hygroma, cystic adenomatoid malformation of the lung, fibroelastosis, prenatal closure of foramen ovale, prenatal closure of ductus arteriosus, idiopathic arterial calcification, AV block, atrial flutter, tachyarrhythmia, congenital heart block, maternal collagen disease, congenital syphilis, lethal multiple pterygium syndromes, fetal coagulopathy, bronchopulmonary sequestration, tension hydrothorax

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INTRODUCTION	Section 2 of 10

<mark>**Background:**</mark> Hydrops fetalis (ie, fetal hydrops) is usually defined as the presence of fetal subcutaneous tissue edema accompanied by serous effusion(s) in 1 or more body cavities. As the effects of gravity are blunted in the relatively weightless fetus, the edema is generalized, not dependent. The fetus may accumulate a much greater excess of fluid than is possible after birth because of key differences between fetal and postnatal circulations (eg, parallel flow vs serial flow, low-resistance systemic circuit) and differences between the organs of gas exchange (placenta vs lungs). The degree of edema observed in the fetus or newborn with hydrops is thus massive and may appear grossly bloating and deforming to the clinician who is more accustomed to children or adults. Placental edema invariably accompanies fetal edema, and hydramnios is usually present.

Massive edema of the newborn infant has been recognized for at least 3 centuries. While fetal hydrops was considered idiopathic a century ago, a causal relationship with maternal-fetal blood group incompatibilities was recognized soon after red cell antigens were identified. During the mid years of this past century, fetal hydrops was considered to be primarily the consequence of severe maternal isoimmunization to fetal blood group antigens foreign to the mother, most commonly those in the Rhesus (Rh) family. More recent recognition of factors other than isoimmune hemolytic disease that can cause or be associated with fetal hydrops led to the use of the term nonimmune hydrops to identify those cases in which the fetal disorder was caused by factors other than isoimz.

In the 1970s, the major cause of immune hydrops (ie, Rh D antigen) was conquered with the use of immunoglobulin (Ig) prophylaxis in at-risk mothers. This conquest was quickly followed by recognition that the nonimmune causes of hydrops were, in fact, more common than had been suspected. Arbitrarily classifying fetal hydrops into these categories is probably no longer clinically useful since so few current cases are immune, so many are nonimmune, and so many causes for nonimmune hydrops are currently recognized.

Pathophysiology: Until recently, many speculations but few facts existed about the pathophysiologic events leading to fetal hydrops. The bewildering heterogeneity of conditions causing or associated with the syndrome added to the confusion. Studies in sheep, most of which occurred in the past decade, provide a much clearer picture of fetal hydrops. Hydrops has been produced in the ovine fetus by anemia, tachyarrhythmia, occlusion of lymphatic drainage, and obstruction of cardiac venous return. Hypoproteinemia and hypoalbuminemia are common in human hydrops, and reduced intravascular oncotic pressure has been speculated to be a primary cause for the disorder. However, in the sheep model, a 41% reduction in total serum protein accompanied by a 44% decline in colloid osmotic pressure failed to produce fetal hydrops. Furthermore, normal concentrations of serum proteins are found in a sizable proportion of human hydrops. A closer look at the animal studies provides the clues necessary to piece together the puzzle of the pathophysiology of hydrops.

In one study, profound anemia was induced in fetal sheep; the hydrops that resulted was unrelated to hematocrit levels, blood gas levels, acid-base balance, plasma proteins, colloid oncotic pressure, or aortic pressure. A difference was found in central venous pressure (CVP), which was much higher in persons with hydrops. The hematocrit level was reduced by 45% in a study of particular notation; however, CVP was maintained unchanged, and no fetus developed hydrops under these conditions.

Induced fetal tachyarrhythmia has led to fetal hydrops in several studies. Key to the development of fetal hydrops in these studies was an elevation in CVP; the anemia was only of indirect importance. CVP was elevated markedly, with a range of 25-31 mm Hg in one study. In other reports, hydrops induced by sustained fetal tachycardia was unrelated to blood gases, plasma protein, or albumin turnover;however,a 75-100% increase in CVP was observed in the fetuses that developed hydrops.

Excision of major lymphatic ducts produces fetal hydrops in the sheep model. A related study demonstrates an exquisite, linear, inverse relationship between lymphatic outflow pressure and CVP; a rise in CVP of 1 mm Hg reduces lymph flow 13%, and flow stops at a CVP of 12 mm Hg. These results are confirmed by other observations of linear decline in lymph flow when CVP exceeds 5 mm Hg and a cessation of flow at CVPs greater than 18 mm Hg.

Placement of an inflatable tissue expander in the right chest, designed to mimic the effects of a space-occupying chest mass, has been demonstrated to produce hydrops in fetal sheep. Of particular note is the 400% rise in CVP, which accompanied both inflation of the expander and development of fetal hydrops, as well as the parallel decline in CVP and resolution of hydrops when the expander was deflated. Just how sensitive the fetus can be to obstruction of venous return is demonstrated in another study in which fetal hydrops was induced by cannulation of 1 carotid artery and 1 jugular vein or by catheter placement in a single jugular vein in the midgestation ovine fetus.

Also of note is a computer simulation model in which cardiovascular and fluid electrolyte disturbances (eg, severe anemia, lymphatic obstruction, excess fluid and electrolyte loads, elevation in angiotensin levels) and compensating homeostatic mechanisms have been examined. This model demonstrated that "...fetal cardiac failure constituted the strongest stimulus for the formation of fetal edema..." (Shinbane, 1997), thus further substantiating the pivotal role of CVP in the development of fetal hydrops.

Many other physiologic disturbances are associated with human fetal hydrops. Elevations in aldosterone, renin, norepinephrine, and angiotensin I levels are likely to be secondary consequences. While infusion of angiotensin I led to fetal hydrops in nephrectomized sheep, the 4-fold rise in CVP was probably the primary cause of the hydrops. An elevation in erythropoietin has been observed after 24 weeks' gestation in humans; however, this is likely a normal response to the fetal anemia in the observed cases. The meaning of increased levels of coenzyme Q10, placental vascular endothelial growth factor, and endothelin and decreased cytokine interleukin-3 levels is unclear at this time.

However, of particular interest is the 3- to 5-fold increase in atrial natriuretic peptide (ANP) that accompanies both human fetal hydrops (with cardiac anomaly or isoimmunization) and ovine hydrops (induced by obstruction of venous return, sustained tachycardia, or induced anemia). A return of ANP levels to normal parallels the resolution of hydrops. These observations and the observations that vascular permeation of albumin is enhanced and cardiovascular and renal homeostatic adaptations are influenced by this peptide suggest an important role for ANP in fetal hydrops. Recent evidence of low fetal plasma levels of cyclic guanosine monophosphate suggests that reduced nitric oxide production due to injury of fetal vascular endothelial cells may be involved in the development of fetal hydrops. This isolated observation requires confirmation and further study.

Frequency:

- **In the US:** An attempt to provide a precise incidence figure would be misleading. Recent estimates of the frequency of fetal hydrops depend, among other factors, on date (more common in recent reports because of earlier and more precise fetal diagnoses), season of the study reported (differences in exposure and immunity to viral infections), and ethnicity of the population studied (differences in genetic instructions for hemoglobin alpha-chain production). Variations in the use of sensitive, specific, and sophisticated prenatal, neonatal, and postmortem diagnostic tools also differ greatly among studies. The best estimate for how common hydrops fetalis is in the United States is approximately 1 in 600 to 1 in 4000 pregnancies.
- **Internationally:** Hydrops fetalis is much more common in Southeast Asia. The best figures come from Thailand, where the expected frequency of hydrops, from homozygous alpha-thalassemia or Bart hydrops alone, is 1 in 500 to 1 in 1500 pregnancies. Accurate figures from the Mediterranean region are not available; however, the commonness of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and of defects in alpha-chain hemoglobin production in several populations from this region lead to the suspicion that the incidence of hydrops in that region is much higher than it is in the United States.

Mortality/Morbidity: Estimates of mortality also vary widely, from nearly zero to virtually 100%. Most case series report 60-90% mortality, although some improvements are notable in more recent reports. Many causes for these variations exist, not the least of which include the sophistication of diagnostic methods used and the complexity and costs of treatment. However, the most important single factor is the cause of the hydrops. A significant proportion of these cases are caused or accompanied by multiple and complex congenital malformations of genetic and/or chromosomal origin, which by themselves are fatal at an early age. Many other causes are accompanied by masses or fluid accumulations, which compress the developing fetal lung and preclude its normal development. Thus, the presence or absence and potential prevention of pulmonary hypoplasia are of crucial importance.

Another highly important factor is the very premature delivery of most babies with hydrops, consequent to conditions, which distend the uterus and provoke early labor (fetal fluid

accumulations and/or hydramnios), or to therapeutic interventions (fetal thoracentesis, paracentesis, and/or complex fetal surgical procedures). Generally, the earlier in gestation that fetal hydrops is recognized, the poorer the prognosis.

Race: Ethnic influences are related almost entirely to cause. Selected examples include the importance of genetic variations in the alpha-chain structure of hemoglobin in Asian and Mediterranean populations in addition to the more serious nature of the hemolytic disease in the African American fetus affected by maternal ABO-factor isoimmunization.

Sex: Sex influences in incidence or outcome of hydrops fetalis are related largely to the cause of the condition. A significant proportion of hydrops is caused by or associated with chromosomal abnormalities or syndromes. Many of these are X-linked disorders.

Since most individuals with hydrops fetalis are delivered quite prematurely, and since fetal pulmonary maturation takes place earlier in female than in male fetuses, male preterm infants are at greater risk for the pulmonary complications of very preterm delivery. They are also at greater risk for infections (nosocomial or otherwise), which are so common in the very preterm infant. A striking example of greater male risk is the nearly 13-fold increase in the odds ratio for development of hydrops in the male fetus with Rh D hemolytic disease. While a single precise risk figure is not available for the heterogenous collection of cases that comprise hydrops fetalis, saying that the male fetus is at greater risk for occurrence, morbidity, and mortality appears to be safe.

CLINICAL	**Section 3 of 10**

History: A history suggesting the presence of any of the following factors should trigger an extensive diagnostic study:

- Maternal history

  o Rh negative (d;d) blood type
  o Known presence of isoimmune blood group antibodies
  o Prior administration of blood products
  o Risks of illicit drug use
  o Collagen disease
  o Thyroid disease or diabetes
  o Organ transplant (liver, kidney)
  o Blunt abdominal trauma (abuse, auto accident)
  o Coagulopathy
  o Use of indomethacin, sodium diclofenac, or potentially teratogenic drugs during pregnancy
  o Younger (<16 y) or older (>35 y) maternal age
  o Risk factors for sexually transmitted diseases
  o Hemoglobinopathy (especially with Asian or Mediterranean ethnicity)
  o Occupational exposure to infants or young children
  o Pet cat
  o Current or recent community epidemic of viral illness

- Family history

  o Jaundice in other family members or in previous child
  o Family history of twinning (specifically, monozygotic)
  o Family history of genetic disorders, chromosomal abnormalities, or metabolic diseases
  o Congenital malformation(s) in previous child
  o Previous fetal death(s)
  o Hydramnios in earlier pregnancies
  o Prior hydrops fetalis
  o Previous fetomaternal transfusion
  o Congenital heart disease in previous child

Physical: The presence of any of the following physical findings should prompt further diagnostic evaluation:

- Twinning
- Hydramnios
- Exanthem or other evidence of intercurrent viral illness
- Herpetic lesion(s) or chancre(s)
- Decrease in fetal movements

Causes: The underlying physiologic flaw for the usual hydropic fetus is an elevated CVP secondary to faltering cardiac output.

- Hematologic events, which lead to profound anemia and have been recognized to trigger hydrops fetalis, are summarized in Table 1.

Table 1. Hematologic Causes

Isoimmunization (hemolytic disease of the newborn, erythroblastosis)

- Rh (most commonly D; also C, c, E, e)
- Kell (K, k, Kp, Js[B])
- ABO
- MNSs (M, to date)
- Duffy (Fy[b])

Other hemolytic disorders

- Glucose phosphate isomerase deficiency (autosomal recessive)
- Pyruvate kinase deficiency (autosomal recessive)
- G-6-PD deficiency (X-linked dominant)

Disorders of red cell production

- Congenital dyserythropoietic anemia types I and II (autosomal dominant)
- Diamond-Blackfan syndrome (autosomal dominant)
- Lethal hereditary spherocytosis (spectrin synthesis defects) (autosomal recessive)
- Congenital erythropoietic porphyria (Günther disease) (autosomal recessive)
- Leukemia (usually associated with Down or Noonan syndrome)
- Alpha-thalassemia (Bart hemoglobinopathy)
- Parvovirus B19 (B19V)

Fetal hemorrhage

- Intracranial or intraventricular
- Hepatic laceration or subcapsular
- Placental subchorial
- Tumors (especially sacrococcygeal teratoma)
- Fetomaternal hemorrhage
- Twin-to-twin transfusion
- Isoimmune fetal thrombocytopenia

- Several years ago, Rh disease was considered the usual cause of fetal hydrops. More recently, the use of Ig in the at-risk mother, administered prior to maternal isoimmunization, should have made this an entirely preventable disorder. Sadly, this has not been the case. While a dramatic reduction in Rh D sensitization has been realized, the disorder has stubbornly persisted in a small group of women, many of whom have become isoimmunized from repeated exposure to foreign red blood cell (RBC) antigens that contaminate needles used for illicit drug use. One recent study notes this cause for 1 in 5 women with Rh sensitization; the prevalence of hydrops in this group was a stunning 80%.

  o The reduced prevalence of Rh D disease has made fetal hemolytic anemias secondary to maternal isoimmunization with other Rh-group and other blood group antigens more apparent. Many of these result in profound fetal anemia and hydrops (see Table 1). Because many others probably also exist, maternal antibody screening should at least search for those already demonstrated to lead to fetal hydrops. Molecular genetic technologies, specifically polymerase chain reaction (PCR) testing, have been demonstrated particularly to provide more precise and complete genotyping. Other heritable fetal hemolytic anemias have been associated with fetal hydrops. Most are uncommon, autosomal-recessive genetic diseases (pyruvate kinase deficiency, glucose phophate isomerase deficiency), and their association with fetal hydrops is limited to 1 or 2 reports. G-6-PD deficiency is a more common, X-linked recessive disorder; however, G-6-PD has been infrequently associated with fetal hydrops.
  o Diagnosis is important in these rare conditions because they are compatible with a relatively normal life, and fetal transfusions should be effective. Fetal RBC hemolysis from placental transfer of maternal IgG antibody against fetal RBC antigen(s) (termed isoimmune disease) continues to account for approximately 15-20% of individuals with hydrops fetalis. Early and precise diagnosis is of enormous importance because highly effective fetal therapy is now available, and long-term outcome is unimpaired in babies with these causes for hydrops. While fetal imaging confirms the presence of hydrops, it does so only after the fact. Studies preceding and predicting fetal deterioration include amniotic fluid (AF) bilirubin (delta optical density at 450 μ using Liley extrapolations) and, more recently, measurement of fetal hematocrit and hemoglobin levels by direct sampling using cordocentesis.

- Disorders of RBC production, resulting in functional fetal aplastic anemia, cause of hydrops

  o The importance of infection with B19V is increasingly recognized. Use of a sensitive and precise diagnostic test (PCR) has demonstrated that perhaps 20% of fetal hydrops is associated with this maternal/fetal infection. During seasons of particularly high prevalence, the proportion is much higher. Early diagnosis is of crucial importance because fetal treatment by direct transfusion has been demonstrated to be effective, the virus has not been demonstrated to have teratogenic effects, and growth and development of the survivors appear to be normal.
  o Heritable disorders of hemoglobin alpha-chain production are important causes of hydrops in Asian populations. These hemoglobinopathies have become increasingly important in the United States because of recent immigration patterns, particularly in the West. A recent report from Hawaii over a 10-year period identifies alpha-thalassemia as the single most important cause of fetal hydrops. Homozygous alpha-thalassemia, with deletion of all 4 alpha-globin genes, results in the total absence of alpha-hemoglobin chains in the fetus. This condition, ranging from 1 in 500 to 1 in 1500 in a Thai population, has been considered to be a fatal fetal condition (Bart hydrops).
  o More recently, a handful of survivors of hydrops fetalis due to alpha-thalassemia has been reported; however, all required fetal transfusions, all required repeated frequent transfusions after birth, and all surviving males had hypospadias. Thus, some health care professionals have questioned the practical and ethical basis of fetal and neonatal treatment. However, opportunities for treatment, such as stem cell transplantation, bone marrow transplantation, and gene replacement therapy, may hold promise for babies with this condition in the future. Fetal diagnosis of the condition has been confirmed (using PCR) from fetal deoxyribonucleic acid (DNA) samples of chorionic villus, fetal fibroblast (AF), and from fetal blood.

- Once disorders of hemoglobin alpha-chain production are confirmed, fetal interventions have been based on hematocrit and hemoglobin levels obtained by direct cordocentesis. Ultrasound findings are nonspecific, and they occur late. Several simple maternal screening techniques have been suggested, but DNA-based studies using a testing system that allows unequivocal identification of haplotypes commonly detected in Asian Americans (-SEA in 62%, -alpha 3.7 in 27%, -FIL in 11%) appear to be most promising in this country. Despite the current generally gloomy outlook and uncertain treatment of the baby with fetal hydrops, early diagnosis of the condition is important because maternal morbidity is very high with fetal hydrops due to alpha-thalassemia.
  - Other heritable disorders of RBC production are listed in Table 1, but none is very common. Some are fatal, but most are manageable after birth; some are associated with malformation syndromes. These heritable disorders all lead to hydrops in the same manner, as do the other conditions listed in Table 1.
  - Profound anemia leads to high-output cardiac failure and increased CVP. Early and precise diagnosis is important for fetuses with correctable conditions (eg, need for and timing of fetal transfusions) and for fetuses with conditions that are not correctable (to permit parents to understand options and participate in decisions about pregnancy management). Gene therapy may also hold promise for some of these babies in the future.
- Fetal hemorrhage is another important cause of fetal hydrops. Acute bleeding may be local or more generalized. Unless the origin is from a tumor mass, the bleeding may not be recognized early enough to intervene. Thus, fetal imaging is of critical importance, and a careful examination, particularly of those sites where bleeding has been associated with hydrops, is essential for prompt and proper fetal treatment.
  - Isoimmune fetal thrombocytopenia is probably more common than has been reported, and, because treatment may be effective in this condition, maternal screening for platelet antibodies should be routine in all incidents in which the cause of fetal hydrops remains undetermined. Sacrococcygeal teratoma is relatively common, accounting for a measurable proportion of incidents of fetal hydrops. Controlled trials are needed to be certain that currently proposed interventions are more helpful than harmful, but these interventions hold considerable promise. Effective treatment is especially important for this condition since associated anomalies are rare, and fully normal development is possible. Once again, fetal imaging studies are the cornerstone for diagnosis and management of sacrococcygeal teratoma.
  - The fetus may bleed into the mother, and this hemorrhage may be severe enough to lead to fetal death or hydrops. Disruptions of the fetomaternal circulation may be placental or related to tumors (choriocarcinoma, chorangioma), trauma, or partial placental abruption.
  - Early diagnosis of fetomaternal hemorrhage is deceptively simple, requiring a maternal blood smear to assess the proportion of circulating cells with fetal hemoglobin (resistant to acid elution). Unfortunately, recent automated modifications of this test are less specific and sensitive than the original Betke-Kleihauer test, and several newer tests have been proposed. Of these tests, the most promising appear to be either immunofluorescent flow cytometry or DNA analysis using PCR. More difficult than determining which test to use is knowing when to perform the tests since, in most reported cases, the diagnosis is usually too late to allow effective fetal intervention.
  - The earliest warning of the condition in most recent series has been reduced fetal body movements accompanied by sinusoidal fetal heart rate patterns and altered fetal biophysical profile. Confirmation of fetal anemia by direct cordocentesis is the final step to transfusion. Unfortunately, fetal transfusion often has been ineffective due to continued, repeated, massive fetal hemorrhages.
  - Placental vascular anastomoses are present in virtually all monochorionic monozygotic pregnancies. Twin-to-twin transfusion is balanced in most circumstances, with no excessive accumulation or loss for either twin. Sizable hemorrhages occur in 5-30% of these pregnancies when the shunting is unbalanced, leaving one twin anemic and the other polycythemic. These bleeds may lead to fetal death, impaired fetal growth, high-output cardiac failure from hypovolemic shock, congestive failure from volume overload, or hydrops fetalis, depending on the size of the bleed and whether it is acute or chronic. Extreme early hemorrhages may result in fetal acardia; somewhat later, they may be detected as fetus papyraceous or as a stuck twin or vanishing twin.

- While some placental studies suggest fewer (rather than more) vascular anastomoses with resultant trapping of blood in the recipient fetus, other placental studies demonstrate excessive and abnormal placental vascular communications. Velamentous cord insertion is much more common in those fetuses with large shunts. Curiously, the recipient (polycythemic) twin usually develops hydrops, not the (anemic) donor. Even more curiously, death of the hydropic twin (whether untreated and/or spontaneous, following fetal therapy, or after selective feticide) is not uncommonly followed by the development of hydrops in the remaining twin.
- Reasons for all these events remain causes for speculation. Definitive diagnosis also is surprisingly difficult, since hydrops may occur in either (or both) twin, disparities in fetal size may not be present, and fetal hemoglobin or hematocrit levels may be well outside the reference range (high or low) in the absence of any hydrops.
- Ultrasound evidence of same-sex twins, a monochorionic placenta, with hydramnios in one sac and oligohydramnios in the other sac, often is used to make the diagnosis. These findings and disparities in fetal sizes (15-25%) are useful, but unfortunately they are not definitive. Determination of fetal hemoglobins by cordocentesis is employed; however, differences in fetal hemoglobin concentration exceeding 5 g/dL are common in the absence of hydrops, and, conversely, differences less than this may be found in individuals with hydrops.
- Significant differences in serum protein levels also may be observed in twins with hydrops fetalis, and atrial natruretic factor concentrations usually are high. Unfortunately, none of these findings are diagnostic. Clearly, earlier and more precise fetal diagnostic methods, which measure degree of functional dysfunction, are needed. Most promising in this regard are pulsed Doppler ultrasound measurements of umbilical vessel blood velocity. Such studies hold promise of providing an earlier window of opportunity for fetal diagnosis and treatment. Outcome is surprisingly poor in this condition. Most twins with hydrops die before birth (42-86%), and a shocking proportion of survivors of the condition have cardiovascular and neurologic damage. Ultrasound studies demonstrate cerebral white matter damage, suggesting antenatal necrosis in approximately one third. Follow-up studies of neurodevelopment suggest serious impairment in approximately one quarter of surviving twins.
- Many (if not most) surviving twins have significant cardiomyopathy (predominantly right-sided), usually associated with pulmonary outflow obstruction; pulmonary artery calcification and endocardial fibroelastosis also are common. Neutropenia, impaired fetal growth, reduced bone density, and mineralization have been observed in the surviving donors. Optic nerve hypoplasia has been reported, and peripheral vascular ischemic necrosis with gangrene of distal extremities has been observed in several individuals with the condition. Coagulopathy and embolic phenomena were speculated in many early studies; however, scant evidence for them exists in recent reports. Very premature delivery is common and contributes undoubtedly to the morbidity and mortality.
- Treatment successes have been reported with transfusion of the anemic fetus, plasmapheresis of the polycythemic twin, laser ablation of placental vascular anastomoses, and amnioreduction; however, failures and serious complications also have been reported with each of these.

- Cardiovascular problems causing or associated with hydrops are summarized in Table 2. While extensive, the list is inevitably incomplete as new associations are reported each year.

Table 2. Cardiac Causes

Structural anomalies

- Abnormalities of left ventricular outflow
  - Aortic valvular stenosis
  - Aortic valvular atresia
  - Coarctation of the aorta
  - Aortico-left ventricular tunnel
  - Atrioventricular canal
  - Left ventricular aneurysm
  - Truncus arteriosus
  - Hypoplastic left heart
  - Spongiosum heart
  - Endocardial fibroelastosis
- Abnormalities of right ventricular outflow
  - Pulmonary valvular atresia or insufficiency
  - Ebstein anomaly
  - Arteriovenous malformations
  - Diffuse hemangiomatosis
  - Placental hemangioma
  - Umbilical cord hemangioma
  - Hepatic hemangioendothelioma
  - Abdominal hemangioma
  - Pulmonary arteriovenous fistula
  - Cervical hemangioendothelioma
  - Paratracheal hemangioma
  - Cutaneous cavernous hemangioma
  - Arteriovenous malformations of the brain

No structural anomalies

- Obstruction of venous return
  - Superior or inferior vena cava occlusion
  - Absent ductus venosus
  - Umbilical cord torsion or varix
  - Intrathoracic or abdominal tumors or masses
  - Disorders of lymphatic drainage
- Supraventricular tachycardia
- Congenital heart block
- Prenatal closure of the foramen ovale or ductus arteriosus
- Myocarditis
- Idiopathic arterial calcification or hypercalcemia

- Congenital structural anomalies of the heart may accompany as many as 1 in 4 babies with hydrops; both right-heart and left-heart anomalies, systolic-overload and diastolic-overload conditions, high-output, and congestive situations are represented.

  - Structural cardiac defects are commonly accompanied by other anomalies and often are associated with cytogenic abnormalities. Examples include the association between coarctation of the aorta and Turner syndrome, the relation between atrioventricular (AV) canal and/or endocardial cushion defects and Down syndrome, and the common association of Turner syndrome with cystic hygroma, left-sided lymphatic flow defects, and left-heart outflow defects.

- o Fibroelastosis may be an isolated abnormality; however, fibroelastosis more commonly represents an endocardial response to chronic fetal myocardial stress. Prenatal detection of a cardiac defect should always trigger a careful search for other malformations, and karyotyping should be performed in all such fetuses. Arteriovenous malformations (AVMs) are often cited causes of hydrops; they are listed individually in [Table 2].

- Impaired right-heart filling is also an important cause of hydrops. Although uncommon, umbilical or vena caval thromboses are noted, since they theoretically may be correctable if diagnosed early enough. Conversely, tumor compression is a frequently reported cause of hydrops. Several of these masses involve lymphatic malformation and/or obstruction; cystic hygroma is a particularly important example.
- Prenatal closure of the foramen ovale or ductus arteriosus prematurely converts the (parallel) fetal circulation to a (serial) postnatal circulation; associated problems are obvious.

  - o Most recorded instances of premature ductal closure are iatrogenic, related to maternal administration of indomethacin or sodium diclofenac.
  - o Several instances of idiopathic arterial calcification with hydrops have been reported. In one such incident, fetal serum calcium levels were elevated, and a possible association with Williams syndrome was suggested. In 3 other cases, lysosomal storage diseases were present (Gaucher, sialidosis, galactosialidosis). No associations were noted in 4 cases. Hydropic recipients of twin-twin transfusion who survive usually also have pulmonary artery calcification.

- Fetal supraventricular tachycardias are important causes of hydrops because they can be diagnosed accurately by cardiac imaging in early pregnancy, they may be treated effectively before hydrops develops, and, since associated malformations or syndromes are rare, they have anticipated good outcomes. Whether an AV block is present (atrial flutter) or not (tachyarrhythmia), survival rates of 85-95% are typical, and neurodevelopmental outcome usually is normal. The condition is more common in males than in females (2:1), and hypoglycemia is a commonly associated finding, at least after birth. Clinical experience and animal model studies indicate that hydrops occurs with sustained cardiac rates of less than 220-230 beats per minute (bpm) and that the risk is related directly to the degree of prematurity.
- Congenital heart block (CHB) is also often associated with hydrops. Diagnosis is made using cardiac imaging; rates are always less than 90 bpm and usually less than 65 bpm. Approximately two thirds to three fourths occur in pregnancies complicated by maternal collagen disease. Maternal IgG antinuclear antibodies cross the placenta and attack fetal collagen in the conduction bundle.
  - o Why some fetuses develop CHB and some do not is unclear; however, an association with human leukocyte antigen (HLA) types (HLA-DR3, among others) has been suggested.
  - o Treatment with a variety of drugs has generally been unsuccessful, as has fetal surgery for pacing. Recent evidence suggests corticosteroid therapy may be of benefit.
- Virtually all of the remaining babies, whose mothers have no collagen disorder, have serious, complicated, cardiac structural defects. The most common lesions are AV canal and/or endocardial cushion defects, transposition of the great vessels, and other isomerisms. Outcomes for these babies are grim. Mortality is 25-35% if cardiac structure is normal; many survivors require neonatal surgery for pacing, and no information is available on long-term outlooks. Since the cardiac structural abnormalities are so serious and complex, mortality and morbidity are much higher if cardiac anomalies are present.
- The immature fetus is particularly susceptible to overwhelming viral and bacterial infection. Those agents, which do not kill quickly, may cause smoldering generalized infections with myocarditis, suppressed erythropoiesis and myelopoiesis, hemolysis, and hepatitis. Such infections may lead to hydrops fetalis. Those agents reported to be causative, to date, are listed in [Table 3]. This list will change with time as other agents, yet to be unidentified, are demonstrated to cause hydrops.

<p align="center">**<mark>Table 3.</mark> Infectious Causes**</p>

- B19V
- Cytomegalovirus (CMV)
- Syphilis
- Herpes simplex
- Toxoplasmosis
- Hepatitis B
- Adenovirus
- *Ureaplasma urealyticum*
- Coxsackievirus type B
- *Listeria monocytogenes*

- The association of congenital syphilis with hydrops is classic. Fetal and placental edema accompanied by serous effusions first was described generations ago. However, the surprising frequency with which maternal serologic tests for syphilis may appear negative in this condition is less well known.
  - The prozone phenomenon, observed during primary and secondary maternal syphilis, occurs when a higher-than-optimal amount of antisyphilis antibody in the tested maternal sera prevents the flocculation reaction typifying a positive result in reagin tests. In these circumstances, dilution of the tested serum is necessary to make the correct diagnosis. Thus, serum dilution (to as much as 1:1024 or greater) should be routine in high-risk situations and should certainly be used in any individual in whom fetal hydrops of unknown etiology exists.
  - Early, accurate diagnosis of this infection is critical, since fetal treatment is available and effective. Several viral infections have been associated with fetal hydrops.

- The number of viruses implicated and the frequency of these cases have paralleled the increased recognition of this association and the improved simplicity and sensitivity of diagnostic methods. Hydrops in these conditions appears to be the cumulative result of viral effects on marrow, myocardium, and vascular endothelium. Currently, reports of effective fetal treatment are rare.
- Of particular interest is recent evidence of how commonly acute B19V infection is a cause of fetal hydrops. The virus was first identified in 1974 and first linked with fetal hydrops 10 years later. Evidence published since then suggests this virus may be the single most important currently recognized cause of fetal hydrops.

  - Parvovirus may be the cause of as much as one third of all incidents of hydrops fetalis. The virus directly attacks red cell precursors and is visible as intranuclear inclusions in stained RBC preparations. Thrombocytopenia is usually present, also.
  - Outcome in such fetuses is surprisingly good; spontaneous resolution occurs in approximately one third of such incidents, and approximately 85% of those who receive fetal transfusions survive. The virus is not teratogenic and, despite reports of viral persistence in myocardial and brain tissues, neurodevelopmental outcome in survivors appears to be normal. Early, accurate diagnosis, using maternal serologic and/or molecular biologic PCR techniques, is essential. Positive results are usually confirmed by direct fetal PCR, hemoglobin, hematocrit, and platelet studies to plot a proper treatment plan.

- An interesting association of hydrops exists with fetal meconium peritonitis. At least 16 such cases are found in the literature. No baby reported before 1991 had evidence of infection; however, CMV (1), hepatitis B (1), and B19V (5) were found in 7 of 8 cases reported since 1991. The only instance of meconium peritonitis and hydrops without confirmed infection in these later reports was probably iatrogenic, since it followed

paracentesis with subsequent placement of a peritoneoamniotic shunt. These observations suggest that the coexistence of hydrops and meconium peritonitis should be assumed to be related to fetal infection until proven otherwise.

- Hydrops fetalis has been associated with more than 75 inborn errors of metabolism, chromosomal aberrations, and genetic syndromes. Approximately 50 of the more common errors are listed in Table 4. An additional 20 or more reports of imprecisely defined chromosomal or genetic syndromes identify hydrops as an incidental finding.

<mark>Table 4.</mark> Associated Metabolic Disorders, Genetic Syndromes, and Chromosomal Abnormalities

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Inborn errors of metabolism

- Glycogen-storage disease, type IV
- Lysosomal storage diseases
    - Gaucher disease, type II (glucocerebroside deficiency)
    - Morquio disease (mucopolysaccharidosis, type IV-A)
    - Hurler syndrome (mucopolysaccharidosis, type 1H; alpha1–iduronidase deficiency)
    - Sly syndrome (mucopolysaccharidosis, type VII; beta-glucuronidase deficiency
    - Farber disease (disseminated lipogranulomatosis)
    - G_{M1} gangliosidosis, type I (beta-galactosidase deficiency)
    - Mucolipidosis I
    - I-cell disease (mucolipidosis II)
    - Niemann-Pick disease, type C
- Salla disease (infantile sialic acid storage disorder [ISSD] or sialic acid storage disease, neuroaminidase deficiency)
- Hypothyroidism and hyperthyroidism
- Carnitine deficiency

Genetic syndromes (autosomal recessive, unless otherwise noted)

- Achondrogenesis, type IB (Parenti-Fraccaro syndrome)
- Achondrogenesis, type II (Langer-Saldino syndrome)
- Arthrogryposis multiplex congenita, Toriello-Bauserman type
- Arthrogryposis multiplex congenita, with congenital muscular dystrophy
- Beemer-Langer (familial short-rib syndrome)
- Blomstrand chondrodysplasia
- Caffey disease (infantile cortical hyperostosis; uncertain inheritance)
- Coffin-Lowry syndrome (X-linked dominant)
- Cumming syndrome
- Eagle-Barrett syndrome (prune-belly syndrome; since 97% males, probably X-linked)
- Familial perinatal hemochromatosis
- Fraser syndrome
- Fryns syndrome
- Greenberg dysplasia
- Lethal congenital contracture syndrome
- Lethal multiple pterygium syndrome (excess of males, so probably X-linked)
- Lethal short-limbed dwarfism
- McKusick-Kaufman syndrome
- Myotonic dystrophy (autosomal dominant)
- Nemaline myopathy with fetal akinesia sequence
- Noonan syndrome (autosomal dominant with variable penetrance)
- Perlman/familial nephroblastomatosis syndrome (inheritance uncertain)
- Simpson-Golabi-Behmel syndrome (X-linked [Xp22 or Xp26])

- Sjögren syndrome A (uncertain inheritance)
- Smith-Lemli-Opitz syndrome
- Tuberous sclerosis (autosomal dominant)
- Yellow nail dystrophy with lymphedema syndrome (autosomal dominant)

Chromosomal syndromes

- Beckwith-Wiedemann syndrome (trisomy 11p15)
- Cri-du-chat syndrome (chromosomes 4 and 5)
- Dehydrated hereditary stomatocytosis (16q23-qter)
- Opitz G syndrome (5p duplication)
- Pallister-Killian syndrome (isochrome 12p mosaicism)
- Trisomy 10, mosaic
- Trisomy 13
- Trisomy 15
- Trisomy 18
- Trisomy 21 (Down syndrome)
- Turner syndrome (45, X)

- The heterogeneity of this collection of associations is bewildering at first glance. However, the common thread that runs through is useful for the clinician to understand. Most of the babies with hydrops associated with the conditions listed in Table 4 have severe complex cardiac defects, disorders of lymphatic drainage, arteriovenous malformations, impaired production of properly functioning red cells, and/or thoracoabdominal masses that impair venous return to the heart. Thus, the same disturbed pathophysiology identified as causing hydrops in the animal studies is reflected in these conditions.

  - Inheritance for most of these conditions (when known) is autosomal, most commonly recessive. Since a few of these conditions are X-linked recessive, slightly more males are affected among this particular set of causes. Gene therapy may hold therapeutic promise for the future; however, outcomes are generally grim for babies with hydrops related to these causes. Accurate diagnosis is particularly important in these babies, despite their poor prognosis, since parental counseling is of critical importance in the management of current and future pregnancies for these families.
  - Fetal hydrops has been associated with approximately 10 of the approximately 50 lysosomal storage disorders. Little doubt appears to exist that hydrops will be linked with most such inborn errors of metabolism in the near future.
  - Cystic hygroma is often found in several of these conditions. These vascular tumors are associated commonly with complex profound aberrations of lymphatic drainage. They are usually found in the neck but may also be present in the abdomen or thoracic cavity. Two thirds to three fourths of fetuses with this tumor have chromosomal abnormalities (most commonly 45,XO), and those fetuses with normal chromosomes often have major malformations. This association with Turner, Noonan, and lethal multiple pterygium syndromes is particularly notable. Mortality is extremely high (85-96%), but early precise diagnosis is important for purposes of genetic counseling and pregnancy management. The reports of spontaneous remissions with healthy long-term survival are important to note.

- Thoracic and abdominal tumors are common causes of fetal hydrops. This association makes physiologic sense because the location and size of these masses are likely to obstruct the return of venous or lymphatic fluids to the heart. Some are commonly associated with major malformations and/or chromosomal abnormalities and, consequently, have a poor long-term prognosis. For example, upper airway obstructions are associated with other major malformations in more than one half of the cases reported, and the association of fetal rhabdomyomas with tuberous sclerosis and complex cardiac malformations is well recognized.

<p align="center">**<mark>Table 5.</mark> Tumor or Mass Causes**</p>

Intrathoracic tumors or masses

- Pericardial teratoma
- Rhabdomyoma
- Mediastinal teratoma
- Cervical vascular hamartoma
- Pulmonary fibrosarcoma
- Leiomyosarcoma
- Pulmonary mesenchymal malformation
- Lymphangiectasia
- Bronchopulmonary sequestration
- Cystic adenomatoid malformation of the lung
- Upper airway atresia or obstruction (laryngeal or tracheal)
- Diaphragmatic hernia

Abdominal tumors or masses

- Metabolic nephroma
- Polycystic kidneys
- Neuroblastoma
- Hepatic mesenchymal hamartoma
- Hepatoblastoma
- Ovarian cysts

Other conditions

- Placental choriocarcinoma
- Placental chorangioma
- Cystic hygroma
- Intussusception
- Meconium peritonitis
- Intracranial teratoma
- Sacrococcygeal teratoma

- Venous return is directly impaired by such conditions as pericardial teratomas and cardiac rhabdomyosarcomas. Upper airway (laryngeal, tracheal) atresia or obstruction leads to massive pulmonary overdistention and, thus, to impaired cardiac filling. Cystic hygromas (see Table 5) are mentioned again since they comprise an important and common example of mass compression with obstruction of venous-lymphatic return. Meconium peritonitis is noted in Table 5 and in Table 3. This redundancy is excused by the fact that some observers have postulated an association with hydrops on the basis of mass effects on venous return; as noted earlier, the association is almost certainly one with fetal infection and consequent red cell aplasia.

  - Some of these conditions may lead to fetal hydrops not because of mass compression effects but because their intense vascularization may lead to arteriovenous shunting and/or to massive fetal hemorrhage. Such consequences are especially common with sacrococcygeal teratomas and with placental chorioangiomas. In both instances, fetal high-output cardiac failure ultimately may lead to fetal hydrops and/or death. Sacrococcygeal teratoma is associated with hydrops in one fifth to one third of cases in several case series; fetal coagulopathy,

most commonly thrombocytopenia, is found in approximately the same proportion of cases. Tumor size by sonography has not been demonstrated to be an independent prognostic factor; however, solid, highly vascular tumors lead to hydrops more often than those with a more cystic, less vascular structure.

- o Since chromosomal abnormalities and life-threatening anomalies are rare with sacrococcygeal sequestration, early diagnosis and aggressive fetal treatment are particularly important with this condition. While bloody AF secondary to rupture of the highly vascular teratoma is not uncommon, diagnosis in most cases has been made only after hydrops has developed.
- o Early routine fetal imaging may be the only way in which early diagnosis can be made in this condition; however, the low incidence of sacrococcygeal teratoma may preclude cost-effective screening for this condition. Elevated concentrations of alpha-fetoprotein (AFP) and/or acetylcholinesterase in AF have been found to accompany fetal sacrococcygeal teratoma, but the invasive sampling and low specificity appears to preclude these tests as routine screening procedures. While placental chorioangiomas are common (present in approximately 1% of pregnancies), large vascular tumors with cardiovascular and hematologic consequences are very uncommon. When present, the pathophysiology is remarkably similar to that found with fetal sacrococcygeal teratomas. Diagnosis and techniques for early intervention are also similar.

- Bronchopulmonary sequestration is a condition in which abnormal vascular supply and misplacement of a portion of the lung may lead to torsion of the affected lobes, profound obstruction of lymphatic and venous return, and tension hydrothorax. This sequence of events leads to fetal hydrops in perhaps one third of such cases. Although drainage of the hydrothorax, definitive diagnosis using color Doppler imaging, and fetal angiography have been described, and though fetal surgical excision of the affected portion of the lung may improve survival in this condition, nearly two thirds of these cases fail to be diagnosed before fetal death or birth occurs.

- Cystic adenomatoid malformation of the lung may also lead to hydrops by mass compression of venous return. Because this condition is seldom associated with other malformations or with chromosomal abnormalities and because fetal surgical maneuvers have demonstrated considerable promise with some forms of the disorder, early and precise diagnosis using fetal imaging techniques is of critical importance. Pulmonary capillary-alveolar development is abnormal in this condition, and 3 degrees of severity, described initially by Stocker, have been used to predict prognosis.
  - o Type I: The fetus with large (>2 mm), isolated cysts seldom develops hydrops, and spontaneous remissions have been reported. Drainage or excision of individual cysts has also been reported with generally favorable outcomes.
  - o Type II: Poorer prognosis is associated in the fetus with smaller (<2 mm) diffuse macrocysts, and isolated fetal pulmonary excisions have been proposed in those who develop hydrops.
  - o Type III: In the fetus with microcystic disease, the affected lung appears solid, hydrops is common, and outcome is generally unfavorable.

- Compression of fetal lung, common in so many of the conditions listed in Table 5, not only impairs cardiac return but also has an additional particularly serious consequence. External compression of developing fetal lung is known to impair both anatomic and biochemical maturation. Pulmonary hypoplasia, with a profound reduction in the number of functional alveolar units, is a common finding when fetal hydrops accompanies these conditions. Delayed or impaired maturation of pulmonary surfactant production is another consequence of impaired expansion of the fetal lung, thus worsening the already serious compromise of extreme prematurity in these babies.

Gaucher Disease

Heart Failure, Congestive

Hemochromatosis,

Neonatal Hepatitis B

Hepatoblastoma

Hepatocellular Carcinoma

Herpes Simplex

Virus Infection Hypercalcemia

Hypernatremia

Hypoplastic Left Heart Syndrome

Hypoprothrombinemia

Hypospadias

Hypothyroidism

Hypoxic-Ischemic Encephalopathy

Infant of Diabetic Mother

Interrupted Aortic Arch

Intussusception

Kasabach-Merritt Syndrome

Klippel-Trenaunay-Weber Syndrome

Listeria Infection

Methemoglobinemia

Mitral Valve Insufficiency

Mucopolysaccharidosis Type IV

Mucopolysaccharidosis Type VI

Mucopolysaccharidosis Type VII

Multicystic Renal Dysplasia

Myelodysplasia

Myocarditis, Nonviral

Myocarditis, Viral

Neonatal Resuscitation

Neonatal Sepsis

Noonan Syndrome

Oliguria

Omphalocele and Gastroschisis

Osteogenesis Imperfecta

Pacemaker Therapy

Parvovirus B19 Infection

Patent Ductus Arteriosus

Pericardial Effusion, Malignant

Pericarditis, Constrictive

Pericarditis, Viral

Pleural Effusion

Polycystic Kidney Disease

Polycythemia

Polycythemia of the Newborn

Polyhydramnios and Oligohydramnios

Posterior Urethral Valves

Progressive Familial Intrahepatic Cholestasis

Pulmonary Hypertension, Persistent-Newborn

Pulmonary Hypoplasia

Pulmonary Sequestration

Pulmonary Stenosis, Infundibular

Pulmonary Stenosis, Valvar

Pyruvate Kinase Deficiency

Rhabdomyosarcoma

Shock

Shock and Hypotension in the Newborn

Single Ventricle

Sinus Node Dysfunction

Smith-Lemli-Opitz Syndrome

Splenomegaly

Supraventricular Tachycardia, Atrial Ectopic Tachycardia

Supraventricular Tachycardia, Atrioventricular NodeReentry

Supraventricular Tachycardia, Junctional Ectopic Tachycardia

Supraventricular Tachycardia, Wolff-Parkinson-White Syndrome

Syphilis

Systemic Lupus Erythematosus

Tetralogy of Fallot With Absent Pulmonary Valve

Tetralogy of Fallot With Pulmonary Atresia

Thalassemia

Thyroid Storm

Toxoplasmosis

Turner Syndrome

Ureteropelvic Junction Obstruction

Urethral Anomalies and Urethral Prolapse

Ventricular Septal Defect, General Concepts

Ventricular Septal Defect, Muscular

Ventricular Septal Defect, Perimembranous

Ventricular Septal Defect, Supracristal

Ventricular Tachycardia

Williams Syndrome

Other Problems to be Considered:

Hypoxic-ischemic brain injury in newborn
Laryngeal stenosis
Pulmonary hypertension, congenital heart disease
Prune-belly syndrome
Uncommon Coagulopathies

Lab Studies:

- Diagnostic studies may be considered best by temporal grouping (ie, fetal, maternal, placental, neonatal, postmortem). Assessments generally proceed from low-risk noninvasive tests to higher-risk invasive techniques as required for precise and complete diagnosis to properly manage the individual pregnancy.
- Obtain several maternal laboratory studies concurrent with the initial fetal imaging assessment.

  o Assessment of maternal blood type (red cells) and antibody screen (identification, and quantitation when indicated, of maternal plasma antibodies) are standard screening tests recommended in most guidelines for prenatal care. Over the past few years, the introduction of new molecular genetic techniques (PCR) has demonstrated considerable promise; however, definitive comparisons with standard methods are not yet available. More than 85% of Rh-sensitized women whose anti-D titers were 1:512 or higher were found to be HLA type DQBI allele*0201. Although this single study suggests that HLA typing may be of value in the prospective management of isoimmunization, this observation requires confirmation and further study.
  o Qualitative and quantitative estimates of the proportion of red cells containing fetal hemoglobin in the maternal circulation are of particular value.

    ▪ The Betke-Kleihauer technique depends on the different vulnerability of cells containing fetal hemoglobin from those with adult hemoglobin when subjected to acid-elution.
    ▪ A newer method using flow cytometry has also been found to be useful.
    ▪ Results using either method must be interpreted with considerable caution, since poor sensitivity and specificity of these diagnostic tests has been demonstrated in several studies.

  o The search for maternal-fetal infection must be intensive. Syphilis serology was a standard prenatal screening test for decades. More recently, the test has been used more selectively, despite the absence of any good evidence for this change. If fetal hydrops is suspected, syphilis serology is mandatory with repeat serial testing and, very importantly, with dilution of maternal serum. The prozone effect has been demonstrated repeatedly with fetal hydrops due to syphilis, thus dilution of maternal serum to avoid false-negative results is required.
  o Antibody screens for common fetal infections (toxoplasmosis, other infections, rubella, CMV infection, and herpes simplex [TORCH]) and more sensitive and specific enzyme-linked immunosorbent assay (ELISA) studies for individual infectious agents have been used for many years. More recently, the PCR technique generally is accepted as the criterion standard and should be employed whenever possible.
  o Hemoglobin electrophoresis for alpha-thalassemia heterozygosity has been useful in ethnically at-risk populations. In regions where ethnic diversity is high, routine screening may be preferable to selection based on ethnicity. More recently, PCR screens and colorimetric monoclonal antizeta antibody tests for heterozygote alpha-thalassemia have been demonstrated as economically feasible screening procedures.
  o Maternal serum screening tests (multiple-marker, triple-screen, triple-marker), commonly used if fetal anomaly is suspected, are of uncertain value with fetal hydrops.

    ▪ In one study, positive screening tests (any of the 3 used) with a sensitivity of only 60% in 19 cases of Turner syndrome distinguished some fetuses with cystic hygroma and/or hydrops from those without. Individual components of these tests were examined separately in several other studies.
    ▪ Elevated AFP levels have been reported in hydrops associated with fetomaternal hemorrhage, umbilical cord hemangioma, polycystic kidneys, CMV, and Parvovirus;

however, AFP levels are similar in babies with Turner syndrome with or without hydrops. Use of AFP screening as an index of fetal aplastic crisis in maternal Parvovirus infection has been recommended but is of dubious value, since several fetal deaths have been observed with AFP levels within reference range. The precise diagnostic value of AFP screening is uncertain, since definitive studies are not available.

- Low levels of unconjugated estriol (uE3) have been found in one hydropic baby with Smith-Lemli-Opitz syndrome, but the test has not demonstrated value in distinguishing between babies with or without hydrops, and normal levels have been observed in several hydropic deaths.
- Human chorionic gonadotropin levels have been reported as significantly elevated in hydrops with sacrococcygeal teratoma, choriocarcinoma, Parvovirus, Turner syndrome, and Down syndrome; however, these levels have also been normal in several hydropic fetal deaths related to Parvovirus.
- In a single study, inhibin-A levels were elevated markedly in 12 fetuses with Turner syndrome with hydrops and were reduced significantly in those fetuses without hydrops.
- Maternal serum IgG placental alkaline phosphatase levels are increased with fetal hydrops; currently, clinical utility of this finding is untested.

- Direct invasive sampling studies of fetal AF or placental tissues or fluids have demonstrated value for definitive diagnosis, monitoring of treatment efficacy, and accurate prognosis in a number of conditions associated with hydrops.

  o Elevated levels of AF bilirubin, as measured by the spectrophotometric extrapolation technique first described by Liley, have been demonstrated to be highly sensitive predictors of the severity of fetal anemia due to isoimmunization.
    - Specificity is somewhat less, since alpha-feto bilirubin may also be elevated due to maternal hemoglobinopathy or hepatitis and in association with impaired fetal swallowing due to fetal gastrointestinal obstruction and a number of fetal central nervous system disorders.
    - Recent reports have suggested the use of sonographic methods to detect fetal anemia; however, routine use of such noninvasive methods is not justified in the absence of definitive evidence of their superior sensitivity and specificity, at less risk, when compared with the standard proven method of AF bilirubin analysis.

  o Direct enzyme assays or biochemical analyses of measurements of levels of specific metabolic products may be indicated in the pregnancy at risk of hydrops because of inborn errors of metabolism.
    - Such studies may use samples from the mother and father (red cells, serum, urine, tissue), fetus (skin fibroblast cultures or leukocytes from AF, fetal red cells, white cells, serum samples from direct cordocentesis, serous effusions), placenta (chorionic villous sampling, placental biopsy), or AF.
    - Examples include biochemical analyses of urine or AF for abnormal oligosaccharide, mucopolysaccharide, and sphingolipid metabolites when lysosomal disorders are suspected or determination of AF 7-dehydrocholesterol reductase if history and findings suggest Smith-Lemli-Opitz syndrome.

  o Fetal serum endothelin levels are elevated more than 2-fold in recipients; however, these levels are normal in donors with twin-twin transfusion syndrome. Endothelin levels were related to presence of and severity of hydrops in these cases. Changes in fetal serum liver enzymes, particularly alanine transaminase and glutamyl transpeptidase, have been demonstrated to occur following correction of the anemia by fetal transfusion. Whether or not these observations may be of diagnostic or prognostic use is currently untested.
  o Direct fetal diagnostic studies for Parvovirus include histologic staining methods (RBC), digoxigenin-labeled B19. DNA probe (PCR), and avidin-biotin complex immunohistochemical and immunofluorescent studies, among others. Currently, PCR methods appear to be best, although definitive studies providing sensitivity and specificity are not available.

- o Karyotyping is always indicated if history or ultrasound results reveal a constellation of findings consistent with a chromosomal aberration or if maternal or family history is suggestive.
  - Chromosome studies are indicated whenever initial diagnostic studies have failed to identify with certainty a specific cause for the fetal hydrops.
  - Chromosomal analyses may be performed on desquamated fetal epithelial cells in AF, fetal tissue biopsy samples, or placental (fetal tissue) biopsy samples.
  - An increase in AFP has been observed in almost 1 in 10 (8.4%) genetic amniocenteses; fetal mortality exceeded 1 in 10 (14%) when such AFP elevations occurred. Evidence of fetomaternal bleeding is present in 3 of 4 chorionic villous samplings. Thus, careful weighing of benefit versus risk must be made whenever direct invasive diagnostic methods are considered.
- o To obtain more precise information concerning fetal status, direct fetal sampling by cordocentesis (or periumbilical sampling) has been used with increasing frequency.
  - Acidemia, hypoxemia, and hypercarbia are found in most studies of fetal acid-base balance and blood-gas status obtained at time of direct fetal treatment. These results are nonspecific and anticipated and, while they may be of use in immediate management, are unlikely to be of value in longer-term care of the fetus with hydrops.
  - Analyses of serous effusion fluids (pleural, pericardial, or ascitic, most commonly) have been of surprisingly little value. For example, lymphocyte counts considered characteristic of congenital chylothorax when found in the newborn infant have been observed in pleural effusions from fetuses with CMV disease.
  - Serologic tests for specific infections, hemoglobin or hematocrit measurements, platelet counts, white cell counts and morphologic analyses, specific enzyme analyses, and karyotyping are just a few of the more common measurements obtained. While this information may be invaluable in specific cases, use of such invasive methods on a routine basis carries significant risks.
  - Fetal sampling by cordocentesis is followed by significant bradycardia in almost 1 in 20 samplings (3.8%); of those with such complications, almost two thirds die (61.5%).

- o Elevated AF alkaline phosphatase has been observed in association with fetal hydrops due to Turner syndrome; while likely to be a nonspecific finding, further study is necessary.

- The fetal biophysic profile has been demonstrated to be abnormal in severe fetal hydrops.
  - o Cardiotocographic records obtained 12 hours prior to fetal death demonstrate absence of short-term and long-term variability, absence of tachycardia, presence of late decelerations, and terminal bradycardia.
  - o Sinusoidal heart-rate patterns have been observed consistently in hydrops associated with severe fetal anemia related to isoimmunization and fetomaternal hemorrhage.

Imaging Studies:

- Once the possibility of fetal hydrops is considered or suspected, sophisticated and complete fetal imaging studies are an initial absolute necessity. Hydrops is defined by the presence of serous effusion(s) in a fetus with subcutaneous tissue edema. Some authors have distinguished the presence of a single effusion (pleural, peritoneal) as an entity distinct from hydrops; however, recent evidence suggests that an isolated effusion often (if not usually) progresses to overt fetal hydrops. Exceptions appear to be isolated chyloperitoneum/ascites (usually associated with obstructive uropathy and, thus, not true hydrops) and pleural or peritoneal effusions that regress spontaneously (see Treatment). Thus, careful and complete imaging is required to establish the diagnosis and the extent of the hydrops.
- Equipment employed must be capable of providing high-resolution images at large depth.
  - o Linear array transducers are commonly used; however, sector scanners provide better views of the heart and many other structures.
  - o Range-gated Doppler capability is optimal for functional physiologic assessments. Use of high-frequency transvaginal 2-dimensional and pulsed-wave/color Doppler flow mapping particularly has been promising.
- The initial imaging study may provide important clues concerning the origin of the fetal

condition. For example, most arrhythmias and anomalies may be detected even in the process of establishing the initial diagnosis. However, in most cases, more complex, serially repeated studies may be required to accurately define the constellation of findings in the fetus.

- Specific echocardiographic assessment of fetal cardiac structure and function is required in most cases of fetal hydrops. Essential elements of this examination should include definitive results concerning (1) assessment of biventricular outer dimensions in diastole and of the cardiothoracic ratio, (2) presence or absence of AV valve regurgitation, and (3) umbilical vessel blood flow velocities and pulsations.

  - Biventricular diameter in diastole had 100% sensitivity and 86% specificity for detection of cardiac failure in one study. These observations, confirmed by results from several other reports, address the basic underlying pathophysiologic disturbance in faltering cardiac output of the fetus with hydrops and increased CVP.
  - Presence of AV valve regurgitation is a common finding, suggesting right-heart failure or increased preload. Persistence of serious functional AV valve incompetence following treatment interventions is ominous, particularly in terms of fetal outcome. The proportion of atrial area taken up by the regurgitant jet is related to hydrops. The proportion of systolic time during which AV valve insufficiency is demonstrated is also related to hydrops. In one study, AV valve insufficiency was pansystolic in all babies with hydrops.
  - Umbilical and fetal abdominal vessel pulsations, flow velocities, and waveforms have been studied by several investigators in hydrops caused by tachyarrhythmias, alpha-thalassemia, and twin-twin transfusion.

    - Because sensitivity, specificity, and predictive values are not available, the practical clinical value of these studies is uncertain.
    - However, the results available to date suggest that they may provide valuable quantitative and qualitative pathophysiologic information and may even be predictive of fetal deterioration prior to the development of overt hydrops in some situations.

  - Umbilical venous (UV) blood flow, normally nonpulsatile, demonstrates pulsatile (or double-pulsatile) flow, a finding consistent with an increased fetal CVP.
    - Pulsed Doppler duplex ultrasound studies demonstrate higher UV and inferior vena cava (IVC) blood velocity and blood flow, suggesting an increase in the preload (cardiac) index. Studies of IVC, hepatic vein, and ductus venosus blood flow demonstrate similar results.
    - In hydrops caused by sustained tachycardia, reversal of blood flow (or increased retrograde flow) with systolic forward flow and diastolic reverse flow is present at heart rates exceeding 220 bpm; these abnormalities are reversed by successful fetal treatment with return of the heart rate to 210 bpm or less. Great interindividual differences exist in the time required for this reversal.

  - Myocardial function is impaired with hydrops, and the severity of this functional cardiomyopathy is reflected by the degree and persistence of AV valve incompetence and UVC/IVC flow patterns in the fetus.
  - Abnormalities in umbilical artery (UA) blood flow are also found. UA early-diastolic blood flow velocity is absent, and end-diastolic UA velocity is reversed. The UA pulsatility index (PI) is increased in feto-fetal transfusion hydrops, and, most importantly, this abnormal finding usually precedes and predicts the development of hydrops in the recipient/hydropic twin. PI also improves parallel to clinical improvement in fetal condition. Abnormal UA blood flow patterns in alpha-thalassemia hydrops include an increased acceleration slope, more linear decline from maximum systole to end diastole, and reduced spectral broadening; fetal aortic waveforms also demonstrate distorted systolic peaks, flow turbulence, and greatly elevated diastolic frequencies.
  - Elevated umbilical venous pressures, found in approximately two thirds of individuals with fetal hydrops, return to normal with successful treatment. Such measurements, obtained by cordocentesis at time of fetal treatment, may be useful in assessing the success of fetal therapies that require a direct invasive approach.

Medical Care: The single most important factor to ensure proper treatment of the fetus with hydrops is a precise and detailed diagnosis. Until the underlying pathophysiology is clearly understood and the extent of the abnormalities leading the development of hydrops is defined completely, any attempt at treatment is futile and potentially harmful.

- Once the underlying problems are understood completely, address the question of whether the abnormalities present are compatible with life, whether fetal survival would be at the cost of an unacceptably poor quality of life, and what the consequences may be for future generations. Currently, parental involvement and guidance are fundamental requirements and require full knowledge by the parents of all possible potential consequences.
- If the decision is made to continue the pregnancy, the next steps are to decide whether to intervene with invasive fetal treatment(s) and to determine at what point preterm delivery represents less risk for the fetus than continued gestation. Because major uncertainties about these questions inevitably exist, regardless of the underlying cause(s), full parental involvement is essential.
- Decisions about fetal treatment are inevitably uncertain because the necessary evidence is not available. While many anecdotal approaches are found in the literature, no properly designed clinical trials are available for the clinician concerned with evidence-based management.
  - Many treatment schemes exist; however, all are based on the biases and experiences of the individual author(s). In such circumstances, treatment decisions are difficult, particularly for the prudent clinician who requires evidence to balance risks against benefits of a specific treatment.
  - To further complicate the issue, spontaneous remission of the hydropic process has been reported in hundreds of cases. Underlying causes in these cases include cardiac arrhythmias, twin-to-twin transfusion syndrome, pulmonary sequestration, cystic adenomatoid malformation of the lung, lysosomal storage diseases, cystic hygroma with or without Noonan syndrome, both Parvovirus and CMV infections, placental chorangioma, and idiopathic ascites or pleural effusions. Both clinician(s) and parent(s) completely must understand that decisions at this point basically are uncertain and arbitrary.
- Unproven high-risk treatments are easier to accept when they consist of procedures targeted to correct the underlying pathophysiology leading to fetal hydrops. Thus, the most widely accepted management schemes include fetal transfusion to correct anemia (regardless of cause), drug treatments for cardiac arrhythmias, correction or reduction of space-occupying lesions that impede cardiac venous or lymphatic return, and procedures designed to stop fetal loss of blood, regardless of cause.

- Treatment reported for fetal arrhythmias has included doing nothing, administering drugs, and immediate delivery.
  - If fetal maturity permits, the most simple and direct approach is obviously delivery of the affected fetus and direct neonatal treatment of the arrhythmia.
  - When fetal immaturity prevents this approach, use of drugs has generally been accepted as appropriate. However, whether this is justified is not supported by any evidence from controlled clinical trials, and the frequency with which spontaneous cessation of the arrhythmia and remission of the hydrops has been reported should promote more skepticism and caution about fetal drug treatment than generally has been standard.
  - Drugs have been administered to the mother (oral, intramuscular, intravenous), to the fetus (intraperitoneal, intramuscular, intravenous via cordocentesis), and to both, attempting to correct fetal arrhythmias.
  - Even fetal pacing has been reported. As perhaps expected, the failures are infrequently reported while the successes serve as topics for case or case-series reports (ie, reporting bias). Such treatment is not without risk, partly consequent to the drugs used and not uncommonly related to the mode of administration.
  - Drugs used have included digitalis, furosemide, flecainide, verapamil, amiodarone,

propanolol, procainamide, quinidine, adenosine, sotalol, terbutaline, corticosteroids, and immunoglobulins; a variety of combinations of these drugs have also been used. While adenosine appears to be particularly effective with supraventricular arrhythmias, and corticosteroid therapy seems effective for complete fetal heart block associated with maternal collagen diseases, choice of drug remains empiric and arbitrary, until such time as definitive evidence from clinical trials becomes available.

- o The prudent physician may choose the approach that offers the least risk to fetus and mother until more definitive data are available.

- The success of intrauterine intraperitoneal fetal transfusion with packed RBCs in the treatment of the severely anemic fetus of the isoimmunized pregnancy has been a modern success story for perinatal medicine. Unfortunately, historic controls form the basis for this conclusion, and definitive evidence from clinical trials will probably never be available.
  - o Use of this procedure to correct fetal anemia from a variety of other causes (eg, hemorrhage into a twin, from highly vascularized tumor masses, consequent to marrow aplasia with severe fetal infection, hemoglobinopathy) has been reported with many favorable outcomes. Again, whether this is real or a consequence of reporting bias is uncertain.
  - o Nevertheless, fetal transfusion using the intraperitoneal route has apparently become accepted as the standard of care for the fetus with severe anemia.
- However, more recently a more direct approach has been used with increasing frequency.
  - o Reported routes of fetal administration of blood products have included percutaneous umbilical vein, intrahepatic umbilical vein, umbilical artery, and a variety of combined approaches. Even intracardiac transfusions have been reported. Success has been claimed with fetal partial packed-cell exchange transfusion, maternal plasmapheresis, maternal promethazine or corticosteroid treatment, fetal intravenous Ig-G, fetal platelet transfusion, and fetal administration of human granulocyte-stimulating factor, again using a variety of routes.
  - o Use of more direct invasive methods may appear to increase fetal risk. This may not appear justified in view of the very low risks demonstrated to accompany the intraperitoneal route. The prudent clinician may be justified in taking a very cautious approach to these newer therapeutic techniques until such time as definitive evidence is available that the benefit-to-risk ratio of them is better.

- Severe hemorrhage from friable, highly vascular tumor masses and acute, massive hemorrhage from one twin to another often result in quick fetal death. While those who survive may appear to benefit from fetal transfusion, as described above, continued hemorrhage may make such efforts futile. Thus, a more aggressive approach in such conditions may be justified.
  - o For example, surprising success has been reported with tumor debulking surgery for the fetus with sacrococcygeal tumor and with surgical removal of actively bleeding, highly vascularized fetal intraabdominal, thoracic, or placental masses.
  - o Photocoagulation and radiofrequency thermal ablation techniques also demonstrate much promise in this regard. The information is preliminary; most of it comes from animal studies, and no extensive clinical trial experience in the human fetus is currently available. Nevertheless, life-threatening disease may justify life-threatening treatment in some cases, and use of such technology in situations of active fetal hemorrhage may hold considerable promise. Use of these techniques to correct massive arteriovenous shunting causing fetal hydrops also demonstrates real promise of effectiveness.
- The twin-to-twin transfusion syndrome presents a somewhat more puzzling problem. The temptation to transfuse the anemic fetus is apparent in the literature; however, no evidence of overall benefit from this approach exists.
  - o As noted earlier, if 1 twin has developed hydrops in this situation, it is most often the recipient twin, not the donor. Thus, volume reduction in the recipient or combined transfusion/reduction procedures to the twins appears to be more logical but has seldom been used.
  - o Feticide of the affected twin has often been reported; however, subsequent development of hydrops in the previously normal twin is surprisingly commonly reported. Thus, the management of the twin-to-twin transfusion syndrome is currently an unresolved problem.

- Space-occupying masses, which impair venous or lymphatic return, are among the more important causes of fetal hydrops. Management varies depending on the type of lesion and from center to center. However, the fundamental basis for most treatments has been reduction or removal of the mass when immediate delivery is not practical.
  - Pleural effusions have been managed with single or serial fetal thoracenteses, pleurothoraco-amniotic shunts, and direct fetal surgical maneuvers to correct the underlying cause(s).
  - Pericardial effusions have been managed similarly with single or serial pericardiocenteses or continuous drainage maneuvers.
  - Ascites has also been treated with single or multiple taps, peritoneo-amniotic shunts, and intraperitoneal albumin. Successes and failures have been reported with all methods; no evidence exists that 1 approach is any better than another because proper comparative trial data do not exist in the literature.
  - Fetal surgery with definitive correction of the underlying anomaly has been reported with increasing frequency. Improved fetal survival with cystic adenomatoid malformation and with bronchopulmonary sequestration has been observed in several large series in which these direct corrective measures have been employed. While this success has been measured against outcomes using historic controls, such measures make physiologic sense and, thus, demonstrate considerable promise.

- Resuscitation and delivery room management of hydrops fetalis pose a unique set of problems for the neonatologist.
  - Once hydrops has been diagnosed antenatally, make every effort to establish the cause; this is helpful in treating the infant at birth.
  - In addition to appropriate equipment and supplies, a skilled team of experienced health care professionals (neonatologists, nurses, respiratory therapists, radiograph technician, ultrasound technician) should be present in the delivery room.
  - Perform or repeat antenatal ultrasound examination to assess the presence and extent of pleural effusion, pericardial effusion, or ascites prior to delivery because the fluid may require aspiration in the delivery room to establish adequate ventilation and circulation.
  - Fetal blood assessment by percutaneous umbilical sampling, although risky, may be helpful in selected cases for early management.
  - After establishing the infant's airway and ventilation, place umbilical arterial and venous catheters to monitor arterial pressure, blood gases, and venous pressure.
  - Packed erythrocytes or whole blood crossmatched with the mother's blood should be available for partial exchange transfusion to correct severe anemia, even when due to nonimmune causes.
  - Anticipate and promptly correct metabolic derangements such as acidosis and hypoglycemia.
  - Surfactant deficiency and hypoplastic lungs may be associated with hydrops and are managed accordingly.

The number of drugs that have been used for the correction of fetal arrhythmias reflects the amount of uncertainty about dosage, effectiveness, and hazards. Fetal pharmacokinetic studies are not available, and dosage schedules for these very immature infants are uncertain. Thus, consider each case individually; the prudent physician must be aware that therapeutic misadventures remain possible if not probable.

Drug Category: *Cardiac glycosides* -- These are used for fetal cardiac failure. Positive inotropic agents (eg, digoxin) increase force of contraction of myocardium and are used to treat acute and chronic CHF.

Drug Name	Digoxin (Lanoxin, Lanoxicaps) -- Recommended dosages require considerable modification because of individual variations in sensitivity to drug in adults, children, and (probably) fetuses. Usually administered to mother; thus, adult dosages are used. Transplacental transfer is normally excellent; however, impaired fetal perfusion of placental circulation due to severe cardiac failure results in impaired drug pickup; thus, fetal drug levels may be much lower than maternal concentrations.
Adult Dose	400-750 mcg PO initial loading dose; 100-375 mcg PO 6-8 h after initial dose; repeat in 6-8 h 400-600 mcg IV initial loading dose; 100-300 mcg in 6-8 h; repeat in 6-8 h
Pediatric Dose	Preterm infants 29 weeks' gestation or less: 5-10 mcg/kg IV initial loading dose, followed by 2-5 mcg/kg in 6-8 h; repeat 2-5 mcg/kg in 6-8 h Extrapolation of this data to preterm fetus has been made, with direct IM or IV administration Much higher doses have been used; in 1 report, 88 mcg/kg/dose IM repeated in 12-24 h was used successfully Pharmacokinetic data to support this extrapolation are not available
Contraindications	Documented hypersensitivity; beriberi heart disease; idiopathic hypertrophic subaortic stenosis; constrictive pericarditis; carotid sinus syndrome; uncertain in preterm fetus
Interactions	Medications that may increase digoxin levels include alprazolam, benzodiazepines, bepridil, captopril, cyclosporine, propafenone, propantheline, quinidine, diltiazem, aminoglycosides, oral amiodarone, anticholinergics, diphenoxylate, erythromycin, felodipine, flecainide, itraconazole, nifedipine, omeprazole, quinine, ibuprofen, indomethacin, esmolol, and verapamil Medications that may decrease serum digoxin levels include aminoglutethimide, antihistamines, cholestyramine, neomycin, penicillamine, aminoglycosides, oral colestipol, hydantoins, hypoglycemic agents, antineoplastic treatment combinations (including carmustine, bleomycin, methotrexate, cytarabine, doxorubicin, cyclophosphamide, vincristine, procarbazine), aluminum or magnesium antacids, rifampin, sucralfate, sulfasalazine, barbiturates, kaolin/pectin, and aminosalicylic acid; uncertain in preterm fetus
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Use is supported by very little evidence

Drug Category: *Loop diuretics* -- These are used to treat fetal edema. They promote excretion of water and electrolytes by kidneys and are used to treat heart failure or hepatic, renal, or pulmonary disease when sodium and water retention has resulted in edema or ascites.

Drug Name	Furosemide (Lasix) -- Diuretic, in conjunction with digoxin, that has been employed in management of fetal hydrops. Both transplacental (maternal administration) and direct fetal routes have been used. No satisfactory pharmacokinetic data exist to support these recommendations.
Adult Dose	20-80 mg PO initial dose; if no diuresis, may be repeated in 6-8 h with 40-120 mg dose
Pediatric Dose	2 mg/kg PO initial dose; if no diuresis, 3-4 mg/kg may be repeated in 6-8 h
Contraindications	Documented hypersensitivity; hepatic coma; anuria; state of severe electrolyte depletion; uncertain in premature fetus
Interactions	Metformin decreases concentrations; interferes with hypoglycemic effect

	of antidiabetic agents and antagonizes muscle-relaxing effect of tubocurarine; auditory toxicity appears to be increased with coadministration of aminoglycosides; hearing loss of varying degrees may occur; anticoagulant activity of warfarin may be enhanced when taken concurrently; increased plasma lithium levels and toxicity are possible when taken concurrently; uncertain in premature fetus
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Usual electrolyte monitoring is not available

Drug Category: *Antiarrhythmic agents* -- These agents alter electrophysiologic mechanisms responsible for arrhythmia and are used to treat fetal arrhythmia.

Drug Name	Quinidine (Cardioquin, Quinalan, Quinidex, Quinora) -- Scant data to support use in fetus.
Adult Dose	324-648 mg PO of gluconate (202-403 mg of base quinidine) q8h for 3-4 doses
Pediatric Dose	Fetal or preterm: Not established
Contraindications	Documented hypersensitivity; complete AV block or intraventricular conduction defects, presently taking ritonavir or sparfloxacin; uncertain in premature fetus
Interactions	Phenytoin, rifampin, and phenobarbital may decrease concentrations; toxicity increased when taken with ritonavir, sparfloxacin, beta-blockers, amiodarone, verapamil, cimetidine, alkalinizing agents, or nondepolarizing and depolarizing muscle relaxants; may enhance effect of anticoagulants; uncertain in premature fetus
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Use limited by scant data
Drug Name	Verapamil (Calan, Calan SR, Covera-HS, Verelan) -- Anecdotal use.
Adult Dose	240-320 mg/d PO divided tid
Pediatric Dose	Fetal or preterm: Not established <2 years: Not recommended (see precautions)
Contraindications	Documented hypersensitivity; severe CHF; sick sinus syndrome or second-degree or third-degree AV block; hypotension (<90 mm Hg systolic); age <2 y or weight <15 kg; uncertain in premature fetus
Interactions	May increase carbamazepine, digoxin, and cyclosporine levels; coadministration with amiodarone can cause bradycardia and decrease in cardiac output; when administered concurrently with beta-blockers may increase cardiac depression; cimetidine may increase levels; may increase theophylline levels; uncertain in the premature fetus
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Limited data to support use in fetus; IV use in neonates and young infants may cause apnea bradycardia, hypotension, cardiac arrest, and potential death
Drug Name	Amiodarone (Cordarone) -- Limited use in fetus.
Adult Dose	Loading: 800-1600 mg PO qd
Pediatric Dose	Fetal or preterm: Not established
Contraindications	Documented hypersensitivity; complete AV block; intraventricular conduction defects; patients taking ritonavir or sparfloxacin; uncertain in premature fetus

Interactions	Increases effects and blood levels of theophylline, quinidine, procainamide, phenytoin, methotrexate, flecainide, digoxin, cyclosporine, beta-blockers, and anticoagulants; ritonavir increases toxicity; cardiotoxicity of amiodarone is increased by ritonavir, sparfloxacin, and disopyramide; coadministration with calcium channel blockers may cause additive effect and decrease myocardial contractility further; cimetidine may increase amiodarone levels; uncertain in premature fetus
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Limited information about usefulness and risks
Drug Name	Adenosine (Adenocard) -- Recent use has been promising; however, most information is in form of case reports.
Adult Dose	6 mg IV over 1-2 s; may be repeated in 1-2 min, with dosage increase not to exceed 12 mg if arrhythmia does not resolve For rapid IV use only
Pediatric Dose	50 mcg/kg IV over 1-2 s; has been repeated at 1- to 2-min intervals with 100 mcg/kg dosage; not to exceed total dose of 12 mg In one report, single dose of as much as 150 mcg/kg was administered successfully through umbilical venous route For rapid IV use only
Contraindications	Documented hypersensitivity; second-degree or third-degree AV block or sick sinus syndrome (except in patients with functioning artificial pacemaker); atrial flutter; atrial fibrillation; ventricular tachycardia; uncertain in premature fetus
Interactions	Uncertain in premature fetus
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Limited data to support use; use in fetus requires direct administration by cordocentesis
Drug Name	Procainamide (Procanbid, Pronestyl) -- Use in children well established; however, little data available on use in preterm neonate or fetus.
Adult Dose	250-500 mg PO q3-6h 1000 mg IM loading dose followed by 250 mg q3h 100-200 mg IV repeated in 5 min prn, not to exceed 1000 mg, maintain with 1-6 mg/min by continuous infusion
Pediatric Dose	20-30 mg/kg/d IM divided q4-6h, not to exceed 4 g/d 3-6 mg/kg IV over 5 min, maintained with 20-30 mcg/kg/min by continuous infusion Preterm and fetus: 1.5-2 mg/kg IV over 20-30 min has been used
Contraindications	Patients diagnosed with complete, second-degree, or third-degree heart block, if pacemaker is not in place; torsade de pointes; documented hypersensitivity; SLE; uncertain in premature fetus
Interactions	Can expect increased levels of procainamide metabolite NAPA in patients taking cimetidine, ranitidine, beta-blockers, amiodarone, trimethoprim, and quinidine; may increase effects of skeletal muscle relaxants, quinidine, lidocaine, and neuromuscular blockers; ofloxacin inhibits tubular secretion of procainamide and may increase bioavailability; when taken concurrently with sparfloxacin, may increase risk of cardiotoxicity; uncertain in premature fetus
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Limited data available concerning use in very preterm neonates and fetuses

Drug Name	Sotalol (Betapace) -- Recent use in fetal arrhythmias has been promising; however, data are scarce, and definitive pharmacokinetic studies have not been performed.
Adult Dose	80-160 mg PO q12h
Pediatric Dose	Fetal or preterm: Not established
Contraindications	Documented hypersensitivity; sinus bradycardia, second-degree and third-degree AV block
Interactions	Aluminum salts, barbiturates, NSAIDs, penicillins, calcium salts, and rifampin may decrease bioavailability and plasma levels, possibly resulting in decreased pharmacologic effect; cardiotoxicity may increase when administered concurrently with calcium channel blockers, quinidine, and flecainide; toxicity increases when coadministered with digoxin, flecainide, acetaminophen, clonidine, epinephrine, nifedipine, phenothiazines, and catecholamine-depleting agents
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Accumulation of drug with renal failure is worrisome, since renal perfusion is poor in hydropic fetus
Drug Name	Flecainide (Tambocor) -- Limited data from infants suggest that half-life at birth may be prolonged. These data have not been extended backward to fetal life. Maternal (transplacental) use, in conjunction with digoxin, has been promising anecdotally.
Adult Dose	50-100 mg PO q12h, may be increased prn, not to exceed 300-400 mg/d
Pediatric Dose	Fetal or preterm: Not established
Contraindications	Documented hypersensitivity; third-degree AV block and myocardial depression; uncertain in premature fetus
Interactions	Amiodarone, cimetidine, and digoxin may increase plasma concentrations; beta-adrenergic blockers, verapamil, and disopyramide may have additive inotropic effects with coadministration; ritonavir may increase cardiotoxicity; uncertain in premature fetus
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Lack of data still limits widespread use

FOLLOW-UP

Further Inpatient Care:

- No unique features exist to the follow-up care necessary for a perinatal patient who survives hydrops fetalis.
- If the precipitating cause was profound anemia, red cell survival may remain reduced in patients with isoimmune hemolytic anemia, and red cell production may be impaired in the fetus or newborn who has received multiple red cell transfusions.
- If the cause of hydrops fetalis was a treatable infection, assurance of total eradication of the offending agent is obviously necessary.
- In situations in which multiple anomalies and/or chromosomal abnormalities are present, family counseling is recommended.
- Follow-up measures targeted toward the specific pathophysiologic disturbances present in individual cases may be required (eg, any baby who has experienced a compromised perinatal period).
- Despite the profound compromise in perfusion and fetal function of multiple organ systems in the fetus with hydrops, the limited follow-up data that are currently available provide an unexpectedly optimistic outlook for babies who survive fetal hydrops.

Medical/Legal Pitfalls:

- Unique medicolegal issues primarily concern the difficult access to the fetus.

  - Medications given to the mother place her at risk; however, the same medications may ultimately reach the fetus in concentrations too low to be effective.
  - The option of direct fetal access for drug administration has often been used; however, the invasive methods used inevitably place both mother and fetus at increased risk.
  - Similarly, direct fetal surgical maneuvers carry more risk for the fetus than similar procedures performed after birth; direct fetal surgical maneuvers also place the mother at increased risk.
  - Finally, inadvertent harm to the fetus places the physician at risk for a considerably longer period than is usual.

- The keystone of management of hydrops fetalis is developing parental knowledge and understanding of all choices to obtain truly informed consent. Because the fetal condition is always urgent and time is short, development of this parental knowledge and understanding may represent a considerable challenge.

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Hydrops Fetalis excerpt

Hypoxic-Ischemic Encephalopathy

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Synonyms and related keywords: HIE, perinatal asphyxia, birth asphyxia, neonatal asphyxia, hypoxia, acidosis, ischemia

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INTRODUCTION	Section 2 of 10

Background: In spite of major advances in monitoring technology and knowledge of fetal and neonatal pathologies, perinatal asphyxia or, more appropriately, hypoxic-ischemic encephalopathy (HIE), remains a serious condition, causing significant mortality and long-term morbidity.

HIE is an acquired syndrome characterized by clinical and laboratory evidence of acute brain injury due to asphyxia (ie, hypoxia, acidosis). The American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) have published guidelines to assist in the diagnosis of HIE (see History).

Pathophysiology: Brain hypoxia and ischemia from systemic hypoxemia and reduced cerebral blood flow (CBF) are the primary triggering events for HIE. In this regard, HIE is similar to stroke syndromes in adults, except that in neonates, the pathology is more generalized and the causes are different. Initial compensatory adjustments, which include hypoxia (drop in partial pressure of oxygen [PO_2]) and hypercapnia (increased partial pressure of carbon dioxide [PCO_2]), are important and powerful stimuli, increasing CBF and thus oxygen delivery. During the early phase of shock, the cardiac output is redistributed and the systemic BP increases (due to increased epinephrine release) to maintain CBF.

Cerebral autoregulation of CBF maintains brain perfusion (for awhile) in spite of an initial drop in the mean BP. In experimental animals, CBF autoregulation has been shown to be intact in hypotension. However, the range of BP within which CBF is maintained is unknown for human infants. This range is likely to be narrower and set at lower limits than the adult range (ie, 60-100 mm Hg).

With prolonged asphyxia, the early compensatory adjustments fail; CBF may become "pressure-passive," at which time brain perfusion is dependent on systemic BP. As BP falls, CBF falls below critical levels and brain hypoxia occurs. This results in intracellular energy failure. During the early phases of brain injury, brain temperature drops and local release of the neurotransmitter GABA increases; these changes reduce cerebral oxygen demand, transiently minimizing the impact of asphyxia.

At the cellular level, neuronal injury in HIE is an evolving process. The magnitude of final neuronal damage depends, first, on the extent of the initial insult. The nature, severity, and duration of the primary injury are extremely critical in determining the extent of ultimate residual damage. Following the initial phase of energy failure from the asphyxial injury, cerebral metabolism may recover, only to deteriorate in the second phase.

Reperfusion injury is a second determinant of the extent of brain damage. By 6-24 hours after the initial injury, a new phase of neuronal destruction sets in, characterized by apoptosis (ie, programmed cell death). Also known as "delayed injury," this phase may continue for days to weeks. The severity of brain injury in this phase correlates well with the severity of long-term adverse neurodevelopmental outcome in infants. Modern treatment interventions are geared to reducing the neuronal destruction that occurs during this phase of HIE. Local and systemic factors such as intrauterine growth retardation (IUGR), preexisting brain pathology, or developmental defects noted below (ie, low Apgar scores, frank neurologic deficits) increase the magnitude of neuronal damage.

A large cascade of biochemical events follow HIE injury. Both hypoxia and ischemia increase the release of excitatory amino acids (EAAs [glutamate and aspartate]) in the cerebral cortex and basal ganglia. EAAs begin causing neuronal death immediately through the activation of receptor subtypes such as kainate, N-methyl-D-aspartate (NMDA), and amino-3-hydroxy-5-methyl-4 isoxazole propionate (AMPA). Activation of receptors with associated ion channels (eg, NMDA) leads to cell death due to increased intracellular concentration of calcium. A second important mechanism for the destruction of ion pumps is the lipid peroxidation of cell membranes, in which enzyme systems, such as the Na^+/K^+-ATPase, reside. This leads to influx into the cell water, cell swelling, and death. EAAs also increase the local release of nitric oxide (NO), which may exacerbate neuronal damage, although its mechanisms are unclear.

It is quite possible that EAAs disrupt factors that normally control apoptosis, increasing the pace and extent of programmed cell death. The regional differences in severity of injury may be explained by the fact that EAAs particularly affect the CA1 regions of the hippocampus, the developing oligodendroglia, and the subplate neurons along the borders of the periventricular region in the developing brain. This may be the basis for the disruption of long-term learning and memory faculties in infants with HIE.

Frequency:

- **In the US:** Severe (stage 3-4) HIE is rare; 2-4 cases per 1000 births are reported.

- **Internationally:** Incidence in most technologically advanced nations of the world is the same as that in the United States. However, in developing nations the incidence of HIE is likely to be higher. Accurate statistics are not available.

Mortality/Morbidity: In severe HIE, the mortality rate is as high as 50%. Half of the deaths occur in the first month of life. Some infants with severe neurologic disabilities die in infancy from aspiration pneumonia and other infections.

Among infants who survive severe HIE, the most frequent sequelae are mental retardation, epilepsy, and cerebral palsy. Careful arrangements must be made to have such infants treated in special clinics capable of providing coordinated care, which addresses the multisystem problems of this population.

The incidence of long-term complications depends on the severity of HIE. Up to 80% of infants surviving severe HIE are known to develop serious complications, 10-20% develop moderately serious disabilities, and up to 10% are normal. Among the infants who survive moderately severe HIE, about 30-50% have serious long-term complications, and 10-20% have minor complications. Infants with mild HIE tend to be free from serious CNS complications. Even in the absence of obvious neurologic deficits in the newborn period, there may be long-term functional impairments. Of school-aged children with a history of moderately severe HIE, 15-20% had significant learning

difficulties, even in the absence of obvious signs of brain injury. Because of this, all children who have moderately severe or severe HIE as infants should be monitored well into their school-age years.

Race: No predilection exists.

Sex: No predilection exists.

Age: By definition, this disease is seen in the newborn period. Most neonates are term at birth. In most cases, the disease manifests at birth or within a few hours after birth.

CLINICAL	Section 3 of 10

History: Per the guidelines of the AAP and ACOG, all of the following must be present for the designation of asphyxia. However, infants may have experienced asphyxia or brain hypoxia remote from the time of delivery and exhibit the signs and symptoms of hypoxic encephalopathy at the time of birth.

- Profound metabolic or mixed acidemia (pH <7.00) in an umbilical artery blood sample, if obtained
- Persistence of an Apgar score of 0-3 for longer than 5 minutes
- Neonatal neurologic sequelae (eg, seizures, coma, hypotonia)
- Multiple organ involvement (eg, of the kidney, lungs, liver, heart, intestines)
- On rare occasions, difficulties with delivery, particularly problems with delivering the "after-coming" head in breech presentation, suggest an alternate diagnosis of hemorrhage in the posterior cerebral fossa, which is a rare condition.

Physical: Clinical manifestations and course vary depending on HIE severity.

- Mild HIE

  o Muscle tone may be increased slightly and deep tendon reflexes may be brisk during the first few days.
  o Transient behavioral abnormalities, such as poor feeding, irritability, or excessive crying or sleepiness, may be observed.
  o By 3-4 days of life, the CNS examination findings become normal.

- Moderately severe HIE

  o The infant is lethargic, with significant hypotonia and diminished deep tendon reflexes.
  o The grasping, Moro, and sucking reflexes may be sluggish or absent.
  o The infant may experience occasional periods of apnea.
  o Seizures may occur within the first 24 hours of life.
  o Full recovery within 1-2 weeks is possible and is associated with a better long-term outcome.
  o An initial period of well-being may be followed by sudden deterioration, suggesting reperfusion injury; during this period, seizure intensity might increase.

- Severe HIE

  o Stupor or coma is typical. The infant may not respond to any physical stimulus.
  o Breathing may be irregular, and the infant often requires ventilatory support.
  o Generalized hypotonia and depressed deep tendon reflexes are common.
  o Neonatal reflexes (eg, sucking, swallowing, grasping, Moro) are absent.

- o Disturbances of ocular motion, such as a skewed deviation of the eyes, nystagmus, bobbing, and loss of "doll's eye" (ie, conjugate) movements may be revealed by cranial nerve examination.
  - o Pupils may be dilated, fixed, or poorly reactive to light.
  - o Seizures occur early and often and may be initially resistant to conventional treatments. The seizures are usually generalized, and their frequency may increase during the 2-3 days after onset, correlating with the phase of reperfusion injury. As the injury progresses, seizures subside and the EEG becomes isoelectric or shows a burst suppression pattern. At that time, wakefulness may deteriorate further, and the fontanelle may bulge, suggesting increasing cerebral edema.
  - o Irregularities of heart rate and BP are common during the period of reperfusion injury, as is death from cardiorespiratory failure.

- Infants who survive severe HIE

  - o The level of alertness improves by days 4-5 of life.
  - o Hypotonia and feeding difficulties persist, requiring tube feeding for weeks to months.

- Involvement of multiple organs besides the brain is a hallmark of HIE.

  - o Severely depressed respiratory and cardiac functions and signs of brainstem compression suggest a life-threatening rupture of the vein of Galen (ie, great cerebral vein) with a hematoma in the posterior cranial fossa.
  - o Reduced myocardial contractility, severe hypotension, passive cardiac dilatation, and tricuspid regurgitation are noted frequently in severe HIE.
  - o Patients may have severe pulmonary hypertension requiring assisted ventilation.
  - o Renal failure presents as oliguria and, during recovery, as high-output tubular failure, leading to significant water and electrolyte imbalances.

  - o Intestinal injuries may not be apparent in the first few days of life. Poor peristalsis and delayed gastric emptying are common; necrotizing enterocolitis occurs rarely.

- The staging system proposed by Sarnat and Sarnat in 1976 is often useful.

Table 1. **Sarnat and Sarnat's 3 Clinical Stages of Perinatal Hypoxic Ischemic Brain Injury**

	State 1	Stage 2	Stage 3
Level of Consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular Control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent

Complex Reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart Rate	Tachycardia	Bradycardia	Variable
Bronchial and Salivary Secretions	Sparse	Profuse	Variable
Gastrointestinal Motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram Findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-to 1-Hz spike-and-wave	Early: periodic pattern with Isopotential phases Later: totally isopotential
Duration	<24 h	2-14	Hours to weeks

Methylmalonic Acidemia

Brain tumors
Developmental defects
Infections
Inherited metabolic disorders such as disorders of urea cyclase deficiency

Lab Studies: No specific test excludes or confirms a diagnosis of HIE. The diagnosis is based on the history and physical examination. All tests are performed to assess the severity of brain injury and to monitor the functional status of systemic organs. Choice of tests depends on the evolution of symptoms. As with any other disease, test results should be interpreted in conjunction with clinical history and the findings of physical examination.

- Serum electrolytes: In those affected by severe HIE, daily assessment of serum electrolytes would be of value until the infant's status improves. Markedly low serum sodium, potassium, and chloride in the presence of reduced urine flow and excessive weight gain may indicate acute tubular damage or inappropriate antidiuretic hormone (IADH), particularly during the initial 2-3 days of life.
- Similar changes during recovery, with increased urine flow, might indicate ongoing tubular damage and excessive sodium loss relative to water loss.
- Renal function studies: Serum creatinine, creatinine clearance, and BUN suffice in most cases.

Imaging Studies:

- Since, in most HIE cases, imaging studies are inconsistent in revealing abnormal findings, a normal imaging study finding cannot be used to rule out HIE.
- Cranial ultrasound: Ultrasound is portable and provides a quick assessment of brain lesions. Although it reveals intracranial hemorrhages and cerebral edema (decreased ventricular size), it is not ideal for detailed mapping of the posterior cranial fossa.
- CT scan of the head: This study, especially if done with contrast infusion, may reveal evidence of cerebral edema (eg, obliteration of cerebral ventricles, blurring of sulci) manifested as narrowness of the lateral ventricles and flattening of gyri. Areas of reduced density might indicate regions of infarction. Rarely, evidence of hemorrhage in the ventricles may be seen.

  - In suspected posterior cranial fossa hemorrhage, CT scan must be obtained as soon as clinically feasible because early diagnosis helps in obtaining early neurosurgical consultation.
  - Intracranial hemorrhage is a rare finding in term infants; however, cerebral artery occlusions and infarctions can be diagnosed with radiographic imaging studies.

- MRI is valuable in moderately severe and severe HIE, particularly to note the status of myelination, white-grey tissue injury, and to identify preexisting developmental defects of the brain. MRI is also useful during follow-up. In any newly diagnosed case of cerebral palsy, MRI should be considered, since it may help in establishing the cause. However, the interpretation of MRI in infants requires considerable expertise.
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- Echocardiography: In infants requiring inotropic support, echocardiography (ECHO) helps to define myocardial contractility and the existence of structural heart defects, if any.

Other Tests:

- Choice of tests depends on the evolution of symptoms.
- EEG: Even in the absence of obvious seizures, EEG should be obtained early, particularly in moderately severe and severe cases. In infants on assisted ventilation, drugs such as pancuronium bromide (for muscle paralysis) and morphine (for sedation) may mask the symptoms of early seizures.

  - Generalized depression of the background rhythm and voltage, with varying degrees of superimposed seizures, are the early findings.
  - A burst suppression pattern (ie, isoelectric EEG) is particularly ominous. If clinically correlated, this EEG pattern usually is regarded as representing irreversible brain injury, akin to the legal definition of brain death.

- Special sensory evaluation: Screening for hearing is now mandatory in many states in the United States; in infants with HIE, a full-scale hearing test is preferable because of an increased incidence of deafness among HIE infants requiring assisted ventilation.
- Retinal and ophthalmic examination: This examination may be valuable, particularly as part of an evaluation for developmental abnormalities of the brain.

Histologic Findings: The neuropathology of neonatal HIE varies considerably. Depending on the cause of HIE, more than one type of lesion may be seen in a single patient. Brain maturity at the time of the insult is an important factor in the evolution of neuropathology. In the preterm infant, the damage is at the germinal matrix area, leading to hemorrhage in the subependymal region, the germinal matrix, or the intraventricular region. In the full-term infant, the pathology is mainly in the cerebral cortex and in the basal ganglia. Selective neuronal necrosis is the most common neuropathology. Major sites of necrosis are the cerebral cortex, diencephalon, basal ganglia, brain stem, and cerebellum. The injuries correlate with clinical symptoms, such as disturbances of consciousness, seizures, hypotonia, oculomotor-vestibular abnormalities, and feeding difficulties.

- Parasagittal cerebral necrosis: This lesion is bilateral, usually symmetrical, and occurs in the cerebral cortex and the subcortical white matter, especially in the parietooccipital sides. These regions represent the border zones of perfusion from major cerebral arteries.
- Status marmoratus: In this lesion, the basal ganglia, especially the caudate nucleus, putamen, and thalamus, demonstrate neuronal loss, gliosis, and hypermyelination, leading to a marble white discoloration of these regions. This is the least common type of neuropathology, and its full evolution may take months to years.
- Focal and multifocal ischemic brain necrosis: These lesions are relatively large, localized areas of necrosis of cerebral parenchyma, cortex, and subcortical white matter. The most frequently affected region is the zone perfused by the middle cerebral artery.
- Periventricular leukomalacia: This lesion is characterized by necrosis of white matter, which is seen grossly as white spots adjacent to the external angle of the lateral ventricles. These sites are the border zones between penetrating branches of major cerebral arteries. These lesions are more common in preterm than in term infants.

Medical Care: Treatment of seizures is an essential component of management. Seizures are generally self-limited to the first days of life but may significantly compromise other body functions, such as maintenance of ventilation, oxygenation, and blood pressure. Additionally, seizures should be treated early and be well controlled, since even asymptomatic seizures (ie, seen only on EEG) may continue to injure the brain. Seizures should be treated with phenobarbital or lorazepam; phenytoin may be added if either of these medications fails to control the seizures.

No specific therapy for HIE exists; after seizure control, supportive care remains the cornerstone of management. The elements of supportive care are as follows:

- Maintain adequate ventilation, perfusion, and metabolic status; most infants with HIE need ventilatory support during the first week.
- Prevent hypoxia, hypercapnia, and hypocapnia; the latter is due to inadvertent hyperventilation, which may lead to severe hypoperfusion of the brain.
- Maintain the blood gases and acid-base status in the physiological ranges including partial pressure of arterial oxygen (PaO_2), 80-100 mm Hg; partial pressure of arterial carbon dioxide ($PaCO_2$), 35-40 mm Hg; and pH, 7.35-7.45.
- Maintain the mean BP above 35 mm Hg (for term infants). Dopamine or dobutamine can be used to maintain adequate cardiac output.
- Fluid, electrolyte, and nutritional status should be monitored and corrected and adequate calories and proteins provided.

  - Avoid hypoglycemia or hyperglycemia, as both are known to cause brain injury.
  - In the first 2 days of life, restrict intravenous fluids to two thirds of the daily requirement for gestational age and nursing environment in light of the high frequency of acute tubular necrosis and IADH.
  - Individualize fluid and electrolyte therapy on the basis of clinical course, changes in weight, urine output, and results of serum electrolyte and renal function studies. When infants begin to improve, urinary output increases, and fluid administration must be adjusted. Similarly, in high-output renal tubular failure, the fluid volume and electrolyte composition need to be adjusted. For infants on high-frequency ventilators, the administered fluid volumes must be increased since in those infants, venous return may be impaired, affecting cardiac preload.

Surgical Care: In cases of posterior cranial fossa hematoma, surgical drainage may be lifesaving if no additional pathologies are present.

Consultations:

- A pediatric neurologist should help assist in the management of seizures, interpretation of EEG, and overall care of the infant with HIE. The neurologist should also work with the primary care physician to address long-term disabilities.
- A developmental specialist also can help plan for long-term assessments and care.

Diet: In most cases (particularly in moderately severe and severe HIE), the infant is restricted to nothing by mouth (NPO) during the first 3 days of life or until the general level of alertness and consciousness improves. Begin trophic feeding with dilute formula or expressed breast milk, about 5 mL every 3-4 hours. Monitor abdominal girth and the composition of stools and for signs of gastric retention; any of these may be an early indicator of necrotizing enterocolitis, for which infants with perinatal asphyxia are at high risk. Individualize increments in feeding volume and composition.

Providing standard intensive care support, correcting metabolic acidosis, limiting fluid intake to two-thirds the maintenance volume for the first 3-4 days, and seizure control are the main elements of treatment. Anticonvulsants are the only specific drugs used often in this condition.

Treat seizures early and control them as fully as possible. Even asymptomatic seizures (ie, seen only on EEG) may continue to injure the brain.
Drug Category: *Anticonvulsants --* Used to control seizures.

Drug Name	Phenobarbital (Luminal) -- DOC when clinical or EEG seizures are noted; is continued on the basis of both EEG and clinical status. In most cases, can be weaned and stopped during the first month of life; however, treatment is continued for several months to 1 year in infants with persistent neurological abnormalities and clinical or EEG evidence of seizures; EEG and clinical status should guide decision. In high doses, has been used prophylactically by a few researchers, but its efficacy has not been established. In infants who are heavily sedated or paralyzed, phenobarbital may be used prophylactically at standard dose.
Pediatric Dose	20 mg/kg IV over 10-15 min as loading dose; in refractory cases, additional 5-10 mg/kg IV as loading dose; followed by 3-5 mg/kg/d PO/IV/IM/PR divided bid, to begin no earlier than 12-24 h after loading dose; slow IV push gives most rapid control In a few experimental studies, 20-40 mg/kg IV has been given prophylactically to achieve higher serum concentrations; however, this is not universally accepted
Contraindications	Documented hypersensitivity; severe respiratory disease, marked impairment of liver function, and nephritic patients
Interactions	May decrease effects of digitoxin, corticosteroids, carbamazepine, theophylline, metronidazole, and anticoagulants (patients stabilized on anticoagulants may require dosage adjustments if added to or withdrawn from their regimen); coadministration with alcohol may produce additive CNS effects and death; valproic acid may increase phenobarbital toxicity; rifampin may decrease phenobarbital effects
Pregnancy	D - Unsafe in pregnancy
Precautions	May lead to respiratory distress, so respiratory status should be monitored; immediate assisted ventilatory support should be available Monitor serum therapeutic concentrations, which should be 15-30 mcg/mL; prolonged serum half-life during the first 1-2 wk of life may cause drug accumulation, requiring adjustment of maintenance doses, due to low GFR in the first week of life and ATN (if present) Allowing serum concentrations of 40 mcg/mL is not a universally accepted practice Observe IV sites for extravasation and phlebitis
Drug Name	Phenytoin (Dilantin) -- Usually the third DOC in neonatal seizures; may be used in patients with seizures that do not respond to phenobarbital or lorazepam. Oral absorption is negligible for the first several months of life.
Pediatric Dose	15-20 mg/kg IV over >30 min as loading dose; followed by 4-8 mg/kg IV slow push q24h; rate of infusion not to exceed 0.5 mg/kg/min; flush IV line with 0.9% NaCl before and after administration
Contraindications	Documented hypersensitivity; sinoatrial block, second- and third-degree AV block, sinus bradycardia, or Adams-Stokes synd; IM administration

Interactions	Benzodiazepines, cimetidine, fluconazole, isoniazid, metronidazole, miconazole, phenylbutazone, succinimides, sulfonamides, omeprazole, trimethoprim, and valproic acid may increase phenytoin toxicity Phenytoin effects may decrease when taken concurrently with barbiturates, diazoxide, rifampin, antacids, charcoal, carbamazepine, theophylline, and sucralfate Phenytoin may decrease effects of acetaminophen, corticosteroids, doxycycline, haloperidol, carbamazepine, cardiac glycosides, quinidine, theophylline, methadone, valproic acid
Pregnancy	D - Unsafe in pregnancy
Precautions	Monitor serum concentrations, which should be 6-15 mcg/mL; monitor for bradycardia, arrhythmias, and hypotension during infusion; highly unstable in IV solution, avoid using in central lines because of risk of precipitation; incompatible in D5W or D10W or with dextrose plus amino acids and lipids, most antibiotics, heparin, insulin, and many other drugs (consult compatibility text); drug extravasation at IV site may lead to severe local necrosis
Drug Name	Lorazepam (Ativan) -- Second DOC for acute control of seizures refractory to phenobarbital. By increasing the action of gamma-aminobutyric acid (GABA), which is a major inhibitory neurotransmitter in the brain, may depress all levels of CNS, including limbic and reticular formation.
Pediatric Dose	0.05-0.1 mg/kg/dose IV slow push; doses repeated on basis of clinical response
Contraindications	Documented hypersensitivity; preexisting CNS depression and hypotension
Interactions	CNS toxicity increases when used concurrently with alcohol, phenothiazines, barbiturates, or MAOIs
Pregnancy	D - Unsafe in pregnancy
Precautions	May cause respiratory depression and rhythmic myoclonic jerking in premature infants receiving lorazepam for sedation

Drug Category: *Cardiovascular (inotropic) agents --* Increase BP and combat shock. Drugs in this category act primarily by increasing systemic vascular resistance, cardiac contractility, and stroke volume, thus increasing cardiac output. Most inotropic agents also have dose and gestational age-dependent effects on vessels, particularly those of the renal and GI systems. For the most part, these effects are beneficial but, at higher doses, the systemic side effects may be unpredictable.
No clear information is available on the effects of these drugs on CBF in neonates.

Drug Name	Dopamine (Intropin) -- Stimulates both adrenergic and dopaminergic receptors. Hemodynamic effect is dependent on the dose. Lower doses predominantly stimulate dopaminergic receptors that in turn produce renal and mesenteric vasodilation. Cardiac stimulation and renal vasodilation produced by higher doses.
Pediatric Dose	2-20 mcg/kg/min IV continuous infusion; begin at lower doses, increase on basis of systemic BP appropriate for age and gestational age
Contraindications	Documented hypersensitivity; pheochromocytoma or ventricular fibrillation
Interactions	Phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong effects of dopamine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May cause tachycardia and arrhythmias; may increase pulmonary artery pressure; may reversibly suppress prolactin and thyrotropin secretion

Drug Name	Dobutamine (Dobutrex) -- Second inotropic DOC, preferred by some as first choice in severe cardiogenic shock. Produces vasodilation and increases inotropic state. At higher dosages may cause increased heart rate, exacerbating myocardial ischemia.
Pediatric Dose	2-25 mcg/kg/min IV continuous infusion; begin at lower doses, increase as needed on basis of BP and heart rate; wean on basis of BP response
Contraindications	Documented hypersensitivity; idiopathic hypertrophic subaortic stenosis and atrial fibrillation or flutter
Interactions	Beta-adrenergic blockers antagonize effects of dobutamine; general anesthetics may increase toxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	May cause arrhythmias, hypertension, tachycardia, and vasodilation of cutaneous microcirculation; assess volume status before administering, since may cause hypotension, especially in infants with clear evidence of hypovolemia; may cause tissue sloughing at IV site, particularly when the drug infiltrates soft tissue

FOLLOW-UP Section 8 of 10

Further Inpatient Care:

- Close physical therapy and developmental evaluation are needed before discharge.

Further Outpatient Care:

- As noted before, most infants do not need specific outpatient care. However, they should be monitored in a regular pediatric clinic. Severely disabled children may need to be monitored in multispecialty clinics and by a developmental neurologist.

In/Out Patient Meds:

- Continuation of seizure medications should depend on evolving CNS symptoms and EEG findings.

    o   In most infants who are developing normally and have a normal EEG before hospital discharge, phenobarbital is discontinued within 3-4 weeks of birth.
    o   In those with significant CNS disability with or without persistent episodes of seizures, phenobarbital is continued for 3-6 months; the decision to wean off the drug depends on later changes in EEG and clinical course.

Transfer:

- Infants delivered in a level I or II center may require transfer to a tertiary neonatal intensive care unit for definitive neurodiagnostic studies (EEG and neuroimaging) and consultation with a pediatric neurologist.

Deterrence/Prevention:

- The era of neuroprotection may be near. Most of the treatments discussed here are experimental. With the exception of hypothermia, which is still being examined in clinical trials, none of the therapies cited below has been consistently shown to have efficacy in human infants.

- Allopurinol: Slight improvements in survival and CBF were noted in a small group of infants tested with this free-radical scavenger in one clinical trial.
- High-dose phenobarbital: In another study, 40 mg/kg phenobarbital was given over 1 hour to infants with severe HIE. Treated infants had fewer seizures (9 of 15) than untreated control infants (14 of 16). Treated infants also had fewer neurological deficits at age 3 years (4 of 15) than untreated infants (13 of 16). This is the only study showing a benefit of this magnitude in using high-dose phenobarbital for severe HIE. As of this writing, this treatment is not considered the standard of care.
- EAA antagonists: MK-801, an EAA antagonist, has shown promising results in experimental animals and in a limited number of adult trials. It has not been tested in newborn infants. This drug has serious cardiovascular adverse effects.
- Hypothermia: Currently being intensely tested as a neuroprotective therapy, hypothermia's mechanism of protection is not completely understood. Explanations include (1) reduced metabolic rate and energy depletion; (2) decreased excitatory transmitter release; (3) reduced alterations in ion flux; and (4) reduced vascular permeability, edema, and disruptions of blood-brain barrier functions. The current state-of-the-art on hypothermia is summarized by the following:

  - Brain cooling to about 3-4°C below the baseline temperature (ie, to 33-34°C) may be neuroprotective. The optimal level of hypothermia for maximal neuroprotection is not known. Extreme hypothermia may cause significant systemic side effects.
  - Up to 48-72 hours of cooling may be needed to prevent secondary neuronal loss. The greater the severity of the initial injury, the longer the duration of hypothermia needed for optimal neuroprotection.
  - Cooling must be begun early, within 1 hour of injury, if possible; however, favorable outcome may be possible if cooling is begun up to 6 hours after injury.
  - A special device that selectively cools the head is now being tested in clinical studies; it is not available in the market. Some investigators believe that total body cooling (as done for open-heart surgery) may be superior to selective head cooling. The relative merits and limitations of different methods of brain cooling have not been studied.
  - Hypothermia may cause significant side effects, including coagulation defects, leukocyte malfunctions, pulmonary hypertension, and worsening of metabolic acidosis. Until more is learned, hypothermia remains an experimental modality.

Complications: See Clinical.

Prognosis:

- See Mortality/Morbidity for data on outcomes.
- Accurate prediction of the severity of long-term complications is difficult, although the following pointers may be used:

  - Lack of spontaneous respiratory effort within 20-30 minutes of birth is associated with almost uniform mortality.
  - The presence of seizures is an ominous sign. The risk of poor neurological outcome is distinctly greater in such infants, particularly if seizures occur frequently and are difficult to control.
  - Abnormal clinical neurological findings persisting beyond the first 7-10 days of life usually indicate poor prognosis. Among these, abnormalities of muscle tone and posture (hypotonia, rigidity, weakness) should be carefully noted.
  - Persistent feeding difficulties, which generally are due to abnormal tone of the muscles of sucking and swallowing, also suggest significant CNS damage.
  - Poor head growth during the postnatal period and the first year of life is a sensitive finding predicting higher frequency of neurologic deficits.

Medical/Legal Pitfalls:

- Birth asphyxia, birth injury, and perinatal asphyxia are terms often used incorrectly to describe HIE. This must be avoided, because their improper usage has medicolegal implications.

    o Birth injury is a condition in which fetal or neonatal injury has occurred during the process of birth (ie, during the first and second stages of labor). Examples include brachial plexus injury; fracture of the clavicle; forceps-induced damage to the facial nerve or soft tissues; and cuts or bruises from scissors, clips, or scalp monitors.
    o Birth asphyxia is similar to birth injury in that asphyxia occurs during the first and second stages of labor when the fetus was otherwise normal.
    o Perinatal asphyxia signifies that asphyxia occurred at any time in the perinatal period, namely, from conception through the first month of life.

- The AAP and ACOG recommend using HIE because this term accurately describes the clinical condition, encephalopathy from asphyxia, without implying the time of brain injury. The AAP and ACOG also advise not using the terms perinatal asphyxia or birth asphyxia because it is difficult to identify the time of brain injury and nearly impossible to ascertain that the brain had been "normal" before such injury. These terms are vague and do not reflect all components of HIE.
- Avoid inappropriate designation of the diagnosis as asphyxia and ascribing asphyxia as a cause of any neurological symptom. The medical records should contain objective information on maternal and neonatal history and on clinical findings on the infant.
- The findings from any brain imaging procedures that have been carried out must be included in the total assessment of the infant's clinical status. The findings of neuroimaging tests and EEG (if performed) must be documented.
- No diagnostic tests conclusively prove that a given magnitude of asphyxia has led to a specific neurological injury. Acute perinatal and intrapartum events have been found in only about 20% of children diagnosed as having cerebral palsy.
- Parents must be given realistic explanations about their infant's clinical status and prognosis. It should be emphasized that, except under controlled experimental conditions, cause-and-effect is nearly impossible to establish.
- Good medical records are always better than poor medical records: all details about the infant's status and parental counseling must be documented carefully.

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Hypoxic-Ischemic Encephalopathy excerpt

Infant of Diabetic Mother

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INTRODUCTION	Section 2 of 10

Background: Diabetes has long been associated with maternal and perinatal morbidity and mortality. Before the discovery of insulin in 1921, diabetic women rarely reached reproductive age or survived pregnancy. In fact, pregnancy termination was recommended routinely for pregnant diabetic patients because of high mortality rates.

Fetal and neonatal mortality rates were as high as 65% before the development of specialized maternal, fetal, and neonatal care. Since then, infants of diabetic mothers (IDMs) have experienced a nearly 30-fold decrease in morbidity and mortality rates. Today, 3-10% of pregnancies are affected by abnormal glucose regulation and control. Of these, 80% are related to abnormal glucose control of pregnancy or gestational diabetes mellitus.

Infants born to mothers with glucose intolerance are at an increased risk of morbidity and mortality related to the following:

- Respiratory distress
- Macrosomia
- Hyperviscosity secondary to polycythemia
- Hypoglycemia
- Congenital malformations
- Hypocalcemia and hypomagnesemia

These infants are likely to be born by cesarean section for many reasons, among which are such complications as shoulder dystocia with potential brachial plexus injury related to the infant's large size. It is important for these mothers to be monitored closely throughout pregnancy. If optimal care is provided, the perinatal mortality rate, excluding congenital malformations, is nearly equivalent to that observed in normal pregnancies.

Pathophysiology: It is necessary to understand the physiology of fetal glucose control to appreciate the causes of the associated complications. Increased levels of both estrogen and progesterone affect glucose homeostasis as counter-regulatory hormones in the mother early in pregnancy. As a result, beta-cell hyperplasia occurs in the pancreas, stimulating an increased release of insulin.

Increased insulin levels stimulate glycogen deposition and decrease hepatic glucose production. It is not uncommon to recognize a decreased need for insulin in the diabetic patient in early pregnancy. Furthermore, amino acids decrease and fatty acid triglycerides and ketones both increase with increased fatty acid deposition. As a result, increased protein catabolism and accelerated renal gluconeogenesis occurs. As pregnancy progresses, human placental lactogen is released by the syncytiotrophoblast, leading to lipolysis in the mother. The subsequent release of glycerol and fatty acids reduces maternal use of glucose and amino acid, thus preserving these substrates for the fetus.

The release of increasing amounts of contrainsulin factors as placental growth continues causes up to a 30% increase in maternal insulin needs as pregnancy progresses. Mothers with previous borderline glucose control, obesity, or frank diabetes may require initiation of or increase in their insulin requirements to maintain glucose homeostasis. Glucose and amino acids traverse the placental membrane. On the other hand, insulin is unable to cross from maternal to fetal circulations. Using a carrier-mediated facilitated diffusion mechanism, fetal glucose levels are maintained at a level that is 20-30 mg/dL lower than those of the mother.

The fetus is subjected to high levels of glucose at times of maternal hyperglycemia. The fetus responds to this with pancreatic beta-cell hyperplasia and increased insulin levels. Proinsulin (IGF-1, IGF-BP3) also acts as a growth factor that, in the presence of increased fetal amino acids, results in fetal macrosomia.

Frequency: In the US: The 1988 National Maternal and Infant Health Survey reported that diabetes complicated 4% of pregnancies resulting in live births. Of these, 88% were the result of gestational diabetes mellitus, 8% were the result of non–insulin-dependent diabetes, and 4% were from insulin-dependent diabetes mellitus. Given recent estimates of 0.2-0.3% of pregnancies complicated by preexisting diabetes and a further 1-5% complicated by gestational diabetes mellitus, approximately 50,000-150,000 infants are born to diabetic mothers every year.

Internationally: Women of Asian, Indian, or Middle-Eastern descent are at a higher risk than the general population.

Mortality/Morbidity:

- Birth defects in infants of diabetic mothers have risen from 1-2% to 8-15% as a consequence of increased perinatal survival. Major congenital malformations are found in 5-9% and account for 30-50% of perinatal deaths of infants of mothers with gestational diabetes.
- In mothers with insulin-dependent diabetes, the perinatal mortality rate doubles and the neonatal mortality rate triples when compared with that of the general population. These infants are 3 times more likely to be born by cesarean delivery, twice as likely to suffer serious birth injury, and 4 times as likely to be admitted to a neonatal intensive care unit.
- Major causes of morbidity include the following:

  - Large or small for gestational age infants
  - Hypoglycemia
  - Prematurity
  - Respiratory distress syndrome
  - Intrapartum asphyxia

Race: Incidence is higher in Latinos and African-Americans than in whites. Diabetes occurs more frequently in persons of American Indian descent, particularly among the Pimas of the southwestern United States.

Sex: Frequency of involvement in boy and girl IDMs is equal.

Age: Generally, the first several hours after birth are the most critical for the development of hypogl

History:

- Fetal congenital malformations are most common when maternal glucose control has been poor during the first trimester of pregnancy. Given that many pregnancies are unplanned, the need for preconceptional glycemic control in diabetic women cannot be overstated.
- Maternal hyperglycemia during late gestation is more likely to lead to fetal macrosomia, neonatal electrolyte abnormalities, or cardiomegaly with outflow tract obstruction.

- Fetal macrosomia

  - Quality of fetal growth is determined by plotting birthweight against gestational age on standard growth curves. Infants whose weight exceeds the 90th percentile for gestational age are classified as large for gestational age (LGA). Maternal hyperglycemia during late pregnancy is commonly followed by excessive fetal growth.
  - LGA infants should be routinely screened for potential hypoglycemia. This is particularly important if the mother has received large amounts of glucose-containing fluids during her labor.
  - Fetal macrosomia is observed in 26% of IDMs and in 10% (by definition) of infants of nondiabetic women. While most common as a consequence of maternal hyperglycemia during late pregnancy, fetal macrosomia may occur despite maternal euglycemia.

- Impaired fetal growth

  - Infants whose birthweight is below the 10th percentile, when plotted against gestational age on a standard growth curve, are considered small for gestational age (SGA).
  - Impaired fetal growth may occur in as many as 20% of diabetic pregnancies, compared to a 10% incidence (by definition) for infants born to nondiabetic mothers. Maternal renovascular disease is the common cause of impaired fetal growth in pregnancies complicated by maternal diabetes.

- Pulmonary disease

  - These infants are at an increased risk of respiratory distress syndrome and may present within the first few hours after birth with tachypnea, nasal or intercostal retractions, and hypoxia.
  - Initially, the differential diagnosis might include transient tachypnea of the newborn, respiratory distress syndrome, pneumonia, or persistent pulmonary hypertension.

- Metabolic and electrolyte abnormalities
  - Hypoglycemia may present within the first few hours of life, with such symptoms as jitteriness, irritability, apathy, poor feeding, high pitched or weak cry, hypotonia, or frank seizure activity. More commonly, the neonate is asymptomatic.
  - Hypoglycemia is caused by hyperinsulinemia due to hyperplasia of fetal pancreatic beta cells consequent to maternal-fetal hyperglycemia. Because the supply of glucose is no longer continuous after birth, the neonate develops hyperglycemia substrate is insufficient. Stimulation of fetal insulin release by maternal hyperglycemia during labor significantly increases the risk of early hypoglycemia in these infants.
  - The overall risk of hypoglycemia is anywhere from 25-40%, with LGA and preterm infants at highest risk.
  - Hypocalcemia or hypomagnesemia also may be apparent in the first few hours after

birth; symptoms may include jitteriness or seizure activity. Hypocalcemia (levels <7 mg/dL) is believed to be associated with a failure to increase parathyroid hormone synthesis normally after birth.

- Hematologic problems: Polycythemia, caused by increased erythropoiesis triggered by chronic fetal hypoxia, may present as a clinically "ruddy" appearance, sluggish capillary refill, or respiratory distress.
- Thrombocytopenia: Thrombopoiesis may be inhibited because of an excess of red blood cell precursors within the bone marrow as a result of chronic in utero asphyxia.
- Hyperbilirubinemia: This is common, especially in association with polycythemia. Excessive red cell hemolysis, caused by vascular sludging, leads to elevated bilirubin levels.
- Cardiovascular anomalies

    o Cardiomyopathy with intraventricular hypertrophy and outflow tract obstruction may occur in as many as 30% of these infants. The cardiomyopathy may be caused by congestive failure with a weakly functioning myocardium or to a hypertrophic myocardium with significant septal hypertrophy and outflow tract obstruction. When cardiomegaly or poor perfusion and hypotension are present, it is important to obtain an echocardiogram to differentiate between these processes.
    o These infants also are at an increased risk of congenital heart defects, including (most commonly) ventricular septal defect (VSD) and transposition of the great arteries (TGA).

- Congenital malformations

    o Central nervous malformations are 16 times more likely in these infants. In particular, the risk of anencephaly is 13 times higher, while the risk of spina bifida is 20 times higher. The risk of caudal dysplasia is up to 600 times higher in these infants.
    o Renal (eg, hydronephrosis, renal agenesis, ureteral duplication), ear, cardiovascular (eg, single umbilical artery, VSDs, atrial septal defects, TGA, coarctation of the aorta, cardiomegaly), and gastrointestinal (eg, duodenal or anorectal atresia, small left colon syndrome) anomalies are more frequent in these infants.

Physical:

- Fetal macrosomia (>90th percentile for gestational age or >4000 g in the term infant) occurs in 15-45% of diabetic pregnancies. When present, the infant appears puffy, fat, ruddy, and often mildly limp.
- Impaired fetal growth, secondary to poor placental blood flow, is a consequence of severe maternal diabetics with diabetic nephropathy. Perinatal asphyxia, more common in such infants, may be anticipated by prenatal history, thus stressing the importance of communication between obstetrician and pediatrician.

Causes:

- HbA1C levels

    o Complications caused by maternal hyperglycemia during pregnancy are reflected by HbA1C levels, particularly during the first trimester of pregnancy.
    o Because HbA1C is a direct measure of glucose control in the mother, higher levels are predictive of increased risks for congenital complications. Thus, the incidence of complications has been reported as 3.4% with HbA1C levels lower than 8.5% and 22.4% with levels higher than 8.5%.

- There is speculation that birth defects in IDMs may be related to reduced arachidonic acid and myoinositol levels and elevated sorbitol and trace metal levels in the fetus.
- Others speculate about the role of excess oxygen radicals and hydroperoxides in the mitochondria of susceptible fetal tissues because these prostacyclin inhibitors may cause disruption in the vascularization of developing tissues.
- A past history of LGA infants, diabetes, stillbirth, hypertension, gestational diabetes, obesity, or glycosuria, or a current history of excessive weight gain in the present pregnancy or low socioeconomic class place the mother at an increased risk of poor glucose control during pregnancy and increase her risk of delivering an infant with subsequent complications.

- Fetal macrosomia

  - IDMs experience higher levels of glucose during gestation, resulting in pancreatic beta cell hyperplasia with increased secretion of insulin and proinsulin factors (IGF-1, IGF-BP3). Amino acid availability also is increased. All of these factors are involved in the excessive growth observed in the infants of diabetic mothers.
  - All organ systems, aside from the kidney and brain, are sensitive to the increased glucose and amino acid pools. Increased insulin levels result in an increase in cell number and cell size.

- Impaired fetal growth

  - The major cause of impaired fetal growth is maternal diabetic nephropathy. Maternal vascular disease compromises uteroplacental blood flow and impairs fetal nutrient supply.
  - IDMs are at increased risk of preterm labor, stillbirth, neonatal death, birth injury, and perinatal asphyxia.

- Pulmonary disease
  - These infants are at increased risk for respiratory distress syndrome, transient tachypnea of the newborn, and persistent pulmonary hypertension.
  - Insulin restricts substrate availability for surfactant biosynthesis and interferes with the normal timing of glucocorticoid-induced biosynthesis.
  - Insulin also blocks cortisol action at the fibroblast level by reducing production of fibroblast-pneumocyte factor, which normally would stimulate type II cells to produce surfactant.
  - Several studies agree that the risk of respiratory distress syndrome in well-managed diabetic women delivered at term is no higher than in the general population.

- Electrolyte abnormalities
  - These infants are at high risk for hypoglycemia, especially within the early hours after birth.
  - High levels of fetal insulin with cessation of continued maternal glucose supply take place after birth. The neonatal shift to gluconeogenesis with fatty acid use may provide an insufficient supply of substrate, and, thus, the infant may experience hypoglycemia (<20-40 mg/dL), which may be asymptomatic. Alternatively, the infant may display such symptoms as jitteriness, irritability, lethargy, poor feeding tolerance, and seizures. With hypoglycemia, the body responds with increased counterregulatory hormones and production of ketones for use as an energy source. With continued hyperinsulinemia, this production of ketones is inhibited, thus lowering the source of energy for these infants even further.
  - Hypocalcemia, with or without hypomagnesemia, also may be present and is believed to be secondary to parathyroid hormone suppression.
  - Postnatal parathormone response of IDMs is decreased compared to their gestationally matched controls. The associated hypomagnesemia has been

speculated to be secondary to increased urinary losses associated with a more severe diabetic state. This maternal hypomagnesemia is reflected in the fetus also.

- Cardiovascular anomalies

    o Cardiac hypertrophy may be observed in as many as 30% of IDMs.
    o Fetal growth is regulated by insulin binding to cell receptors. Compared to the adult, the fetus has an increased number of receptors. Because the fetal heart is particularly rich in receptors, this may lead to increased myocardial protein, glycogen, and fat synthesis with hyperplasia and hypertrophy of myocardial cells.

- Congenital malformations

    o Some speculate that many of the congenital anomalies in IDMs may arise from an insult to the developing somite mesoderm and cephalic neural crest cells.
    o Metabolic disturbances, such as hyperglycemia, hypoglycemia, hyperketonemia, and hypoxia, also may be involved.
    o Glucose-induced free radicals of oxygen also have been implicated.

Beckwith-Wiedemann Syndrome

Lab Studies:

- Complete blood cell count

    o Polycythemia, commonly defined as a central hematocrit higher than 65% or hemoglobin concentration higher than 20 g/dL, is a potential concern.
    o Maternal-fetal hyperglycemia is a strong stimulus for fetal erythropoietin production and subsequent increase in fetal hemoglobin concentration secondary to chronic in utero hypoxia, which can be associated with the infant of a diabetic mother. Fetal hyperviscosity, intravascular sludging, regional ischemia, and hypoxemia are all potential complications. Thrombocytopenia may occur because of impaired thrombopoiesis due to "crowding-out" of thrombocytes by the excess of erythroid precursors in the bone marrow.

- Glucose concentration (serum or whole-blood)

    o Seizures, coma, and long-term brain damage may occur if neonatal hypoglycemia is unrecognized and untreated.

    o Most centers recognize levels lower than 20-40 mg/dL within the first 24 hours after birth as abnormal, but the precise level remains controversial. A policy to screen IDMs for hypoglycemia should be in place in every hospital. A recent suggestion of operational thresholds was proposed by Cornblath et al. Their suggestion in an infant with compromised metabolic adaptation (ie, IDMs) should include blood glucose measurements (1) as soon as possible after birth, (2) within 2-3 hours after birth and before feeding, and (3) at any time abnormal clinical signs are observed.

- Magnesium concentration (serum)

  o Hypomagnesemia is related to younger maternal age, severity of maternal diabetes, and prematurity. Neonatal magnesium levels are also related to maternal serum magnesium, neonatal calcium and phosphorus levels, and neonatal parathyroid function.
  o The clinical significance of low magnesium levels in these infants remains controversial and uncertain.

- Calcium concentration (serum, ionized or total levels): Low serum calcium levels in IDMs are common. They are speculated to be caused by a functional hypoparathyroidism; however, their clinical relevance remains uncertain and controversial.
- Bilirubin level (serum, total and unconjugated): Hyperbilirubinemia is notably more common than in the general population of neonates. Causative factors include prematurity, hepatic enzyme immaturity, polycythemia with hyperviscosity and "sludging," and reduced red blood cell half-life.
- Arterial blood gas: Assessing oxygenation and ventilation is essential in infants with clinical evidence of respiratory distress. Although noninvasive methods (eg, transcutaneous oxygen and carbon dioxide electrodes, oximeters) have gained wide acceptance at many centers, comparison of results with those from arterial blood is intermittently required.

Imaging Studies:

- Chest radiograph

  o Clinical evidences of cardiopulmonary distress require a detailed evaluation, which always should include a chest radiograph.
  o Adequacy of lung expansion, evidences of focal or diffuse atelectasis, presence of interstitial fluid, signs of free air in pleural or interstitial spaces, as well as findings of pneumonia should be looked for carefully. The possibility of pulmonary malformations also should be considered. In the macrosomic infant with a history of shoulder dystocia, examination of the clavicles may be indicated.
  o Cardiac size, shape, and great vessel/outflow tract should be examined carefully.

- Cardiac echocardiogram

  o A thickened myocardium and significant septal hypertrophy may be present in as many as 1 in 3 IDMs. Evidence of hypercontractile, thickened myocardium, often with septal hypertrophy disproportionate to the size of the ventricular free walls, may be noted on examination. Myocardial contractility also should be evaluated because the myocardium is overstretched and poorly contractile with congenital cardiomyopathies. Evidence of anatomical malformation must be searched for carefully because cardiac malformations are significantly more common in IDMs, including a VSD and a TGA.

- Abdominal, pelvic, or lower extremity radiographs

  o When caudal dysplasia is present, anatomic details must be evaluated. Orthopedic anomalies may include fusion of the legs, hypoplastic femur, defects of the tibia and the fibula,flexion contractures of the knee and hip,or clubfoot.Sacral agenesis also is describe
  o Lower extremity congenital malformations require radiographic evaluation to determine the exact skeletal defect or defects present.

- Barium enema

  o Infants with feeding intolerance, abdominal distention, nonbilious emesis, or poor passage of meconium may require a barium enema. Congenital anomalies of the gastrointestinal tract are more common in IDMs. These infants may have "small left colon syndrome," also known as "lazy colon."

- Clinical features of the small left colon syndrome may mimic those of Hirschsprung disease and distal tapering of the colon is a radiologic feature of both disorders. The 2 disorders can be distinguished using a biopsy because normal ganglionic cells are present in lazy colon and absent in Hirschsprung disease.

- Nasal or endotracheal continuous positive airway pressure, endotracheal intubation, and mechanical ventilation

  - Nasal continuous positive airway pressure (NCPAP) or endotracheal intubation with CPAP and/or intermittent mandatory or synchronized positive pressure ventilation (IMV, SIMV) may be employed for management of severe respiratory distress.
  - Common criteria for such interventions include inspired oxygen requirements (FiO_2) of 60-100% to maintain arterial PO_2 of 50-80 mm Hg, arterial PCO_2 levels higher than 60-80 mm Hg or rising 10 or more mm Hg/h, and apnea. The specific criteria for using these modes of assisted ventilation may vary considerably among neonatologists or across institutions.

- Indwelling vascular lines (peripheral, umbilical, or central)

  - Noninvasive blood gas monitoring using transcutaneous electrodes (PaO_2 and $PaCO_2$) and oximeters (O_2% saturation) has greatly reduced the need for invasive indwelling catheters. However, indwelling lines often are needed early in the course of cardiorespiratory disease. In some instances, the need for continuous arterial blood pressure monitoring may warrant placement of a peripheral or umbilical arterial line. Once again, use of these invasive methods varies.
  - Placement of an umbilical venous or a central venous catheter often is employed when the infant requires hyperosmolar intravenous fluids or when peripheral access is limited or exhausted.

The pancreas has larger and more numerous islets. Sections from neonatal myocardium show cellular hyperplasia and hypertrophy.

- Communication between members of the perinatal team is of crucial importance to identify infants who are at highest risk of complications from maternal diabetes. A cost-effective screening policy for hypoglycemia during the hours after birth is necessary to detect hypoglycemia.
- Hypoglycemic management

  - It is generally agreed that serum or whole blood glucose levels less than 20-40 mg/dL within the first 24 hours after birth are significantly low. Cornblath et al's recent suggestions for approach at treatment suggest that measurement of the blood glucose level should be determined, as follows:
    1. As soon as possible after birth
    2. Within 2-3 hours after birth and before feeding
    3. At any time abnormal clinical signs are observed
  - Guidelines based on glucose level
    - Level less than 36 mg/dL (2 mmol/L): Close surveillance of glucose levels with intervention is needed if plasma glucose remains below this level, if it does not increase after a feeding, or if the infant develops symptoms of hypoglycemia.
    - Level less than 20-25 mg/dL (1.1-1.4 mmol/L): Intravenous glucose should be administered, with the target glucose level of more than 45 mg/dL (2.5

mmol/L). This goal of 45 mg/dL is accentuated as a margin of safety. Should the infant be significantly symptomatic with profound, recurrent, or persistent hyperinsulinemic hypoglycemia, then a goal of more than 60 mg/dL (3.3 mmol/L) may be more appropriate.

- It is difficult to determine which infants require the highest dextrose administration to maintain euglycemia. The following suggestions represent a guideline for glucose administration to a hypoglycemic, clinically symptomatic, infant.
  - o Immediate intravenous therapy with 2-mL/kg infusion of dextrose 10% (D10 provides 100 mg/mL of dextrose, starting dose is 200 mg/kg of dextrose) is required in any symptomatic hypoglycemic infant. Administration over 5-10 minutes usually is recommended because of the high osmolarity. This is especially true for immature infants younger than 32 weeks' gestational age who are at some risk for intracranial hemorrhage. This procedure originally was described as a 2-minute infusion, and it accomplishes a filling of the glucose space analogous to the volume of distribution of glucose.
  - o Maintenance of a continuous infusion of dextrose at an infusion rate of 6-8 mg/kg/min of dextrose is necessary once bolus therapy is complete. Failure to do so may result in rebound hypoglycemia as a result of heightened pancreatic insulin release triggered by the glucose infusion.
  - o Frequent serum or whole blood glucose analyses are important to properly titrate the dextrose infusion. Should follow-up glucose levels remain less than 40 mg/dL, the dextrose infusion may be increased by 2 mg/kg/min until euglycemia is achieved.
  - o If the infant requires a dextrose concentration more than D12.5 through a peripheral vein at 80-100 mL/kg/d, placement of a central venous catheter may be considered to avoid venous sclerosis. Continued enteral feedings hasten improvement in glucose control because of the presence of protein and fat in the formula.
  - o Once the infant's glucose levels have been stable for 12 hours, intravenous glucose may be tapered by 1-2 mg/kg/min, depending on maintenance of preprandial glucose levels higher than 40 mg/dL.

- Electrolyte management
  - o Hypocalcemia and hypomagnesemia may complicate the clinical course.
  - o Because low serum calcium levels cannot be corrected in the presence of hypomagnesemia, correction of low magnesium levels is an initial step in the treatment of hypocalcemia.
  - o In IDMs, calcium and magnesium levels are commonly measured within the first hours after birth. Ideally, ionized levels of these electrolytes should be obtained and employed to properly manage these electrolyte disturbances.
  - o True symptomatic hypocalcemia is extremely rare in these infants. In most cases, symptoms interpreted to be caused by low calcium or magnesium levels are due to low glucose levels associated with perinatal asphyxia or associated with a variety of central nervous system problems.
  - o When these low levels are treated, an infusion of 10% calcium gluconate at 2 mL/kg often is administered over 5 minutes (18 mg/kg of elemental calcium). This treatment has particular hazards because the hyperosmolal mixture may cause serious tissue necrosis and sclerosis; also, serious cardiac arrhythmias may occur during the infusion. It is routine in many centers to monitor the infant's ECG during infusion.

- Respiratory management
  - o Pulmonary management is tailored to the individual infant's signs and symptoms.
  - o Increased ambient oxygen concentrations may be required to maintain oxygen saturations higher than 90%, transcutaneous oxygen tensions at 40-70 mm Hg, or atrial oxygen tensions at 50-90 mm Hg.
  - o When an inspired oxygen concentration (FiO_2) higher than 40% is required, the most important task is to determine a precise diagnosis of the cause for the hypoxemia. Principals of management, which are generally agreed on, are based on monitoring of blood levels of oxygen and carbon dioxide, as well as their maintenance within physiologic ranges using the least invasive techniques that are successful.

- Cardiac management
  - If signs of congestive heart failure or cardiomyopathy with cardiomegaly, hypotension, or significant cardiac murmur are observed, echocardiographic evaluation is essential to distinguish among cardiac anomalies, septal hypertrophy, and/or cardiomyopathy.
  - Once a precise diagnosis is available, management of the cardiac disorder is no different for the IDM than for any other newborn with a similar cardiac condition. It is imperative to be extremely careful in the use of cardiotonic agents in the presence of any hypertrophic cardiomyopathy or significant septal hypertrophy. These infants are at risk of actual decreased left ventricular output resulting from this form of therapy.

- Congenital anomalies: A precise and complete diagnosis is an essential prerequisite to proper care.

Consultations: Because of the frequency with which cardiac problems occur in these infants, early consultation with a pediatric cardiologist often is necessary. Because malformations in several organ systems are more common in IDMs, consultation with appropriate subspecialists often is required.

Several drugs may be used in the treatment of these infants. Metabolic and electrolyte stabilization (dextrose, calcium, magnesium), cardiotropic support (digitalis, dopamine, or dobutamine in the presence of poor cardiac function), and the use of sedation (infants with pulmonary hypertension or on mechanical ventilation) are commonly employed. In addition, infants with hyaline membrane disease may require surfactant administration.

Drug Category: *Minerals* -- Intravenous calcium or magnesium is indicated for acute treatment to correct symptomatic low serum levels.

Drug Name	Calcium gluconate (Kalcinate) -- Employed by some clinicians to correct hypocalcemia (serum ionized calcium level <4 mg/dL or serum total calcium level <8 mg/dL). The 10% IV solution provides 100 mg/mL of calcium gluconate that equals 9 mg/mL (0.46 mEq/mL) of elemental calcium.
Pediatric Dose	Initial: 100-200 mg/kg (1-2 mL/kg, equivalent to 10-20 mg/kg elemental calcium) IV Maintenance: 200-800 mg/kg (2-8 mL/kg) PO/IV
Contraindications	Documented hypersensitivity; renal calculi, hypercalcemia, hypophosphatemia, renal or cardiac disease, and digitalis toxicity
Interactions	May decrease effects of tetracyclines, atenolol, salicylates, iron salts, and fluoroquinolones; antagonizes effects of verapamil; large intakes of dietary fiber may decrease calcium absorption and levels; incompatible with clindamycin, fluconazole, esmolol, amphotericin B, indomethacin, methylprednisolone, metoclopramide, sodium bicarbonate, and phosphate and magnesium salts
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Use extravasation precautions; may cause severe sclerosing of peripheral veins, administer via central line if possible; administer slowly over at least 5 min; monitor ECG for bradycardia or dysrhythmia; caution in digitalized patients, respiratory failure, acidosis, or severe hyperphosphatemia; calcium chloride is more irritating; calcium gluconate provides less predictable increases in plasma calcium levels

Drug Name	Calcium chloride -- Rarely used in pediatric patients due to vascular irritation and extravasation risk. Employed by some clinicians to correct hypocalcemia (serum ionized calcium level <4 mg/dL or serum total calcium level <8 mg/dL). The 10% IV solution provides 100 mg/mL of calcium chloride that equals 27.2 mg/mL (1.4 mEq/mL) of elemental Ca.
Pediatric Dose	Initial: 35-70 mg/kg (0.35-0.7 mL/kg, equivalent to 10-20 mg/kg elemental calcium) IV Maintenance: 75-300 mg/kg (0.75-3 mL/kg) IV
Contraindications	Ventricular fibrillation not associated with hyperkalemia; digitalis toxicity, hypercalcemia, renal insufficiency, cardiac disease
Interactions	Coadministration with digoxin may cause arrhythmias; coadministration with thiazides, may induce hypercalcemia; may antagonize effects of calcium channel blockers, atenolol, and sodium polystyrene sulfonate; incompatible with amphotericin B, methylprednisolone, metoclopramide, sodium bicarbonate, and phosphate and magnesium salts when mixed directly.
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Use extravasation precautions; may severely sclerose peripheral veins, administer via central line if possible; administer slowly over at least 5 min; monitor ECG for bradycardia or dysrhythmia; caution in digitalized patients, respiratory failure, acidosis, or severe hyperphosphatemia
Drug Name	Magnesium sulfate -- Used to correct low levels of serum ionized or total magnesium. Cofactor in enzyme systems involved in neurochemical transmission and muscular excitability. Magnesium sulfate 1 g equals 98 mg elemental magnesium (8.12 mEq or 4.06 mmol elemental magnesium).
Pediatric Dose	Hypomagnesemia or hypocalcemia: 25-50 mg/kg/dose IV q4-6h for 3-4 doses; repeat prn Maintenance: 30-60 mg/kg IV q24h; not to exceed 1 g/d
Contraindications	Documented hypersensitivity; heart block, Addison disease, myocardial damage, or severe hepatitis
Interactions	Concurrent use with nifedipine may cause hypotension and neuromuscular blockade; may increase neuromuscular blockade observed with aminoglycosides and potentiate neuromuscular blockade produced by tubocurarine, vecuronium, and succinylcholine; may increase CNS effects and toxicity of CNS depressants, betamethasone, and cardiotoxicity of ritodrine
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	May alter cardiac conduction leading to heart block in digitalized patients; respiratory rate, deep tendon reflex, and renal function should be monitored when electrolyte is administered parenterally; caution when administering magnesium dose because may produce significant hypertension or asystole; in overdose, calcium gluconate, 10-20 mL IV of 10% solution, can be given as antidote for clinically significant hypermagnesemia

Drug Category: *Dextrose* -- Emergent blood glucose elevation requires IV dextrose.

Drug Name	Dextrose -- Parenterally injected dextrose is used in patients unable to sustain adequate oral intake. Direct oral absorption results in a rapid increase in blood glucose concentrations. Dextrose is effective in small doses and there is no evidence that may cause toxicity. Concentrated dextrose infusions provide higher amounts of glucose and increased caloric intake in a small volume of fluid.

Pediatric Dose	Glucose level <20-25 mg/dL (1.1-1.4 mmol/L): Administer IV dextrose to maintain blood glucose at 45-60 mg/dL (2.5-3.3 mmol/L) Clinically symptomatic infant: 200 mg/kg (2 mL/kg) IV of D10 over 5-10 min initially; followed by 6-8 mg/kg/min IV continuous infusion; may increase by 2 mg/kg/min prn to achieve euglycemia
Contraindications	Do not administer to a patient in diabetic coma if blood sugar levels are extremely high; avoid in severely dehydrated patients
Interactions	Caution when administering parenteral fluids to patients receiving corticosteroids or corticotropin, especially if the solution contains Na ions
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May cause nausea, which also may occur with hypoglycemia; IV dextrose solutions may result in dilution of serum electrolyte concentrations, or overhydration when fluid overload is present; caution in patients with congestion or pulmonary edema; hypertonic dextrose given peripherally may cause thrombosis (administer instead through central venous catheter); caution in subclinical diabetes mellitus or carbohydrate intolerance; risk of inducing significant hyperglycemia or hyperosmolar syndrome is increased if solution is administered rapidly, especially in patients with chronic uremia or carbohydrate intolerance; concentrated solutions should not be administered SC or IM; rates of dextrose infusion higher than 0.5 g/kg/h may produce glycosuria; at infusion rates of 0.8 g/kg/h, the incidence of glycosuria is 5%; monitor fluid balance, electrolyte concentrations, and acid-base balance closely; dextrose administration may produce vitamin B-complex deficiency

Drug Category: _Cardiotropic agents --_ Used to improve poor cardiac output.

Drug Name	Dopamine (Intropin) -- Stimulates both adrenergic and dopaminergic receptors. Hemodynamic effect is dependent on the dose. Lower doses predominantly stimulate dopaminergic receptors that, in turn, produce renal and mesenteric vasodilation. Cardiac stimulation and renal vasodilation produced by higher doses. After initiating therapy, increase dose by 1-4 mcg/kg/min q10-30min until optimal response obtained. More than 50% of patients are satisfactorily treated on doses <20 mcg/kg/min.
Adult Dose	1-5 mcg/kg/min IV; not to exceed 20 mcg/kg/min
Pediatric Dose	Administer as in adults;premature infant may respond to very small dose
Contraindications	Documented hypersensitivity; pheochromocytoma or ventricular fibrillation
Interactions	Phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong dopamine effects; incompatible with acyclovir, amphotericin B, furosemide, indomethacin, insulin, and sodium bicarbonate
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Continuous heart rate and intraarterial blood pressure monitoring preferred; tachycardia and arrhythmia; may increase pulmonary artery pressure; tissue sloughing with IV infiltration; correct hypovolemia before infusion; caution if evidence of hypertrophic cardiomyopathy exists in infant due to increased risk of decreased left ventricular output resulting from inotropic use
Drug Name	Dobutamine (Dobutrex) -- Used to improve cardiac output. It is a synthetic catecholamine with primarily beta1-adrenergic activity. Increases myocardial contractility, cardiac index, O_2 delivery, and O_2 consumption and is more effective on cardiac contractility than dopamine

Adult Dose	0.5 mcg/kg/min IV initially, titrate until desired therapeutic effect attained, typically up to 20 mcg/kg/min
Pediatric Dose	Administer as in adults; premature infants may respond to very small doses
Contraindications	Documented hypersensitivity; idiopathic hypertrophic subaortic stenosis and atrial fibrillation or flutter
Interactions	Beta-adrenergic blockers antagonize effects of dobutamine; general anesthetics may increase toxicity Incompatible with acyclovir, aminophylline, bumetanide, diazepam, digoxin, furosemide, indomethacin, phenytoin, and sodium bicarbonate
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Continuous heart rate and intraarterial blood pressure monitoring preferred; watch for extravasation associated with infiltration; correct hypovolemia before infusion; caution if evidence of hypertrophic cardiomyopathy exists in infant due to increased risk of decreased left ventricular output resulting from inotropic use

Drug Name	Digoxin (Lanoxin) -- Cardiac glycoside with direct inotropic effects in addition to indirect effects on the cardiovascular system. Acts directly on cardiac muscle, increasing myocardial systolic contractions. Its indirect actions result in increased carotid sinus nerve activity and enhanced sympathetic withdrawal for any given increase in mean arterial pressure.
Adult Dose	0.125-0.375 mg PO qd
Pediatric Dose	Total digitalizing dose: 5-10 years: 20-35 mcg/kg PO divided in 3 doses q6h >10 years: 10-15 mcg/kg PO divided in 3 doses q6h Maintenance dose: Use 25-35% of PO loading dose
Contraindications	Documented hypersensitivity; beriberi heart disease, idiopathic hypertrophic subaortic stenosis, constrictive pericarditis, and carotid sinus syndrome
Interactions	Medications that may increase digoxin levels include alprazolam, benzodiazepines, bepridil, captopril, cyclosporine, propafenone, propantheline, erythromycin, hydroxychloroquine, itraconazole, nifedipine, omeprazole, ibuprofen, indomethacin, tetracycline, verapamil Medications that may decrease serum digoxin levels include aminoglutethimide, antihistamines, cholestyramine, neomycin, penicillamine, aminoglycosides, antineoplastic treatment combinations (eg, carmustine, bleomycin, methotrexate, cytarabine, doxorubicin, cyclophosphamide, vincristine, procarbazine), aluminum or magnesium antacids, rifampin, sulfasalazine, barbiturates, and aminosalicylic acid
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Hypokalemia may reduce positive inotropic effect of digitalis; IV calcium may produce arrhythmias in digitalized patients; hypercalcemia predisposes patient to digitalis toxicity, and hypocalcemia can make digoxin ineffective until serum calcium levels are normal; magnesium replacement therapy must be instituted in patients with hypomagnesemia to prevent digitalis toxicity; patients diagnosed with incomplete AV block may progress to complete block when treated with digoxin; exercise caution in hypothyroidism, hypoxia, and acute myocarditis; in the infant of a diabetic mother, caution must be used with these agents if evidence of hypertrophic cardiomyopathy exists; these infants are at increased risk of decreased left ventricular output resulting from the use of these agents

Further Outpatient Care: Basic outpatient care should consist of routine well-baby care provided by the infant's general pediatrician. Additional follow-up by consultant subspecialists depends on the neonatal clinical problems and their resolution.

Transfer: Infants of diabetic mothers having congenital anomalies, heart disease, or significant respiratory illness may require transfer to a tertiary care neonatal intensive care unit (NICU) for continued care and access to subspecialists.

Deterrence/Prevention: The best prevention is preconceptional diabetes care. Pregnancy planning and accessing early prenatal care with meticulous attention to glycemic control and good obstetric management throughout pregnancy aids in optimizing pregnancy outcome. The consideration of maternal-fetal medicine consultation may be appropriate in many cases of established diabetes. With excellent glycemic control throughout pregnancy and regularly scheduled prenatal visits, the overall mortality rate approaches that of the general population. This should be emphasized excessively, even before pregnancy, in the population at risk for or with a history of poor glycemic control during pregnancy. Furthermore, it should be part of all prenatal counseling.

Complications:

- All risks are directly proportional to the degree of maternal hyperglycemia in utero.
- Thompson and associates found that tight control of euglycemia in the patient with gestational diabetes led to normal perinatal outcomes. When comparing good glucose control (mean plasma glucose level <120 mg/dL) with poor glucose control (mean plasma glucose level >140 mg/dL), the hyperglycemic group was found to have more preeclampsia, maternal urinary tract infections, premature deliveries, cesarean deliveries, macrosomia, respiratory distress, neonatal hypoglycemia, congenital malformations, and perinatal mortality.
- Congenital anomalies: The overall risk is 8-15%, with 30-50% of perinatal fatalities related to major congenital malformations. Poor glycemic control early in pregnancy directly correlates with a higher incidence of congenital malformations.
- Perinatal mortality

  - In the past, 10-30% of pregnancies terminated with sudden and unexplained stillbirth. This is believed to have been secondary to chronic fetal hypoxia with subsequent polycythemia and vascular sludging. A higher incidence was noted in pregnancies further complicated by maternal vascular disease.
  - A considerable proportion of perinatal problems are a consequence of fetal macrosomia. Macrosomia is associated with protracted labor, perinatal asphyxia, shoulder dystocia and brachial plexus injury, other skeletal and nerve injuries, and an elevated rate of operative deliveries.

Prognosis:

- Prognosis is very good when appropriate care is provided during the perinatal period.
- As many as 50% of mothers with gestational diabetes develop insulin-dependent diabetes within 15 years of their pregnancy.
- Neurodevelopmental outcome

  - Overall findings from multiple studies indicate that infants of mothers with poor glucose control during pregnancy are at highest risk for neurodevelopmental deficits.
  - In 1991, Rizzo et al published a study that included 223 pregnant women and their singleton offspring. Of these mothers, 89 had diabetes before pregnancy, 99 had gestational diabetes, and 35 had normal carbohydrate metabolism. The children were examined at ages 2, 3, 4, and 5 years.

- Mental developmental index scores at 2 years correlated inversely with the mother's third-trimester plasma beta-hydroxybutyrate levels, after correcting for socioeconomic status, race, and ethnicity.
- Stanford-Binet Intelligence scores at ages 3, 4, and 5 years were inversely correlated with the third-trimester plasma beta-hydroxybutyrate and free fatty acid levels of the mothers.
- No correlation was found between perinatal complications and cognitive development in the same group of infants. Thus, it appears that the metabolic milieu that the fetus is exposed to in utero may very well affect long-term neurodevelopmental outcome.

- In another study by the same group, 139 women with diabetes in pregnancy and their singleton offspring were followed.
  - After statistically controlling for other influences, Wechsler Intelligence Scale for Children-Revised (WISC-R) verbal, performance, and full scale IQ scores, and Bannatyne indices of verbal conceptualization ability, acquired knowledge, spatial ability, and sequencing ability were inversely correlated with measures of maternal lipid and glucose metabolism in the second and third trimesters.
  - When looking at the neurodevelopmental outcome at early school-aged children born to mothers with gestational diabetes, Ornoy and associates followed 32 school-aged children born to 32 mothers with well-controlled gestational diabetes and 57 control children. They determined that gestational diabetes induces long-term minor neurological deficits that are more pronounced in younger children, with differences tending to disappear with age.

- Concerning episodes of hypoglycemia and overall prognosis, a recent article examining the long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in SGA preterm infants was published by Duvanel et al.
  - They systematically detected hypoglycemia of less than 47 mg/dL in 85 SGA preterm infants. Through prospective serial evaluations of physical growth and psychomotor development, they determined that those infants with repeated episodes of hypoglycemia had significantly reduced head circumferences at ages 18 months and 3 1/2 years. Furthermore, those with recurrent episodes were noted to have lower scores of psychometric tests at ages 3 1/2 and 5 years.
  - Although this article was looking specifically at those infants who were SGA and, therefore, might be at risk for developmental delays and small head size caused by other factors, the fact that those with multiple episodes of hypoglycemia had poorer development and smaller head circumference measurements may be a concern for IDMs with multiple episodes of hypoglycemia.

- Growth

  - Some evidence indicates that IDMs will have obesity as they get older.
  - Silverman and associates followed physical growth from birth to age 8. At birth, 50% of the infants weighed more than the 90th percentile. At 12 months, length and weight were both normal. At age 7 years, height was slightly higher than average. In comparison to infants born to mothers without diabetes, IDMs were noted to have an increase in weight after age 5 years, resulting in weights higher than the 90th percentile in 50% of those infants by the age of 8 years.

Medical/Legal Pitfalls: Failure to recognize and appropriately treat the infant with hypoglycemia can be devastating from a medicolegal standpoint.

Picture 1. An increase in the number and size of the islets is seen in the pancreas of IBDM.
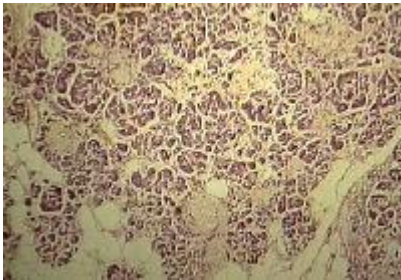
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Jaundice, Neonatal

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INTRODUCTION	Section 2 of 11

Background: Jaundice is the most common condition requiring medical attention in newborns. The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin. In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However, in some infants, serum bilirubin levels may rise excessively, which can be cause for concern because unconjugated bilirubin is neurotoxic and can cause death in newborns and lifelong neurologic sequelae in infants who survive (kernicterus). For these reasons, the presence of neonatal jaundice frequently results in diagnostic evaluation.

Physicians recognized neonatal jaundice as early as the 18th century. Supposedly, Morgagni described 15 infants with jaundice (all of them his). Descriptions of the clinical course and epidemiology of neonatal jaundice are found in a number of 19th-century theses and other publications.

Pathophysiology: Neonatal physiologic jaundice results from simultaneous occurrence of the following 2 phenomena:

- Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates.
- Hepatic excretory capacity is low both because of low concentrations of the binding protein ligandin in the hepatocytes and because of low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation).

Bilirubin is produced in the reticuloendothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contributes. In the first oxidation step, biliverdin is formed from heme through the action of heme oxygenase, the rate-

limiting step in the process, releasing iron and carbon monoxide. The iron is conserved for reuse, while carbon monoxide is excreted through the lungs and can be measured in the patient's breath to quantify bilirubin production.

Next, water-soluble biliverdin is reduced to bilirubin, which, because of the intramolecular hydrogen bonds, is almost insoluble in water in its most common isomeric form (bilirubin IX Z,Z). Due to its hydrophobic nature, unconjugated bilirubin is transported in the plasma tightly bound to albumin. Binding to other proteins and erythrocytes also occurs, but the physiologic role is probably limited. Binding of bilirubin to albumin increases postnatally with age and is reduced in infants who are ill. The presence of endogenous and exogenous binding competitors, such as certain drugs, also decreases the binding affinity of albumin for bilirubin. A minute fraction of unconjugated bilirubin in serum is not bound to albumin. This free bilirubin is able to cross lipid-containing membranes, including the blood-brain barrier, leading to neurotoxicity.

When the bilirubin-albumin complex reaches the hepatocyte, bilirubin is transported into the cell, where it partially binds to ligandin. Uptake of bilirubin into hepatocytes increases with increasing ligandin concentrations. Ligandin concentrations are low at birth, but they increase rapidly over the first few weeks of life. Ligandin concentrations may be increased by the administration of pharmacologic agents such as phenobarbital.

Bilirubin is bound to glucuronic acid (conjugated) in the hepatocyte endoplasmic reticulum in a reaction catalyzed by uridine diphosphoglucuronyltransferase (UDPGT). Monoconjugates are formed first and predominate in the newborn. Diconjugates appear to be formed at the cell membrane and may require the presence of the UDPGT tetramer.

Bilirubin conjugation is biologically critical because it transforms a water-insoluble bilirubin molecule into a water-soluble molecule. Water-solubility allows bilirubin to be excreted into bile. The activity of UDPGT is low at birth, but increases to adult values by age 4-8 weeks. In addition, certain drugs (phenobarbital, dexamethasone, clofibrate) can be administered to increase UDPGT activity.

Once excreted into bile and transferred to the intestines, bilirubin eventually is reduced to colorless tetrapyrroles by microbes in the colon. However, some deconjugation occurs in the proximal small intestine through the action of β-glucuronidases located in the brush border. This unconjugated bilirubin can be reabsorbed into the circulation, increasing the total plasma bilirubin pool. This cycle of uptake, conjugation, excretion, deconjugation, and reabsorption is termed the enterohepatic circulation. The process may be extensive in the neonate, partly because nutrient intake is limited in the first days of life, prolonging the intestinal transit time. Certain factors present in the breast milk of some mothers also may contribute to increased enterohepatic circulation of bilirubin (breast milk jaundice), but the mechanism behind this phenomenon remains unelucidated.

Neonatal jaundice, while a normal transitional phenomenon in most infants, can occasionally become more pronounced. Blood group incompatibilities (Rh, ABO, and others) may increase bilirubin production through increased hemolysis. Historically, Rh isoimmunization was an important cause of severe jaundice, often resulting in the development of kernicterus. While this condition has become relatively rare in industrialized countries following the use of Rh prophylaxis in Rh-negative women, Rh isoimmunization remains common in developing countries. Nonimmune hemolytic disorders (spherocytosis, G-6-PD deficiency) also may cause increased jaundice through increased hemolysis.

A number of other nonhemolytic processes can increase serum bilirubin levels. Accumulation of blood in extravascular compartments (cephalhematomas, bruising, occult bleeding) may increase bilirubin production as the blood is absorbed and degraded. Increased bilirubin production also is seen in patients with polycythemia and in infants of mothers with diabetes. Increased enterohepatic circulation leading to elevated bilirubin levels is seen in patients with bowel obstruction or ileus and when infants are not fed for other reasons.

Decreased clearance of bilirubin is seen in certain inborn errors of metabolism, such as Crigler-Najjar syndrome, Gilbert syndrome, galactosemia, tyrosinemia, and hypermethioninemia. In the latter

3 conditions, elevations of conjugated serum bilirubin occur frequently. Hormone deficiencies, such as hypothyroidism and hypopituitarism, also can decrease bilirubin clearance. Finally, decreased clearance may play a role in breast milk jaundice. Compared to unconjugated hyperbilirubinemia, conjugated (direct) hyperbilirubinemia is rare in neonates. Conjugated hyperbilirubinemia can be broadly classified into the following 2 groups:

- Obstructed bile flow with or without hepatocellular injury
- Hepatocyte injury with normal bile ducts

Obstructed bile flow with or without hepatocellular injury may result from biliary atresia or choledochal cyst. Hepatocyte injury with normal bile ducts may be due to iatrogenic, infectious, or metabolic causes. Iatrogenic causes include intravenous hyperalimentation. Infectious causes may be viral (cytomegalovirus, hepatitis B, other viruses), bacterial (septicemia), or parasitic (toxoplasmosis). Metabolic disorders include enzyme deficiencies (α1-antitrypsin deficiency, galactosemia, cystic fibrosis, tyrosinemia, fructosemia, hypermethioninemia), storage diseases, Rotor syndrome, Dubin-Johnson syndrome, Byler disease, Zellweger syndrome, and Aagenaes syndrome.

<mark>Frequency:</mark>

- **In the US:** Neonatal hyperbilirubinemia is extremely common because almost every newborn develops an unconjugated serum bilirubin level greater than 30 μmol/L (1.8 mg/dL) during the first week of life. Incidence figures are difficult to compare because authors of different studies do not use the same definitions for significant neonatal jaundice. In addition, identification of infants to be tested depends on visual recognition of jaundice by health care providers, which is subject to great variability and depends both on observer attention and on infant characteristics such as race and gestational age. With the above caveats, epidemiologic studies provide a frame of reference for estimated incidence. In 1986, Maisels and Gifford reported 6.1% of infants with serum bilirubin levels greater than 220 μmol/L (12.9 mg/dL). In 1983, Palmer and Drew reported 10.7% of infants with serum bilirubin levels greater than 154 μmol/L (9 mg/dL).

- **Internationally:** Incidence varies with ethnicity and geography. Incidence is higher in East Asians and American Indians and lower in African Americans. Greeks living in Greece have a higher incidence than those of Greek descent living outside of Greece. Incidence is higher in populations living at high altitudes. In 1984, Moore et al reported 32.7% of infants with serum bilirubin levels greater than 205 μmol/L (12 mg/dL) at 3100 m of altitude.

<mark>Mortality/Morbidity:</mark>

- Death from physiologic neonatal jaundice per se should not occur.
- Death from kernicterus may occur, particularly in countries with less developed medical care systems. Mortality figures in this setting are not available.

<mark>Race:</mark>

- Incidence of neonatal jaundice is increased in infants of East Asian, American Indian, and Greek descent, although the latter applies only to infants born in Greece and thus may be environmental rather than ethnic in origin.
- African American infants are affected less often than white infants.
- In 1985, Linn et al reported on a series in which 49% of East Asian, 20% of white, and 12% of African American infants had serum bilirubin levels greater than 170 μmol/L (10 mg/dL).

<mark>Sex:</mark> Risk of developing significant neonatal jaundice is higher in male infants. This does not appear to be related to bilirubin production rates, which appear to be similar to those in female infants.

- Presentation and duration

  - Typically, presentation is on the second or third day of life.
  - Jaundice that is visible during the first 24 hours of life is highly likely to be nonphysiologic jaundice and requires further evaluation.
  - Similarly, infants presenting with jaundice after the third day of life may require closer scrutiny.
  - In infants with severe jaundice or jaundice that continues beyond the first week of life, further family history should be explored.

- Family history

  - Previous sibling with jaundice in the neonatal period
  - Other family members with jaundice
  - Anemia, splenectomy, or bile stones in family members
  - Liver disease

- History of pregnancy and delivery

  - Maternal illness suggestive of viral or other infection
  - Maternal drug intake
  - Delayed cord clamping
  - Birth trauma with bruising

- Postnatal history

  - Loss of stool color
  - Breastfeeding
  - Symptoms of hypothyroidism

- Neonatal jaundice first becomes visible in the face and forehead. Identification is aided by pressure on the skin, since blanching reveals the underlying color. Jaundice then gradually becomes visible on the trunk and extremities. This cephalocaudal (or cephalopedal) progression is well described, even in 19th-century medical texts. Jaundice disappears in the opposite direction. This phenomenon is clinically useful because, independently of other factors, visible jaundice in the feet may be an indication to check the serum bilirubin level.
- In most infants, yellow color is the only finding on physical examination. More intense jaundice may be associated with drowsiness. Brainstem auditory evoked potentials performed at this time may reveal prolongation of latencies, decreased amplitudes, or both.
- Overt neurologic findings, such as changes in muscle tone, seizures, or altered crying characteristics, in a significantly jaundiced infant are danger signs and require immediate attention to avoid kernicterus.
- Hepatosplenomegaly, petechiae, and microcephaly are associated with hemolytic anemia, sepsis, and congenital infections and should precipitate diagnostic evaluation directed towards these diagnoses. Neonatal jaundice may be exacerbated in these situations, but it does not cause the findings.

Causes:

- Physiologic jaundice is caused by a combination of increased bilirubin production secondary to accelerated destruction of erythrocytes, decreased excretory capacity secondary to low levels of ligandin in hepatocytes, and low activity of the bilirubin-conjugating enzyme UDPGT.
- Pathologic neonatal jaundice occurs when additional factors are superimposed on the basic mechanisms described above. Such is the case in immune or nonimmune hemolytic anemia and in polycythemia.
- Decreased clearance of bilirubin may play a role in breast milk jaundice and in several metabolic and endocrine disorders.
- Risk factors

    - Race: Incidence is higher in East Asians and American Indians and is lower in African Americans.
    - Geography: Incidence is higher in populations living at high altitudes. Greeks living in Greece have a higher incidence than those living outside of Greece.
    - Genetics and familial risk: Incidence is higher in infants with siblings who had significant neonatal jaundice. Incidence also is higher in infants with mutations in the gene coding for UDPGT (Gilbert syndrome) and/or in infants with homozygous or heterozygous G-6-PD deficiency.
    - Nutrition: Incidence is higher in infants who are breastfed.
    - Maternal factors: Infants of mothers with diabetes have higher incidence. Use of some drugs may increase incidence, while others decrease incidence.
    - Birthweight and gestational age: Incidence is higher in premature infants and/or in infants with low birthweight.

DIFFERENTIALS	Section 4 of 11

Biliary Atresia
Breast Milk Jaundice
Cholestasis
Cytomegalovirus Infection
Dubin-Johnson Syndrome
Duodenal Atresia
Galactose-1-Phosphate Uridyltransferase Deficiency (Galactosemia)
Hemolytic Disease of Newborn
Hepatitis B
Hypothyroidism

Other Problems to be Considered:

The following conditions may cause nonphysiologic jaundice. In these infants, a baseline physiologic jaundice most likely occurs, which then is exacerbated, for example, by increased enterohepatic circulation in bowel atresia, bile stasis in choledochal cyst, increased bilirubin production in hemolytic anemias, and so on in the following list:

Bowel atresia
Choledochal cyst
Conjugated hyperbilirubinemia
Crigler-Najjar syndrome
Gilbert syndrome
Immune hemolytic anemia
Nonimmune hemolytic anemia

Lab Studies:

- Bilirubin

  - Transcutaneous bilirubinometry can be performed using handheld devices that incorporate sophisticated optical algorithms to filter out most of the unreflected light from the bilirubin molecules.
  - In infants with mild jaundice, transcutaneous bilirubinometry may be all that is needed to assure that total bilirubin levels are safely below those requiring intervention.
  - In infants with moderate jaundice, transcutaneous bilirubinometry may be useful in selecting patients who require phlebotomy for serum bilirubin measurement.
  - Usually, a total serum bilirubin level is the only testing required in a moderately jaundiced infant who presents on the typical second or third day of life without a history and physical findings suggestive of a pathologic process.

- Additional studies may be indicated in the following situations:

  - Infants who present with jaundice on the first or after the third day of life
  - Infants who are anemic at birth
  - Infants who otherwise appear ill
  - Infants in whom serum bilirubin levels are very elevated
  - Infants in whom significant jaundice persists beyond the first 2 weeks of life
  - Infants in whom family, maternal, pregnancy, or case histories suggest the possibility of a pathologic process
  - Infants in whom physical examination reveals findings not explained by simple physiologic hyperbilirubinemia

- In addition to total serum bilirubin levels, other suggested studies may include the following:

  - Blood type and Rh determination in mother and infant
  - Direct Coombs testing in the infant
  - Hemoglobin and hematocrit values
  - Serum albumin levels: This may be a useful adjunct in evaluating risk of toxicity levels, since albumin binds bilirubin in a ratio of 1:1 at the primary high-affinity binding site.
  - Nomogram for hour-specific bilirubin values: This may be a useful tool for predicting, either before or at the time of hospital discharge, which infants are likely to develop high serum bilirubin values. These infants require close follow-up monitoring and repeated bilirubin measurements. The predictive ability has been shown both for bilirubin values measured in serum and for values measured transcutaneously.
  - Measurement of end-tidal carbon monoxide in breath (ETCO): ETCO may be used as an index of bilirubin production. Measurement of ETCO may assist in identifying individuals with increased bilirubin production and, thus, at increased risk of developing high bilirubin levels. An apparatus has been developed that makes measuring ETCO simple (CO-Stat End Tidal Breath Analyzer, Natus Medical Inc).
  - Peripheral blood film for erythrocyte morphology
  - Reticulocyte count
  - Conjugated bilirubin: Note that direct bilirubin measurements are often inaccurate, are subject to significant interlaboratory and intralaboratory variation, and generally are not a sensitive tool for diagnosing cholestasis.
  - Liver function tests: Aspartate aminotransferase (ASAT or SGOT) and alanine aminotransferase (ALAT or SGPT) levels are elevated in hepatocellular disease. Alkaline phosphatase and γ-glutamyltransferase (GGT) levels often are elevated in cholestatic disease. A GGT/ALAT ratio greater than 1 is strongly suggestive of biliary obstruction.

- o Tests for viral and/or parasitic infection may be indicated in infants with hepatosplenomegaly or evidence of hepatocellular disease.
- o Reducing substance in urine is a useful screening test for galactosemia, provided the infant has received sufficient quantities of milk.
- o Blood gas measurements: The risk of bilirubin CNS toxicity is increased in acidosis, particularly respiratory acidosis.
- o Bilirubin-binding tests: Although they are interesting research tools, these tests have not found widespread use in clinical practice. Although elevated levels of unbound bilirubin are associated with an increased risk of bilirubin encephalopathy, unbound bilirubin is but one of several factors that mediate/modulate bilirubin toxicity.
- o Thyroid function tests

Imaging Studies:

- Ultrasound: Ultrasound examination of the liver and bile ducts is warranted in infants with laboratory and/or clinical signs of cholestatic disease.
- Radionuclide scanning: A radionuclide liver scan for uptake of hepatoiminodiacetic acid (HIDA) is indicated if extrahepatic biliary atresia is suspected. At the author's institution, patients are pretreated with phenobarbital 5 mg/kg/d for 3-4 days before performing the scan.

Other Tests:

- Auditory and visual evoked potentials are affected during ongoing significant jaundice; however, no criteria have been established that allow extrapolation from evoked potential findings to risk of bilirubin encephalopathy. Brainstem auditory evoked potentials should be obtained in the aftermath of severe neonatal jaundice to exclude sensorineural hearing loss.
- Crying characteristics are changed in significant neonatal jaundice; however, computerized crying analyses are not used in clinical practice.

Histologic Findings: Organs, including the brain, are yellow in any individual with significant jaundice; however, the yellow color is not evidence of toxicity. This distinction was not always clearly understood in older descriptions of low-bilirubin kernicterus. In the present, this has contributed to confusion and uncertainty regarding therapeutic guidelines and intervention levels. See Kernicterus for a more detailed description.

TREATMENT	Section 6 of 11

Medical Care: Phototherapy and exchange transfusion are the therapeutic modalities used most widely in infants with neonatal jaundice.

Phototherapy

Phototherapy is the primary treatment in neonates with unconjugated hyperbilirubinemia. This therapeutic principle was discovered rather serendipitously in England in the 1950s and now is arguably the most widespread therapy of any kind (excluding prophylactic treatments) used in newborns.

Phototherapy is effective because three reactions can occur when bilirubin is exposed to light, as follows:

- Initially, photooxidation was believed to be responsible for the beneficial effect of phototherapy. However, although bilirubin is bleached through the action of light, the process is slow and is now believed to contribute only minimally to the therapeutic effect of phototherapy.
- Configurational isomerization is a very rapid process that changes some of the predominant 4Z, 15Z bilirubin isomer to water-soluble isomers in which one or both of the intramolecular bonds are opened (E,Z; Z,E; or E,E). In human infants, the 4Z,15E isomer predominates, and

at equilibrium conditions, the isomer constitutes 20% of circulating bilirubin after a few hours of phototherapy. This proportion is not influenced significantly by the intensity of light.

- Structural isomerization consists of intramolecular cyclization, resulting in the formation of lumirubin. This process is enhanced by increasing the intensity of light. During phototherapy, lumirubin may constitute 2-6% of the total serum bilirubin concentration.

The photoisomers of bilirubin are excreted in bile and, to some extent, in urine. The half-life of lumirubin in serum is much shorter than that in E isomers, and lumirubin is the primary pigment found in bile during phototherapy. Thus, although the E isomers predominate in serum, lumirubin is mostly responsible for the therapeutic effect of phototherapy of lowering the serum bilirubin level.

Bear in mind when initiating phototherapy that lowering of the total serum bilirubin concentration is only part of the therapeutic benefit. Since photo-isomers, by virtue of their water-soluble nature, should not be able to cross the blood-brain barrier, phototherapy reduces the risk of bilirubin-induced neurotoxicity as soon as the lights are turned on. At any given total serum bilirubin concentration, the presence of 20-25% of photo-isomers means that only 75-80% of the total bilirubin is present in a form that can enter the brain.

Phototherapy can be administered in a number of ways. To understand the benefits and limitations of the various approaches, some basic principles regarding wavelength and types of light are discussed below with comments and suggestions regarding each system.

First, wavelength must be considered. Bilirubin absorbs light primarily around 450 nm. However, the ability of light to penetrate skin is also important; longer wavelengths penetrate better. In practice, light is used in the white, blue, and green wavelengths.

Second, a dose-response relationship exists between the amount of irradiation and reduction in serum bilirubin up to an irradiation level of 30-40 $\mu W/cm^2/nm$. Most phototherapy units deliver much less energy, some at or near the minimally effective level, which appears to be approximately 6 $\mu W/cm^2/nm$.

Third, the energy delivered to the infant's skin decreases with increasing distance between the infant and the light source. This distance should not be greater than 50 cm (20 in) and can profitably be less provided the infant's temperature is monitored.

Fourth, the efficiency of phototherapy depends on the amount of bilirubin that is irradiated. Irradiating a large skin surface area is more efficient than irradiating a small area, and the efficiency of phototherapy increases with serum bilirubin concentration.

Fifth, the nature and character of the light source may affect energy delivery. Irradiation levels using quartz halide spotlights are maximal at the center of the circle of light and decrease sharply towards the perimeter of the circle. Large infants and infants who can move away from the circle's center may receive less efficient phototherapy.

Although green light theoretically penetrates the skin better, it has not been shown unequivocally to be more efficient in clinical use than blue or white light. Since green light makes babies look sick and is unpleasant to work in, green light has not gained widespread acceptance.

Blue fluorescent tubes are widely used for phototherapy. Narrow-spectrum blue lamps (special blue) appear to work best, while ordinary blue fluorescent lamps are probably equivalent to standard white daylight lamps. Blue lights may cause discomfort in hospital staff members, which can be ameliorated by mixing blue and white tubes in the phototherapy unit. In the regular neonatal nursery at the author's institution, one white fluorescent tube in each of the outermost positions of the phototherapy unit is used, with special blue tubes for the remaining positions.

White (daylight) fluorescent tubes are less efficient than special blue lamps; however, decreasing the distance between infants and lamps can compensate for the lower efficiency. Use of reflecting

materials also helps. Thus, in developing countries where the cost of special blue lamps may be prohibitive, efficient phototherapy is accomplished with white lamps.

White quartz lamps are an integral part of some radiant warmers and incubators. They have a significant blue component in the light spectrum. When used as spotlights, the energy field is strongly focused towards the center, with significantly less energy delivered at the perimeter, as discussed above.

Quartz lamps also are used in single or double banks of 3-4 bulbs attached to the overhead heat source of some radiant warmers. The energy field delivered by these is much more homogeneous than that of spotlights, and the energy output is reasonably high. However, since the lamps are fixed to the overhead heater unit, the ability to increase energy delivery by moving lights closer to infants is limited.

Fiberoptic light also is used in phototherapy units. These units deliver high energy levels, but to a limited surface area. Efficiency may be comparable to that of conventional low-output overhead phototherapy units but not to that of overhead units used with maximal output. Drawbacks of fiberoptic phototherapy units include noise from the fan in the light source and decrease of delivered energy with aging and/or breakage of the optic fibers. Advantages include the following:

- Low risk of overheating the infant
- No need for eye shields
- Ability to deliver phototherapy with the infant in a bassinet next to the mother's bed
- Simple deployment for home phototherapy
- The possibility of irradiating a large surface area when combined with conventional overhead phototherapy units (double/triple phototherapy)

Indications for phototherapy are discussed as follows:

- The purpose of treating neonatal jaundice is to avoid neurotoxicity. Thus, indications for treatment have been based on clinical studies of infants who developed kernicterus. Historical data, much of which was derived from infants with hemolytic jaundice, appeared to suggest that total serum bilirubin levels greater than 350 μmol/L (20 mg/dL) were associated with increased risk of neurotoxicity, at least in full-term infants.
- As treatment of premature infants became more widespread and increasingly successful during the last half of the 20th century, autopsy findings and follow-up data suggested that immature infants were at risk of bilirubin encephalopathy at lower total serum bilirubin levels than mature infants. Treatment was initiated at lower levels for these infants.
- Until the 1940s, a truly effective treatment was not available. At that time, exchange transfusion was shown to be feasible and subsequently was used in the treatment of Rh-immunized infants with severe anemia, hyperbilirubinemia, or hydrops. However, exchange transfusion is not without risk for the infant, and only with the discovery of phototherapy did neonatal jaundice start to become an indication for treatment on a wider scale. Once phototherapy was shown to be a rather innocuous treatment, lights were turned on at lower serum bilirubin values than those that had triggered exchange transfusion. Exchange transfusion became the second-line treatment when phototherapy failed to control serum bilirubin levels.
- Clearly, the scientific data on which current therapeutic guidelines are based have very significant shortcomings. Unfortunately, because the endpoint of bilirubin neurotoxicity is permanent brain damage, a randomized study to reassess the guidelines is ethically unthinkable.
- In most neonatal wards, total serum bilirubin levels are used as the primary measure of risk for bilirubin encephalopathy. Quite a number of people would prefer to add a test for serum albumin at higher bilirubin levels, since bilirubin entry into the brain, a sine qua non for bilirubin encephalopathy, increases when the bilirubin-albumin ratio exceeds unity. Tests for bilirubin-albumin binding or unbound bilirubin levels are used by some but have failed to gain widespread acceptance.

- A number of guidelines for the management of neonatal jaundice have been published, and even more appear to be in local use without submission for critical review. In a survey published in 1996, the author analyzed clinical practices in this field based on responses from 108 neonatal intensive care units (NICUs) worldwide. The survey revealed a significant disparity in guidelines.
  - Image 1 shows a box-and-whisker plot of the range of serum bilirubin values that trigger phototherapy and exchange transfusion, respectively, in these NICUs. Evidently, an infant might receive an exchange transfusion in one NICU for a serum bilirubin level that would not trigger phototherapy in many other NICUs. This disparity illustrates how difficult it has been to translate clinical data into sensible treatment guidelines.
  - In 1994, the American Academy of Pediatrics (AAP) published guidelines for the management of hyperbilirubinemia in healthy full-term newborns. These guidelines have been plotted on the graph in Image 1 and represent a significant departure from the standards applied up to that point.
  - The AAP guidelines were controversial at the time of publication and continue to be a topic of discussion and disagreement among bilirubin experts. Briefly, the objections raised focused mainly on the fact that the AAP guidelines were untested and unproven. In addition, it has been noted that the AAP standard refers to "healthy term newborns," a designation that may be difficult to apply without testing every newborn for congenital hemolytic disease.
  - The above discussion clarifies the finding that therapeutic guidelines for neonatal jaundice are difficult to substantiate with solid scientific facts. At present, the wisest choice may be to apply guidelines that have been in local use for a period sufficient to prove that no cases of kernicterus occurred while the guidelines were followed.
  - With this background, and the clear understanding that this is meant only as an example, Image 2 shows the chart currently in use in the NICU at the author's institution in Oslo. These guidelines have been in use for a quarter of a century in most of Norway, and no known cases of kernicterus have occurred in infants in whom serum bilirubin levels were kept below the stated limits.
  - Readers who are working in different ethnic or geographic situations should not apply these guidelines uncritically to their own populations but must consider factors unique to their settings. Such factors may include racial characteristics, prevalence of congenital hemolytic disease, and environmental concerns.

Key points in the practical execution of phototherapy are maximizing energy delivery and the available surface area.

- The infant should be naked except for diapers (use these only if deemed absolutely necessary and cut them to minimum workable size), and the eyes should be covered to reduce risk of retinal damage.
- Check the distance between the infant's skin and the light source. With fluorescent lamps, the distance should be no greater than 50 cm (20 in). This distance may be reduced if temperature homeostasis is monitored to reduce the risk of overheating.
- Cover the inside of the bassinet with reflecting material; white linen works well. Hang a white curtain around the phototherapy unit and bassinet. These simple expedients can multiply energy delivery by several fold.
- In the well baby unit at the author's institution, energy delivery was measured in the phototherapy bassinets in the horizontal and vertical planes corresponding to the level of the infant's back (when prone) and sides, respectively. Then, new fluorescent tubes were exchanged for the previously used lights and white linen was added as reflecting material in the bed and as curtains. These changes increased the energy delivered from 7-8 to 17-18 $\mu W/cm^2/nm$ in the horizontal plane and from 1 to 10-12 $\mu W/cm^2/nm$ in the vertical plane. The average time infants spent in phototherapy subsequently fell by 5 hours.
- When using spotlights, ensure that the infant is placed at the center of the circle of light, since photoenergy drops off towards the circle's perimeter. Observe the infant closely to ensure that the infant doesn't move away from the high-energy area. Spotlights are probably more appropriate for small premature infants than for larger near-term infants.

- Older data suggested that phototherapy was associated with increased insensible water loss; therefore, many clinicians have routinely added a certain percentage to the infant's estimated basic fluid requirements. Newer data suggest that if temperature homeostasis is maintained, fluid loss is not increased significantly by phototherapy. At the author's institution, routine fluid supplementation for infants under phototherapy is no longer recommended. Rather, the infant is monitored for weight loss, urine output, and urine specific gravity. Fluid intake is adjusted accordingly. In infants who are fed orally, the preferred fluid is milk, since milk serves as a vehicle to transport bilirubin out of the gut.
- Timing of follow-up serum bilirubin testing must be individualized. In infants admitted with extreme serum bilirubin values (>500 μmol/L or 30 mg/dL), monitoring should occur every hour or every other hour. At the author's institution, reductions in serum bilirubin values of 85 μmol/L/h (5 mg/dL/h) have been documented under such circumstances. In infants with more moderate elevations of serum bilirubin, monitoring every 6-12 hours is probably adequate.
- Expectations regarding efficacy of phototherapy must be tailored to the circumstances. In infants in whom serum bilirubin concentrations are still rising, a significant reduction of the rate of increase may be satisfactory. In infants in whom serum bilirubin concentrations are close to their peak, phototherapy should result in measurable reductions in serum bilirubin levels within a few hours. In general, the higher the starting serum bilirubin concentration, the more dramatic the initial rate of decline.
- Discontinuation of phototherapy is a matter of judgment, and individual circumstances must be taken into consideration. In practice, phototherapy is discontinued when serum bilirubin levels fall 25-50 μmol/L (1.5-3 mg/dL) below the level that triggered the initiation of phototherapy. Serum bilirubin levels often rebound after treatment has been discontinued, and follow-up tests should be obtained within 6-12 hours after discontinuation.
- Indications for prophylactic phototherapy are debatable. Phototherapy serves no purpose in an infant who is not clinically jaundiced. In general, the lower the serum bilirubin level, the less efficient the phototherapy. It seems more rational to apply truly effective phototherapy once serum (and skin) bilirubin has reached levels at which photons may do some good.

Generally, phototherapy is very safe, and it may have no serious long-term effects in neonates; however, the following adverse effects and complications have been noted:

- Insensible water loss may occur, but newer data suggest that this issue is not as important as previously believed. Rather than instituting blanket increases of fluid supplements to all infants under phototherapy, the author recommends fluid supplementation tailored to the infant's individual needs as measured through evaluation of weight curves, urine output, urine specific gravity, and fecal water loss.
- Phototherapy may be associated with loose stools. Increased fecal water loss may create a need for fluid supplementation.
- Retinal damage has been observed in some animal models during intense phototherapy. In an NICU environment, infants exposed to higher levels of ambient light were found to have an increased risk of retinopathy. Therefore, covering the eyes of infants undergoing phototherapy with eye patches is routine. Care must be taken lest the patches slip and leave the eyes uncovered or occlude one or both nares.
- The combination of hyperbilirubinemia and phototherapy can produce DNA-strand breakage and other effects on cellular genetic material. It has not been shown that these in vitro and animal data have any implication for treatment of human neonates. However, since most hospitals use cut-down diapers during PThpie, the issue of gonad shielding may be moot.
- Skin blood flow is increased during phototherapy, but this effect is less pronounced in modern servocontrolled incubators. However, redistribution of blood flow may occur in small premature infants. An increased incidence of patent ductus arteriosus (PDA) has been reported in these circumstances.
- Hypocalcemia appears to be more common in premature infants under phototherapy lights. It has been suggested that this is mediated by altered melatonin metabolism. Concentrations of certain amino acids in total parenteral nutrition (TPN) solutions subjected to phototherapy may deteriorate. Shield TPN solutions from light as much as possible.
- Regular maintenance of the equipment is required because accidents have been reported, including burns resulting from failure to replace UV filters.

Exchange transfusion

Exchange transfusion is indicated for avoiding bilirubin neurotoxicity when other therapeutic modalities have failed. In addition, the procedure may be indicated in infants with erythroblastosis presenting with severe anemia, hydrops, or both, even in the absence of high serum bilirubin levels.

Exchange transfusion once was a common procedure. A significant proportion was performed in infants with Rh isoimmunization. Immunotherapy in Rh-negative women at risk for sensitization has reduced the incidence of severe Rh erythroblastosis significantly. Therefore, the number of infants requiring exchange transfusion is now much smaller, and even large NICUs may perform only a few procedures per year. ABO incompatibility has become the most frequent cause of hemolytic disease in industrialized countries.

Recently, immunotherapy has been introduced as treatment in the few remaining sensitized infants. Results are promising and suggest that the number of infants requiring exchange transfusion may be reduced further.

- Early exchange transfusion usually has been performed because of anemia (cord hemoglobin <11 g/dL) and/or elevated cord bilirubin (level >70 μmol/L or 4.5 mg/dL). A rapid rate of increase in the serum bilirubin level (>15-20 μmol/L /h or 1 mg/dL/h) was an indication for exchange transfusion, as was a more moderate rate of increase (>8-10 μmol/L/h or 0.5 mg/dL/h) in the presence of moderate anemia (11-13 g/dL).
- The serum bilirubin level that triggered an exchange transfusion in infants with hemolytic jaundice was 350 μmol/L (20 mg/dL) or a rate of increase that predicted this level or higher. Strict adherence to the level of 20 mg/dL has been jocularly referred to as vigintiphobia (fear of 20).
- Currently, most experts encourage an individualized approach, recognizing that exchange transfusion is not a risk-free procedure, that effective phototherapy converts 15-25% of bilirubin to nontoxic isomers, and that transfusion of a small volume of packed red cells may correct anemia. Administration of IV immunoglobulin 500 mg/kg has been shown to reduce red cell destruction and limit the rate of increase of serum bilirubin levels.

Current AAP guidelines distinguish between infants younger and older than 48 hours. In infants younger than 48 hours, exchange transfusion is recommended when the serum bilirubin level remains greater than 430 μmol/L (25 mg/dL) despite adequately administered phototherapy. In infants older than 48 hours with serum bilirubin levels greater than 510 μmol/L (30 mg/dL), the AAP recommends intensive phototherapy while preparing for an exchange transfusion. If phototherapy has not lowered serum bilirubin levels significantly, the transfusion should be performed.

- The AAP guidelines do not offer specifics regarding the intervention limits for infants with hemolytic jaundice. The practitioner must judge each patient individually, weighing the specifics of the case history and clinical findings.
- Many physicians believe that hemolytic jaundice represents a greater risk for neurotoxicity than nonhemolytic jaundice, although the reasons for this belief are not intuitively obvious, assuming that total serum bilirubin levels are equal. In animal studies, bilirubin entry into or clearance from the brain was not affected by the presence of hemolytic anemia.
- The technique of exchange transfusion, including adverse effects and complications, is discussed extensively elsewhere.

Other therapies :Oral bilirubin oxidase can reduce serum bilirubin levels, presumably by reducing enterohepatic circulation; however, its use has not gained wide popularity. The same may be said for agar or charcoal feeds, which act by binding bilirubin in the gut. Bilirubin oxidase is not available as a drug, and for this reason, its use outside an approved research protocol probably is proscribed in many countries.

Prophylactic treatment of Rh-negative women with Rh immunoglobulin has significantly decreased the incidence and severity of Rh-hemolytic disease.

- Surgical care is not indicated in infants with physiologic neonatal jaundice.
- Surgical therapy is indicated in infants in whom jaundice is caused by bowel or external bile duct atresia.

Consultations:

- For infants with physiologic neonatal jaundice, no consultation is required.
- Gastroenterologists and surgeons may be consulted regarding infants with jaundice resulting from hepatobiliary or bowel disease.

Diet: Breastfeeding concerns associated with neonatal jaundice are as follows:

- Incidence and duration of jaundice have increased as breastfeeding has become more popular. The factors in breast milk that contribute to this phenomenon are unclear. In selected infants, interruption of breastfeeding and its replacement for 24-48 hours by a breast milk substitute may be indicated. This decision should always be discussed in person with the mother before implementation.
- With increasing emphasis on breastfeeding, some new mothers may have difficulty admitting (even to themselves) to a lack of success in establishing lactation. Occasionally, infants of breastfeeding mothers are admitted to hospitals with severe jaundice. They typically weigh significantly less than their birthweight at a time when they should have regained and surpassed that weight. Presumably, the process is one of increased enterohepatic circulation, as bilirubin is left longer in the proximal gut for lack of milk to bind it and carry it onward and out. The author refers to this condition as lack-of-breast-milk jaundice. These infants may respond dramatically to phototherapy plus oral feedings of milk *ad libitum*.

MEDICATION	Section 7 of 11

Medications usually are not administered in infants with physiologic neonatal jaundice. However, in certain instances, phenobarbital, an inducer of hepatic bilirubin metabolism, has been used to enhance bilirubin metabolism. Several studies have shown that phenobarbital is effective in reducing mean serum bilirubin values during the first week of life. Phenobarbital may be administered prenatally in the mother or postnatally in the infant.

In populations in which the incidence of neonatal jaundice or kernicterus is high, this type of pharmacologic treatment may warrant consideration. However, concerns exist regarding the long-term effects of phenobarbital on these children. Therefore, this treatment is probably not justified in populations with a low incidence of neonatal jaundice. Other drugs can induce bilirubin metabolism, but lack of adequate safety data prevents their use outside research protocols. IV immunoglobulin (500 mg/kg) has been shown to significantly reduce the need for exchange transfusions in infants with isoimmune hemolytic disease. The mechanism is unknown but may be related to the way the immune system handles red cells that have been coated by antibodies. Experience is somewhat limited, but it does not appear likely that administration of immunoglobulin incurs greater risks for the infant than an exchange transfusion.

A new therapy currently under development consists of inhibition of bilirubin production through blockage of heme oxygenase. This can be achieved through the use of metal mesoporphyrins and protoporphyrins. Apparently, heme can be excreted directly through the bile; thus, inhibition of heme oxygenase does not result in accumulation of unprocessed heme. This approach may virtually eliminate neonatal jaundice as a clinical problem. However, before the treatment can be applied on a wide scale, important questions regarding the long-term safety of the drugs must be answered. Also, in light of data suggesting that bilirubin may play an important role as a free radical quencher, a more complete understanding of this putative role for bilirubin is required before wholesale inhibition of its production is contemplated.

Further Inpatient Care:

- Infants who have been treated for jaundice can be discharged when they are feeding adequately and have had 2 successive serum bilirubin levels demonstrating a trend towards lower values.
- If the hospital does not routinely screen newborns for auditory function, ordering such tests prior to discharge is advisable in infants who have had severe jaundice.

Further Outpatient Care:

- In the era of early discharge, newborns released within the first 48 hours of life need to be reassessed for jaundice within 1-2 days. Use of the hour-specific bilirubin nomogram (see Nomogram) may assist in selecting infants with a high likelihood of developing significant hyperbilirubinemia.
- Telephone consultations are not recommended because parental reports cannot be gauged appropriately. In recent years, a number of infants have developed kernicterus, resulting, at least in part, from inadequate communication between physicians or their representatives and parents.
- Availability of new devices for transcutaneous measurement of bilirubin levels should facilitate follow-up evaluations of infants discharged before 48 hours of life.
- Home phototherapy

  - Home phototherapy is used in an effort to limit the high cost of applying such therapy in hospitals. Home treatment can avoid or limit parent-child separation. Home treatment should be used with caution, since prevention of neurotoxicity is the goal. Some physicians argue that an infant at risk for neurologic damage should not be at home.
  - With effective treatment strategies, the average duration of phototherapy in the regular neonatal nursery at the author's institution is less than 17 hours. Whether the effort and cost to set up home therapy is worthwhile is debatable. This assessment may be different in different socioeconomic and health financing circumstances.

- Infants who have been treated for hemolytic jaundice require follow-up observation for several weeks because hemoglobin levels may fall lower than seen in physiologic anemia. Erythrocyte transfusions may be required if infants develop symptomatic anemia.

Complications:

- Kernicterus

Prognosis:

- Prognosis is excellent if the patient receives treatment according to accepted guidelines.
- Brain damage due to kernicterus remains a true risk, and the increased incidence of kernicterus in recent years may be due to the misconception that jaundice in the healthy full-term infant is not dangerous and can be disregarded.

Medical/Legal Pitfalls:

- Failure to recognize the potential of significant jaundice to cause brain damage, even in the healthy full-term neonate
- Failure to assess whether a full-term neonate is both healthy and was delivered at term
- Failure of the physician to personally examine an infant reported by parents or other caregivers to be significantly jaundiced

Picture 1. Neonatal jaundice. The graph represents indications for phototherapy and exchange transfusion in infants (with 3500-g birthweight) in 108 neonatal ICUs. The left panel shows the range of indications for phototherapy, while the right panel shows the indications for exchange transfusion. Numbers on the vertical axes are serum bilirubin concentrations in mg/dL (lateral) and μmol/L (middle). In the left panel, the broken line (- - -) refers to current recommendation of the American Academy of Pediatrics (AAP) to consider phototherapy, while the unbroken line (-----) represents the level at which the AAP recommends starting phototherapy in a full-term healthy infant. In the right panel, the broken line (- - -) represents the AAP recommendation to perform an exchange transfusion if intensive phototherapy fails to lower the serum bilirubin levels, while the unbroken line (------) represents the level at which the AAP recommends an exchange transfusion. In this case, intensive phototherapy is recommended while preparations for exchange transfusion are in progress. The box-and-whisker plots show the following values: lower error bar = 10th percentile; lower box margin = 25th percentile; line transecting box = median; upper box margin = 75th percentile; upper error bar = 90th percentile; lower and upper diamonds = 5th and 95th percentiles, respectively.
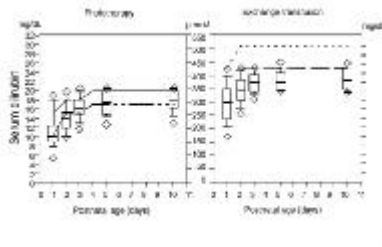
Picture 2. Neonatal jaundice. The graph represents therapeutic guidelines for treatment of neonatal jaundice used at Rikshospitalet (National Hospital) in Oslo, Norway. The 4 lower colored lines represent phototherapy indication levels. The red line (2) represents indication levels for exchange transfusion in the presence of hemolytic disease. The black line (3) represents indication levels for exchange transfusion if effective phototherapy is ongoing. The gray zone (1) is a cautionary zone; visible jaundice during the first 24 hours of life indicates a need for clinical suspicion and workup. Bilirubin values in the green zone (4) also may require closer scrutiny. Reproduced with permission of the Neonatal Fund, Rikshospitalet, Oslo, Norway.
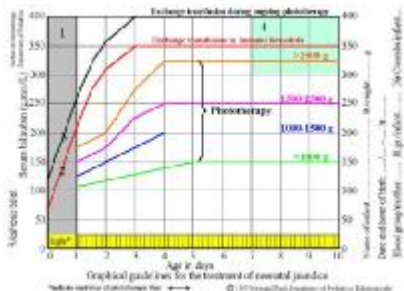
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Jaundice, Neonatal excerpt

Kernicterus

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INTRODUCTION	Section 2 of 11

Background: Traditionally, the term kernicterus (literally yellow kern, with kern indicating the most commonly afflicted region of the brain, ie, the nuclear region) refers to an anatomic diagnosis made at autopsy based on a characteristic pattern of staining found in babies who had marked hyperbilirubinemia before they died. Regions most commonly affected include the basal ganglia; hippocampus; geniculate bodies; and cranial nerve nuclei, such as the oculomotor, vestibular, and cochlear. The cerebellum can also be affected. Acute bilirubin encephalopathy, which refers to the clinical signs associated with bilirubin toxicity, ie, hypotonia followed by hypertonia, opisthotonus or retrocollis, or both, is usually synonymous with kernicterus.

Prevalent in the 1950s and 1960s, kernicterus had virtually disappeared from the clinical scene, only to reappear during the 1990s. Early discharge of term infants (before their bilirubin peaks) may be a factor in the reemergence of this devastating neurologic affliction.

Much of the traditional teaching regarding hyperbilirubinemia is now being questioned as more is learned about bilirubin metabolism and neurologic injury. Kernicterus is now recognized to occur in the premature infant and very rarely in the term infant in the absence of profound hyperbilirubinemia. Conversely, physiologic jaundice (sometimes to levels previously thought to be universally dangerous) has been recognized to be within the reference range in the first week of life in healthy term babies, particularly those who are breastfed. Jaundice of this type resolves spontaneously, without sequelae.

Despite the lack of a clear-cut cause-and-effect relationship between kernicterus and hyperbilirubinemia, laboratory investigations have demonstrated that bilirubin is neurotoxic at a cellular level. Other in vitro studies have shown bilirubin to have more antioxidant capability than vitamin E, which is commonly assumed to be the most potent antioxidant in the human system. This possible role of bilirubin in early protection against oxidative injury, coupled with identification of multiple neonatal mechanisms to preserve and potentiate bilirubin production, has led to speculation about an as-yet-unrecognized beneficial role for bilirubin in the human neonate.

Pathophysiology: Bilirubin staining can be noted on autopsy of fresh specimens in the regions of the basal ganglia, hippocampus, substantia nigra, and brainstem nuclei. Such staining can occur in the absence of severe hyperbilirubinemia; in this situation, factors influencing permeability of the blood-brain barrier (eg, acidosis, infection) and the amount of unbound (versus albumin-bound) bilirubin may play a role.

Characteristic patterns of neuronal necrosis leading to the clinical findings consistent with chronic bilirubin encephalopathy are also essential in the pathophysiology of this entity. Bilirubin staining of the brain without accompanying neuronal necrosis can be observed in babies who did not demonstrate clinical signs of bilirubin encephalopathy but who succumbed from other causes. This staining is thought to be a secondary phenomenon, dissimilar from the staining associated with kernicterus.

Frequency:

- **In the US:** The exact incidence of kernicterus is unknown. A pilot kernicterus registry following the cases of babies with kernicterus in the United States reports 80 babies with chronic kernicterus enrolled in the registry from 1984-1998. All babies reported in the registry had been discharged from the hospital fewer than 72 hours after birth. Most of these babies (60%) were term infants. Total serum bilirubin levels at the time of presentation with the classic physical signs of kernicterus ranged from 26-50 mg/dL. Sixty-seven percent of the patients were male, 54% were white, and 95% were breastfed. Severe hemolytic processes were identified in 19 out of 80 babies; glucose-6-phosphate dehydrogenase (G6PD) deficiency was diagnosed in 18 out of 80, galactosemia occurred in 2 out of 80, and Crigler-Najjar syndrome type I occurred in 1. Nine babies were diagnosed with sepsis. In 21 out of 74 infants, no etiology for the severe hyperbilirubinemia was discovered. Three out of 80 infants died.

Mortality/Morbidity: Classic kernicterus has been defined in the term infant. Increasing experience with premature babies indicates that the clinical presentation in premature infants may be somewhat different. Especially in the premature infant with significant hyperbilirubinemia, concomitant ongoing pathologies may make identifying the cause of death specifically as kernicterus difficult. Neurologic sequelae of bilirubin encephalopathy are variable, and correctly attributing some long-term neurologic deficits to kernicterus as opposed to other neonatal conditions may be difficult.

- In the kernicterus registry mentioned previously, 3 out of 80 patients died (3.75%). How many other patients died without being reported to the registry is unknown, as is the experience in countries other than the United States, especially countries with a high prevalence of hereditary hemolytic disorders.
- Of those patients reported to the kernicterus registry, 66 out of 77 (86%) had chronic kernicterus, 61 of which had severe disease. Ten out of 77 (13%) had no discernible sequelae when older than 1 year.

Race: Asian and Hispanic babies born either in their native countries or in the United States and Native American and Eskimo infants have higher production levels of bilirubin than white infants. African American infants have lower production levels (see Image 1). The reasons for these racial differences have not been fully elucidated.

Sex: Male infants have consistently higher levels of serum bilirubin than do female infants.

Age: Acute bilirubin toxicity appears to occur in the first few days of life of the term infant. Preterm infants may be at risk of toxicity for slightly longer than a few days. If injury has occurred, the first phase of acute bilirubin encephalopathy appears within the first week of life.

History: A history of risk for hemolytic disease can be an important clue to a neonate's increased risk of pathologic hyperbilirubinemia, particularly Rh antigen incompatibility between mother and baby. ABO incompatibility and a family history of red blood cell (RBC) abnormalities (ie, G6PD deficiency, hereditary spherocytosis) are also concerning.

Conversely, if the baby is breastfeeding well and appears healthy and vigorous, this can be reassuring. The mother may have breastfed previous babies who also developed significant jaundice. If so, she may be one of the approximately 20-40% of women who have above-average levels of beta-glucuronidase in their breast milk, which potentiates and prolongs hyperbilirubinemia in their breastfed babies.

Physical:

- Acute bilirubin encephalopathy: The clinical features of this diagnosis have been well described and can be divided into 3 stages. Of babies with kernicterus, approximately 55-65% manifest these features, 20-30% may display some neurologic abnormalities, and approximately 15% have no neurologic signs.

  o Phase 1 (first few days of life): Decreased alertness, hypotonia, and poor feeding are the typical signs. Obviously, these are quite nonspecific and could easily be indicative of a multitude of neonatal abnormalities. A high index of suspicion of possible bilirubin encephalopathy at this stage that leads to prompt intervention can halt the progression of the illness, significantly minimizing long-term sequelae. Of note, seizure is not typically associated with acute bilirubin encephalopathy.
  o Phase 2 (variable onset and duration): Hypertonia of the extensor muscles is a typical sign. Patients present clinically with retrocollis (backward arching of the neck), opisthotonus (backward arching of the back), or both. Infants who progress to this phase develop long-term neurologic deficits.
  o Phase 3 (infants aged >1 wk): Hypotonia is a typical sign.

- Chronic bilirubin encephalopathy: The clinical features of chronic bilirubin encephalopathy evolve slowly over the first several years of life in the affected infant. The clinical features can be divided into phases; the first phase occurs in the first year of life and consists of hypotonia, hyperreflexia, and delayed acquisition of motor milestones. The tonic neck reflex can also be observed. In children older than 1 year, the more familiar clinical features develop, which include abnormalities in the extrapyramidal, visual, and auditory systems. Minor intellectual deficits can also occur.

  o Extrapyramidal abnormalities: Athetosis is the most common movement disorder associated with chronic bilirubin encephalopathy, although chorea can also occur. The upper extremities are usually more affected than the lower ones; bulbar functions can also be impacted. The abnormalities result from damage to the basal ganglia, the characteristic feature of chronic bilirubin encephalopathy.
  o Visual abnormalities: Ocular movements are affected, most commonly resulting in upward gaze, although horizontal gaze abnormalities and gaze palsies can also be observed. These deficits result from damage to the corresponding cranial nerve nuclei in the brain stem.
  o Auditory abnormalities: Hearing abnormalities are the most consistent feature of chronic bilirubin encephalopathy and can develop in patients who show none of the other characteristic features. The most common abnormality is high-frequency hearing loss, which can range from mild to severe. These deficits can result from damage both to the cochlear nuclei in the brain stem and to the auditory nerve, which appear to be exquisitely sensitive to the toxic effects of bilirubin, even at relatively low levels. Clinically, this deficit can manifest as delayed language acquisition. Hence, auditory function must be assessed early in any baby at risk for chronic bilirubin encephalopathy

- o Cognitive deficits: Cognitive function is relatively spared in chronic bilirubin encephalopathy. However, individuals with chronic bilirubin encephalopathy are often mistakenly considered mentally retarded because of their choreoathetoid movement disorders and hearing deficits. The clinician must emphasize that intellectual functioning is not typically severely affected.

- Abnormalities of dentition: Some degree of dental enamel hypoplasia can be observed in about three quarters of patients with chronic bilirubin encephalopathy. A smaller number of individuals develop green-stained teeth.

Causes: Be familiar with bilirubin metabolism to understand factors leading to an increased risk of kernicterus (see Image 2). Bilirubin is produced during the catabolism of the heme component of red blood cells. Red cell destruction is usually increased in the immediate neonatal period; it can be pathologically elevated in the presence of immune- or nonimmune-mediated hemolytic disease. The first enzyme in the catabolic cascade leading to bilirubin is heme oxygenase. A constitutive form and an inducible form exist, which are induced by physiologic stressors. The creation of bilirubin, a potentially toxic water-insoluble compound, from biliverdin, a nontoxic water-soluble substance, consumes energy.

Because of its lipophilic nature, bilirubin must be bound to albumin to travel through the blood stream. In this state, it is not free to cross the blood-brain barrier and cause kernicterus. The albumin-bilirubin complex is carried to the liver, where bilirubin enters the hepatocyte for further metabolism. Once in the liver, bilirubin is conjugated via the action of uridine diphosphate glucuronyl transferase (UDPGT), an enzyme not fully functional until 3 - 4 months of life. Conjugated bilirubin is excreted into the intestinal tract via the biliary system. Beta-glucuronidase, present in the intestinal lumen of human neonates, deconjugates the conjugated bilirubin, allowing it to be reabsorbed across the intestinal lipid cell membranes back into the blood stream where it must be re-bound to albumin to repeat the cycle. This process, called enterohepatic recirculation, is a unique neonatal phenomenon and contributes significantly to physiologic jaundice.

To summarize, the body expends energy to convert biliverdin, a nontoxic, water-soluble, easily excreted compound, into bilirubin, a potentially toxic, water-insoluble, difficult-to-excrete product. Multiple mechanisms in the neonate, some of which are initiated by adverse physiologic events, act to promote and preserve the presence of bilirubin. These mechanisms extinguish as the neonate ages.

- Increased bilirubin production: Most of the circulating bilirubin in the neonate arises from destruction of circulating RBCs. Neonates produce bilirubin at more than double the daily rate of the average adult, primarily because of the larger circulating volume of RBCs and their shorter life span. Any event resulting in increased serum bilirubin load puts the infant at risk for hyperbilirubinemia.

  - o Polycythemia: Prenatal factors, such as maternal smoking, maternal illness, placental insufficiency, and gestation at altitude, can result in neonatal polycythemia. Obstetric factors, such as delayed clamping of the cord, stripping the cord, or holding the baby below the level of the introitus for a prolonged period, can result in increased RBC mass in the baby. This is particularly true for babies born in the absence of a trained birth attendant.
  - o Hemolysis: Immune hemolytic disease, most often Rh isoimmunization (erythroblastosis fetalis), is the prototype etiology for kernicterus. ABO isoimmunization, as well as minor blood group antigens, can also cause hemolytic disease in the newborn, usually of moderate severity. Infants born to mothers of blood type O negative are at greatest risk. Abnormalities of the red cell itself can also predispose to hemolysis. These can be grouped into membrane defects, such as hereditary spherocytosis and elliptocytosis; enzyme defects, such as G6PD deficiency and pyruvate kinase deficiency; and hemoglobinopathies, such as alpha and beta thalassemias. (Sickle cell disease does not typically cause hemolytic disease in the neonatal period.)

- o Extravasated blood: Significant areas of bruising, such as severe cephalohematoma or peripheral ecchymoses from birth trauma, can result in an increased bilirubin load in the serum as the blood collection resolves. Internal areas of hemorrhage, such as pulmonary or intraventricular bleeds, can also be a significant occult source of serum bilirubin.
- o Enzyme induction: As mentioned previously, heme-oxygenase-one (HO-1) is the inducible form of the first enzyme involved in the creation of bilirubin. This enzyme is activated by physiologic stressors, such as hypothermia, acidosis, hypoxia, and infection.
- o Epidemiologic factors: East Asian and Native American babies produce bilirubin at higher rates than do white infants; African American infants have lower production rates than do infants of other racial groups. Male infants have higher serum bilirubin levels than females. Hyperbilirubinemia also runs in families; the etiology is unclear but may relate to genetically increased levels of beta-glucuronidase in the infant, in the mother's breast milk, or both (if the infant breast fed).

- • Decreased elimination: Even with normal bilirubin production, abnormalities in transport, excretion, or both can result in an increased level of free bilirubin in the serum.

  - o Albumin binding
    - ▪ Because of its lipophilic nature, bilirubin must be bound to carrier protein to be transported in the aqueous environment of the serum. Albumin has one primary high-affinity binding site for bilirubin and two lower-affinity sites. At physiologic pH, the amount of free bilirubin (eg, bilirubin not bound to albumin) is very low. This is important because only free bilirubin is available to cross the blood-brain barrier and cause neurotoxicity. Decreased albumin binding capacity, decreased albumin binding affinity, or both can serve to increase the amount of free serum bilirubin. Binding affinity is lower in neonates than in older infants and is lower still in premature and sick infants than in healthy term ones.
    - ▪ Decreased binding capacity can occur in hypoalbuminemia or if the binding sites are filled with other anions. Controversy exists regarding whether parenterally administered lipid can displace bilirubin from its albumin-binding site. If faced with dangerously high levels of serum bilirubin, restricting lipid administration to less than maximal levels may be prudent. Drugs, such as sulfisoxazole and ceftriaxone, can also compete for bilirubin-binding sites on the albumin molecule and must be used with caution or avoided in the neonatal period.

  - o Hepatic uptake and conjugation
    - ▪ Albumin carries bilirubin to the liver, where it is incorporated into the hepatocyte by an acceptor protein called ligandin. Hepatic levels of ligandin do not reach adult values until around age 5 days, but they can be induced by administration of phenobarbital.
    - ▪ Once inside the hepatocyte, bilirubin is conjugated to a sugar moiety, glucuronic acid, via the enzyme UDPGT. Inherent neonatal deficiency of this enzyme is the principal etiology of physiologic jaundice. For the first 10 days of life, UDPGT is present at levels about 0.1% of adult values, and hyperbilirubinemia appears to be the primary stimulus to enzyme production.
    - ▪ Beyond physiologic jaundice, congenital inherited defects in UDPGT cause pathologic hyperbilirubinemia of varying severity. Crigler-Najjar syndrome type I is the virtual absence of UDPGT and is characterized by profound refractory hyperbilirubinemia with the ongoing risk of kernicterus at any point during an individual's lifespan. Currently, liver transplant is the only definitive therapy, although experimental therapies are under investigation. Patients with Crigler-Najjar syndrome type II (ie, Arias syndrome) have a similar clinical presentation as patients with type I. However, patients with type II respond dramatically to therapy with phenobarbital, which is how the diagnosis is made.
    - ▪ Gilbert syndrome is characterized by a benign chronic indirect hyperbilirubinemia without evidence of liver disease or abnormality. The genetic basis for this syndrome has recently been identified as an amplified triplet repeat in the coding

gene for UDPGT, and investigations are continuing to clarify the possible role of Gilbert syndrome in infants with neonatal hyperbilirubinemia.

- o Excretion
    - Once conjugated, water-soluble bilirubin is excreted in an energy-dependent manner into the bile canaliculi for ultimate delivery into the small intestine. Disruption in this system or obstruction in the biliary system results in accumulation of conjugated bilirubin in the serum, identified by an elevation in the direct fraction of total bilirubin. Direct hyperbilirubinemia in the neonate (defined as a direct fraction greater than one third of total bilirubin) is always pathologic, and an etiology must be pursued.
    - In the small intestine, conjugated bilirubin cannot be reabsorbed. Intestinal florae convert it into urobilinogen, which is excreted. In the neonate, the paucity of colonic bacteria impedes this conversion. Furthermore, the neonatal gut (but not that of the adult) produces beta-glucuronidase, an enzyme that deconjugates conjugated bilirubin, releasing free bilirubin for potential absorption across the intestinal cell lipid membrane into the blood stream. Breast milk also contains beta-glucuronidase, and breast milk feedings increase the level of this enzyme in the neonatal intestine. Combined with slow intestinal motility in the first few days of life, the above factors result in what is called enterohepatic recirculation of bilirubin back into the blood stream.

- Systemic factors: Various systemic conditions increase the risk of hyperbilirubinemia and the risk of kernicterus without severe hyperbilirubinemia.

    - o Galactosemia: Patients with this rare inborn error of metabolism may primarily present with hyperbilirubinemia, although the direct fraction typically increases during the second week of life. The baby may manifest other characteristic signs, such as hepatomegaly, poor feeding, or lethargy. Urine for reducing substances, but not glucose, is diagnostic. Many state newborn metabolic screens include a test for this disorder.
    - o Hypothyroidism: Although the etiology is unclear, prolonged indirect hyperbilirubinemia is one of the typical features of congenital hypothyroidism, and this diagnosis must be ruled out in any baby with hyperbilirubinemia persisting after age 2-3 weeks. Most state metabolic screens include an assay of thyroid function, although false-negative results and delayed receipt of results may necessitate individual testing in symptomatic infants.
    - o Drugs: Maternal administration of oxytocin, diazepam, or promethazine may result in increased serum bilirubin in the infant. Similarly, neonatal administration of pancuronium and chloral hydrate increases bilirubin levels. Additionally, some drugs, such as sulfonamides and some penicillins, can displace bilirubin from its albumin-binding site, effectively increasing the serum concentration of free bilirubin available to cross the blood-brain barrier.
    - o Acidosis: Systemic acidosis decreases the binding affinity of albumin for bilirubin, resulting in increased levels of free bilirubin in the blood stream. Ready availability of protons promotes the formation of bilirubin acid (free bilirubin anion plus 2 hydrogen ions); that moiety demonstrates increased binding and transport into neural cell membranes.
    - o Disrupted blood-brain barrier: The neonatal blood-brain barrier is more permeable to substances than is the adult's. Administration of hyperosmolar substances, hypercarbia, asphyxia, infection (particularly meningitis), and impaired autoregulation with variations in blood pressure all may weaken capillary tight junctions, increasing capillary permeability. This, in turn, might lower the concentration at which bilirubin is toxic to the CNS.
    - o Breast milk feedings

        - The well-described physiologic jaundice observed in the first few days of life, particularly in the breastfed infant, is called breastfeeding jaundice. Breastfeeding jaundice is thought to result from multiple mechanisms, described above, which promote production and inhibit excretion of bilirubin, as well as from insufficient

milk intake because of reduced mammary gland milk production in the first few days postpartum. Breastfeeding jaundice should be distinguished from breast milk jaundice.

- Some breastfed infants, while clinically thriving, continue to manifest an indirect hyperbilirubinemia of unidentifiable etiology for several months. If this is witnessed in a breastfed infant, the exclusion diagnosis of breast milk jaundice may be made. Such hyperbilirubinemia is thought to be caused by persistently high levels of as-yet-unidentified components in some women's breast milk, which result in persistence of the infant's hyperbilirubinemia. One clue may be a history of similar hyperbilirubinemia in other breastfed siblings. This entity is benign.

DIFFERENTIALS   Section 4 of 11

Fetal Alcohol Syndrome   Head Trauma
Hearing Impairment   Herpes Simplex Virus Infection
Hyperammonemia   Hypothyroidism
Meningitis, Bacterial   Neonatal Sepsis
Periventricular Leukomalacia
Other Problems to be Considered:

Cerebral palsy   Hypoxic-ischemic brain injury in the newborn
Sepsis

WORKUP   Section 5 of 11

Lab Studies:

- Hematologic studies: Hematologic laboratory evaluation is the cornerstone of evaluation of the baby with hyperbilirubinemia. Although jaundice can be appreciated clinically, observation alone is not a reliable method to assess the severity or estimate risk factors for the infant.
- Total and direct bilirubin: Quantitative measurement of total and direct bilirubin should be undertaken in every baby at risk for significant hyperbilirubinemia or kernicterus. Total bilirubin measures the aggregate of all forms of bilirubin in the serum. The direct fraction measures the amount of conjugated bilirubin. Subtraction of the direct fraction from the total yields the calculated indirect bilirubin, or the unconjugated form. Remember that the indirect fraction is composed of bound bilirubin, free bilirubin, and lumirubin if the baby is under phototherapy. Only the free bilirubin is available to cross the blood-brain barrier and has the potential to cause neurotoxicity. Attempts to measure the amount of bound albumin or to estimate the bound fraction from measures of serum albumin have not proved to be clinically useful.

  o Serial measurements may be necessary to track the evolution of hyperbilirubinemia; frequency of measurements depends on the baby's gestational age, chronologic age, risk factors, and other clinical characteristics.
  o Every baby with hyperbilirubinemia should have a direct fraction measured at least once to rule out direct hyperbilirubinemia. Direct hyperbilirubinemia in the neonate is defined as a direct fraction greater than one third of total bilirubin and is always pathologic. Subsequently, if the hyperbilirubinemia is established as the indirect type, obtaining a direct fraction with every measurement is unnecessary unless the hyperbilirubinemia develops after the expected time frame for typical neonatal hyperbilirubinemia.
  o With the advent of early discharge (before the physiologic peak of serum bilirubin) some clinicians are advocating universal bilirubin measurements in all babies prior to discharge. Nomograms have been published that estimate a baby's risk of disease based on measured levels of bilirubin. The most recently published nomogram uses an hour-specific approach to address the difficulties posed by babies leaving the hospital within 24-48 hours of birth (see Image 3).

- Blood type: The baby's blood type should be determined and compared with that of the mother. Mothers with blood type O may have circulating antibodies to other red cell antigens that can cross the placenta and cause hemolytic disease in a baby with a different blood type, such as blood type A or B. Similarly, mothers who are Rh negative may have antibody to the Rh antigen if they have not been treated with RhoGAM. Antibody to the Rh antigen causes the most fulminant type of hemolytic hyperbilirubinemia, termed erythroblastosis fetalis in its most severe form. ABO incompatibility can cause significant hemolysis as well. Minor antigens on the baby's RBC are also susceptible to immune-mediated hemolysis from maternally acquired antibody but usually to a lesser extent than the major antigens.
- Reticulocyte count: Babies typically have reticulocyte counts higher than older infants and adults. However, significant elevation in the neonate's reticulocyte count (>7 mg/dL) can indicate the presence of an ongoing hemolytic process.
- Direct Coombs test: This test assays for antibody on the RBC membrane. A positive result indicates that antibodies are attached to the RBC, placing it at risk for immune-mediated destruction. This is a qualitative test, so a positive result does not suggest the amount of antibody or the degree of hemolysis. (However, pairing these results with the reticulocyte count can provide some idea of the severity of the process.) This test, although reliable, does not have 100% sensitivity. Because false-negative results do occur, repeating a test with an initial negative result is not unreasonable if the clinical course supports an ongoing hemolytic process.
- Complete blood cell count: A CBC with manual differential should always be included in the evaluation of a jaundiced newborn. Measurement of the hemoglobin and hematocrit can be helpful to determine if ongoing hemolysis severe enough to cause anemia is present. The peripheral smear inspection is particularly valuable because it may reveal large amounts of nucleated RBCs, suggesting active reticulocytosis; it may show abnormally shaped RBCs in the case of hereditary membrane defects such as spherocytosis and elliptocytosis or marked ovalocytosis in the case of hemolytic disease of the newborn. Babies with sepsis can develop hyperbilirubinemia, and, although not conclusive, normal total white blood cell count and manual differential can be reassuring in a healthy-appearing baby with hyperbilirubinemia.
- Serum electrolytes: Breastfed babies are known to normally develop higher levels of serum bilirubin than their formula-fed counterparts. However, with the trend toward earlier discharge, most breastfed babies are being discharged home before breastfeeding is well established, and a concomitant increase has occurred in the number of babies admitted in the first week of life with hypernatremic dehydration. Many of these babies are also significantly hyperbilirubinemic, and the resurgence of kernicterus from its previous virtual obsolescence is being attributed partly to this situation. Therefore, assessing serum sodium, potassium, chloride, bicarbonate, BUN, and creatinine levels is essential; initiate treatment as appropriate
- Lumbar puncture: In the initial evaluation of hyperbilirubinemia, sepsis may be included in the differential diagnosis. If so, collection of spinal fluid for culture and cell count is essential to rule out meningitis. If the baby is having neurologic symptoms, cerebral spinal fluid (CSF) evaluation is imperative; depending on the baby's symptoms, expanding the evaluation beyond the normal aerobic bacterial culture may be prudent. If, on the other hand, the baby is vigorous and well-appearing with isolated hyperbilirubinemia as the only symptom, a spinal tap may not be necessary.

Imaging Studies:

- In the acute phase of bilirubin encephalopathy, neuroimaging has no major diagnostic benefit. However, it can help rule out other diagnoses, particularly in the absence of profound hyperbilirubinemia.

- Head ultrasonography (HUS): This modality is particularly well suited to the neonate because it is painless, portable, and noninvasive; also, the neonatal brain is easily imaged through the fontanelles. Sonographic imaging is not helpful in diagnosing acute bacterial encephalopathy; however, other entities, such as intraventricular hemorrhage or parenchymal abnormalities, can be ruled out.
- CT scanning: Computed tomography scanning has little place in the evaluation of the neonatal brain. It is difficult to perform because the baby must be transported to the radiology

department and must be heavily sedated for the procedure. The subtle abnormalities often present in the neonatal period are not well visualized by CT scanning, and false-negative findings are not uncommon.
- MRI: Previously, the neuronal damage characteristic of kernicterus was thought to only be identifiable on histologic examination postmortem. However, experience has revealed that MRI can be used to depict characteristic bilateral symmetric high-intensity signals in the globus pallidus on both T1- and T2-weighted images in patients surviving with chronic bilirubin encephalopathy (see Image 4). The usefulness and cost-effectiveness of this modality in the diagnosis of more subtle forms of bilirubin toxicity remains to be fully elucidated.

Other Tests:

- Brainstem auditory evoked response (BAER): Hearing impediment is the most common sequela of bilirubin toxicity. Impairment may be subtle and may not be clinically apparent until the baby manifests delayed language acquisition. To maximize the baby's long-term neurologic functioning, early identification of any degree of hearing loss is important so that early developmental assessment and intervention can be initiated in a timely fashion. Serial assessments of hearing function may be necessary.

Histologic Findings: On macroscopic examinations, characteristic yellow staining can be readily observed in fresh or frozen sections of the brain obtained within 7-10 days after the initial bilirubin insult. The regions most commonly involved include the basal ganglia, particularly the globus pallidus and subthalamic nucleus; the hippocampus; the substantia nigra; cranial nerve nuclei, including the oculomotor, cochlear, and facial nerve nuclei; other brainstem nuclei, including the reticular formation and the inferior olivary nuclei; cerebellar nuclei, particularly the dentate; and the anterior horn cells of the spinal cord.

Neuronal necrosis occurs later and results in the clinical findings consistent with chronic bilirubin encephalopathy. Histologically, this appears as cytoplasmic vacuolation, loss of Nissl substance, increased nuclear density with haziness to the nuclear membrane, and pyknotic nuclei (see Image 5).

TREATMENT	Section 6 of 11

Medical Care: The cornerstone of management of hyperbilirubinemia is prevention of neurotoxicity. The definitive method of removing bilirubin from the blood is via exchange transfusion. This is currently the indicated approach in the presence of clinical bilirubin encephalopathy when the bilirubin level has reached dangerous levels despite preventive efforts. Phototherapy is the most common method aimed at prevention of bilirubin toxicity. Current clinical research is evaluating the use of metalloporphyrins to block bilirubin formation by competing with the enzyme heme oxygenase.

- Exchange transfusion: This definitive therapy is used to mechanically remove already-formed bilirubin from the blood. It is indicated whenever clinical signs of acute bilirubin encephalopathy exist in patients who present with critically high serum bilirubin (eg, >25 mg/dL) and dehydration or when the serum bilirubin level continues to rise despite attempts to reduce it. In the presence of Rh isoimmunization, a cord bilirubin level greater than 5 mg/dL or a rate of rise in serum bilirubin greater than 0.5-1 mg/dL/h has been shown to be predictive of the ultimate need for exchange transfusion. This relationship has not been demonstrated in hyperbilirubinemia of other etiologies. This procedure is not without risk.

  - Technique: The procedure involves removing the baby's native blood and replacing it with CPD (citrate phosphate dextrose) banked blood that does not contain bilirubin. Obviously, this must be performed gradually. Using an estimate of 80-90 cc/kg total blood volume, usually double this amount is removed and replaced sequentially in 10-15 cc aliquots over several hours. This approach, called a double volume exchange transfusion, harvests the most efficient amount of bilirubin from the blood for the amount of intervention and results in a decrease in total serum bilirubin levels by about 40%. Because of ongoing pathology

and equilibrium between the intravascular and extravascular spaces, having to repeat the procedure at least once is not uncommon. Using O negative blood rather than the baby's blood type is important because not all circulating antibodies may be removed. Packed RBCs resuspended in fresh frozen plasma must be used for this procedure.

- o Risks

  - This procedure carries both inherent risks and iatrogenic ones and should be carefully performed. The reported overall mortality rate is about 3:1000; the risk of significant morbidity has been reported at about 5:100. In very ill babies, the risks are higher. One series of 25 ill infants reported a mortality rate of 20%.
  - Transfusing with banked blood products carries a risk of infection. Currently, the risk of infection with known pathogens is exceedingly small. However, a risk of infection with pathogens that have not yet been discovered (ie, most recently hepatitis C) continues.
  - During the procedure, continually monitor for attendant physiologic aberrations, such as hypoglycemia, thrombocytopenia, hyperkalemia (particularly if the banked blood is older than 5 d), and hypocalcemia (if ethylenediamine tetra-acetic acid [EDTA] preservative is used in the banked blood).
  - Mechanical issues can contribute to the overall mortality and morbidity of the procedure. The need for central access, catheter- and infusion-related problems, and human error during infusion are all areas that can pose potentially significant risk.
  - Since the advent of phototherapy and obstetric treatment of Rh disease, the need for exchange transfusion has diminished.

- o Indicated bilirubin levels
  - As mentioned above, no clear-cut level of bilirubin exists above which encephalopathy is assured and below which neurologic safety exists. Birthweight, gestational age, and chronologic age are all important, as are a baby's systemic condition, fluid and nutritional status, acid-base status, and the presence or absence of known pathology. In 1994, the American Academy of Pediatrics (AAP) published practice parameters for the management of hyperbilirubinemia in the healthy term infant. In this document, the AAP recommended exchange transfusion for serum bilirubin levels greater than 20-25 mg/dL, depending on the chronologic age of the infant. Some have criticized these parameters as being too aggressive.
  - Studies have reported neurologically normal outcomes in healthy term infants with histories of serum bilirubin levels as high as 46 mg/dL. However, the recent resurgence in kernicterus has been reported to occur exclusively in near-term infants with serum bilirubin levels greater than 30 mg/dL. The level at which to intervene is a clinical question that remains to be answered. The procedure should be highly considered in babies with significant risk factors predisposing for kernicterus (eg, sepsis, acidosis, hemolytic disease) if the bilirubin level has approached the 20- to 25-mg/dL range.

- Agar: Enteral administration of agar has been tried in an attempt to decrease the enterohepatic recirculation of conjugated bilirubin. It has not proved to be clinically useful and may cause intestinal obstruction.
- Sn-mesoporphyrin: Experimental therapy with Sn-mesoporphyrin inhibits bilirubin production by interfering with heme-oxygenase, an essential enzyme in the catabolic pathway of hemoglobin. This therapy is in clinical trials but has not been approved for use by the Food and Drug Administration (FDA).

Consultations: Obtaining input from a pediatric neurologist during the acute presentation of bilirubin encephalopathy may be useful. However, the history and clinical presentation may make the diagnosis apparent. In the chronic phase, involving neurodevelopmental specialists in the care and evaluation of the infant is important. Developmental potential can be maximized by early identification of and intervention for neurologic deficits.

If the patient develops hydrocephalus, consultation with a neurosurgeon is recommended.

Diet: Depending on the degree of neurologic impairment, infants or children may have limitations in their ability to eat normally. Diet and nutrition must be individualized with the help of the neurodevelopmental team caring for the patient.

Activity: Some neurologic deficits typically appear during the phase of motor skill acquisition by the infant. Motor deficits should be identified early, and appropriate intervention should be initiated to maximize the infant's ability in this critical area.

MEDICATION	Section 7 of 11

No medications are available to treat the symptoms of acute or chronic bilirubin encephalopathy. Pharmacologic intervention is aimed at prevention. Current therapies are indicated as adjuncts to phototherapy when total bilirubin is approaching exchange level; experimental therapy continues with the use of bilirubin production inhibitors.

Drug Category: *Blood product derivatives --* These methods decrease the amount of free bilirubin in the intravascular space, thus theoretically reducing the risk of neurotoxicity. Bilirubin is produced via induction of its enzymatic pathway and by RBC degradation. Inhibition of either of those 2 mechanisms can decrease the amount of bilirubin in the blood.

Drug Name	Albumin (Albuminar, Albunex, Albumisol, Buminate) -- Because bilirubin bound to albumin is not available to cross the blood-brain barrier, increasing the amount of serum albumin theoretically increases the amount of available binding sites and decreases free bilirubin. Efforts to quantify albumin-binding capability or serum levels of bound bilirubin have not proved to be clinically useful. Therefore, administration of albumin for the purpose of increasing bilirubin-binding capacity is not a recommended standard of care. It may be considered in cases of significant hypoalbuminemia.
Pediatric Dose	0.5-1 g/kg IV of 5% albumin (ie, 5 g/100 mL)
Contraindications	Documented hypersensitivity; pulmonary edema; severe anemia; cardiac failure
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Use 25% albumin with caution in premature neonates because of the increased risk of intraventricular hemorrhage; caution in renal or hepatic failure, may cause protein overload; rapid infusion may cause vascular overload or hypotension; monitor for volume overload; caution in sodium-restricted patients; common adverse effects include CHF, hypotension, tachycardia, fever, chills, and pulmonary edema; do not dilute albumin 25% with sterile water for injection (produces hypotonic solution and, if administered, may result in life-threatening hemolysis and acute renal failure)
Drug Name	Immune globulin intravenous (Gamimune, Gammagard, Sandoglobulin) -- Parenteral administration has been shown in controlled clinical trials to reduce the need for exchange transfusion in both Rh and ABO immune-mediated hemolytic disease. Its mechanism of action is not entirely clear.
Pediatric Dose	0.5-1 g/kg IV; administration must be initiated very slowly and gradually increased because of the possibility of acute transfusion reaction
Contraindications	Documented hypersensitivity; IgA deficiency
Interactions	Globulin preparation may interfere with immune response to live virus vaccine and reduce efficacy (do not administer within 3 mo of vaccine)
Pregnancy	C - Safety for use during pregnancy has not been established.

Precautions	Associated with other risks accompanying administration of other human blood products (eg, transmission of infection, allergic reaction); unknown if administration of IVIG places the neonate at a theoretically increased risk of susceptibility to infection; check serum IgA before IVIG (use an IgA-depleted product, eg, Gammagard S/D); infusions may increase serum viscosity and thromboembolic events; infusions may increase risk of migraine attacks, aseptic meningitis (10%), urticaria, pruritus, or petechiae (2-30 d postinfusion)

Drug Category: *Anticonvulsant agents* -- Phenobarbital may increase hepatic conjugation and excretion. Decreased hepatic conjugation caused by normal delay in enzyme induction increases the amount of unconjugated bilirubin in the blood stream. Conjugated bilirubin does not pose a threat of neurotoxicity. Once conjugated, this nontoxic form of bilirubin proceeds toward intestinal excretion.

Drug Name	Phenobarbital (Luminal, Solfoton) -- Induces the hepatic enzymes involved in bilirubin conjugation and increases biliary excretion. Do not administer intra-arterially. Dosing can be enteral or parenteral. Maximum IV administration rate of 1 mg/kg/min IV; not to exceed 30 mg/min for infants.
Pediatric Dose	Hyperbilirubinemia: 3-8 mg/kg/d PO/IV initially; may increase up to 12 mg/kg/d
Contraindications	Documented hypersensitivity; severe respiratory disease; marked impairment of liver function; nephritis
Interactions	May decrease effects of chloramphenicol, digitoxin, corticosteroids, carbamazepine, theophylline, verapamil, metronidazole, and anticoagulants (patients stabilized on anticoagulants may require dosage adjustments if added to or withdrawn from their regimen); coadministration with alcohol may cause additive CNS effects and death; chloramphenicol, valproic acid, and MAOIs may increase phenobarbital toxicity; rifampin may decrease phenobarbital effects; induction of microsomal enzymes may result in decreased effects of PO contraceptives in women (must use additional contraceptive methods to prevent unwanted pregnancy; menstrual irregularities may also occur)
Pregnancy	D - Unsafe in pregnancy
Precautions	Use with caution in patients with renal impairment, hepatic impairment, or both; abrupt withdrawal may precipitate status epilepticus; high doses may cause respiratory depression or failure

Further Outpatient Care:

- To help insure that infants may reach their maximum neurodevelopmental potential, referring babies with chronic bilirubin encephalopathy to a neurodevelopmental pediatrician skilled in caring for these patients is important. Early identification of and intervention for neurodevelopmental deficits has been shown to positively impact an infant's long-term neurodevelopmental prognosis.
- The numerous areas of uncertainty surrounding the diagnosis and treatment of hyperbilirubinemia in the infant, coupled with the infrequency of sequelae, make it easy to become cavalier about the evaluation of a jaundiced infant. However, remember that physiologic hyperbilirubinemia is a diagnosis of exclusion, and kernicterus, when it occurs, is a devastating and legally indefensible sequela.
- Sepsis must always be excluded in the jaundiced infant. Uncommon, but treatable, metabolic causes of jaundice include hypothyroidism and galactosemia. The first sign of occult immune or nonimmune hemolytic disease may be hyperbilirubinemia.

The recently reported cases of kernicterus have occurred in near-term or term infants who were discharged from the hospital fewer than 48 hours after birth. Most infants discharged at fewer than 72 hours after birth have clearly not reached their physiologic peak bilirubin level prior to discharge. Any infant at risk for significant hyperbilirubinemia and possible neurotoxicity should be cared for in a nursery capable of rendering appropriate care for the hyperbilirubinemia and any contributing diagnoses. A recently published nomogram predicts which babies may be at risk for significant disease, based on hour-of-life–specific bilirubin levels (see Image 3). Infants whose levels fall in the high-intermediate and high-risk zones should be closely monitored in a nursery capable of caring for sick newborns; they may require transfer from the birth hospital to a regional perinatal center.

- Prevention: Prevention of hyperbilirubinemia is the best way to minimize the incidence of kernicterus. However, because some babies develop kernicterus with relatively modest bilirubin levels, no known absolute level of bilirubin exists below which the infant is completely safe. Additionally, because other factors contribute to the ability of bilirubin to cross the blood-brain barrier, management of these components must be appropriately attended to.
- Serum bilirubin: Total serum bilirubin comprises a conjugated fraction (loosely called direct bilirubin) and an unconjugated fraction (indirect bilirubin). They are additive. However, the indirect fraction is composed of bound bilirubin (bound to albumin), lumirubin if the baby is under phototherapy (unbound but water-soluble and unlikely to cross the blood-brain barrier), and free bilirubin. The free component is potentially toxic, but its exact serum level cannot be readily measured.

  - Risk of reduction of serum bilirubin
    - The current level of knowledge does not recognize the physiologic benefits of bilirubin, despite the multiple mechanisms operant in the neonate to promote and preserve hyperbilirubinemia. In vitro experiments have demonstrated a potent antioxidant capability of bilirubin, more so than the currently identified mechanisms.
    - An emerging field of research in human medicine is the role of oxidative injury in the development of various pathologic processes, which may be contributory to many neonatal diseases, such as retinopathy of prematurity, periventricular leukomalacia, bronchopulmonary dysplasia, and necrotizing enterocolitis. Recent observational studies in the neonate have demonstrated an inverse correlation between peak serum bilirubin levels and the development of these various pathologies. Investigation into this line of research continues.

- Phototherapy
  - Irradiance with light in the blue-green spectrum (440-480 nm) induces a photochemical reaction that changes the bilirubin molecule into other photoisomers that are water-soluble, readily excretable, and unlikely to cross the blood-brain barrier into the lipid-rich neuronal tissue. Such conversion begins immediately upon exposure of the skin surface to the light.
  - The most important photoreaction is an irreversible structural isomerization of bilirubin into a water-soluble substance called lumirubin, which is then excreted in the bile. Reversible configurational isomerization and photo-oxidation also contribute somewhat to the effectiveness of phototherapy to reduce free bilirubin in the baby.
  - To be effective, adequate skin surface must be exposed to the appropriate wavelength, with enough intensity (lux) to induce the desired reaction. Serum bilirubin levels should be closely monitored during phototherapy. A decrease of measured bilirubin by 1-2 mg/dL over a 4- to 6-hour period is an appropriate response to phototherapy.
  - Various devices are commercially available to facilitate provision of phototherapy. Models include overhead lights, blankets, and swaddling devices; selection is based on abilities to cover a broad surface area, ease of administration, and personal preference.
  - When to initiate phototherapy is a thorny clinical issue, compounded by the difficulties posed by early discharge in following these cases. In 1994, the AAP published a practice parameter for the management of hyperbilirubinemia in the healthy term and near-term infant. Some have criticized it for being overly aggressive, while others think it may be too

lenient. A recently published nomogram correlated serum bilirubin levels in the first several hours of life with subsequent risk for significant disease (see Image 3). This reference can be helpful when deciding how closely to follow the cases of babies being discharged home before their bilirubin levels have peaked. Since its development, some experts have recommended universal bilirubin screening (performed with the state metabolic screen to minimize blood draws) before discharge.

- o Current measurement of serum bilirubin has been limited to direct hematologic measurement. Transcutaneous measurement devices have recently become commercially available. The manufacturers claim excellent reliability and validity in babies of all skin types and colors. At present, this technology is not in widespread use.

- o Risks of phototherapy
    - ▪ Phototherapy by itself is generally considered safe in babies, except in some rare genetic skin disorders and congenital porphyria. However, some risks are associated with its use.
    - ▪ Exposure to phototherapy causes photorelaxation of the peripheral vasculature, which can increase insensible fluid loss and lead to dehydration, especially in babies in open warmers. This, in turn, potentiates hyperbilirubinemia.
    - ▪ Some extremely premature infants have reportedly experienced skin burns from fiberoptic blankets on which they were lying. Such devices should be used cautiously in infants with vulnerable skin.
    - ▪ Concern exists about the risk of retinal damage in infants exposed to the extremely bright light of phototherapy. Accordingly, all infants should wear protective eye coverings while being treated.
    - ▪ An observed increase in the prevalence of patent ductus arteriosis (PDA) has been shown to occur in premature infants receiving phototherapy, and foil shields to the chest have been shown to ameliorate this increase. The operant mechanism has not been elucidated fully but is thought to be related to the photorelaxation response observed in these babies' peripheral vascular beds.
    - ▪ Bilirubin photosensitizes the skin, and skin damage is a theoretical risk. Bullous eruptions have been described in several infants with porphyrin abnormalities; congenital porphyria is a contraindication to the use of phototherapy.
    - ▪ Bronze baby syndrome occurs in infants with direct hyperbilirubinemia who are exposed to phototherapy. This seems likely to be the result of dermal accumulation of coproporphyrins. Measurement of the direct fraction of total bilirubin should be performed in every baby before starting phototherapy.
    - ▪ Phototherapy can interfere with maternal-child bonding at a critical time in the dyad's development. If a mother is breastfeeding, initiation of phototherapy introduces mechanical barriers to the breastfeeding process, which can be overwhelming at this critical time. Any comments about the role of breast milk in the development of hyperbilirubinemia may further sabotage this process. Altered parental perceptions of their infant from healthy to ill may further influence their short- and long-term interactions with their infant.

- • Breastfeeding: The link between hyperbilirubinemia and breastfeeding has long been recognized, and, until recently, breastfeeding was typically interrupted in the jaundiced infant. Randomized controlled trials have shown that offering formula or dextrose water to the jaundiced breastfed infant actually increases total serum bilirubin levels and, thus, should not be advocated. Furthermore, this practice has also been shown to result in a decrease in breast milk intake after breastfeeding is reestablished. Study of the effect of continuing breastfeeding versus its interruption has not shown any untoward effect of continued breastfeeding. Because of the clear short- and long-term advantages to the infant of breast milk feeds, the evidence would indicate that breastfeeding should be continued in the infant who is well enough to have enteral feedings.

Complications: The complications of acute bilirubin encephalopathy encompass the classic scope of chronic bilirubin encephalopathy described above. Abnormalities can be expected in the extrapyramidal system and in auditory and gaze function; dental dysplasia can be expected.

Prognosis: The spectrum of neurologic disability from kernicterus can range from mild to severe. Attempts to correlate features of hyperbilirubinemia with prognosis for disability have failed. Despite multiple attempts, no definitive association has been identified between the degree of deficit and parameters such as total serum bilirubin level, duration of hyperbilirubinemia, presence of hemolytic disease, gestational age, birthweight, or concomitant systemic illness.

Patient Education:

- To facilitate the provision of appropriate evaluation and follow-up for babies without recognized risk factors, the AAP has published an hour-of-age-specific guideline that correlates total serum bilirubin levels with degree of risk and recommendations for follow-up.

  The AAP recommends professional medical evaluation in 2-3 days for babies who are discharged from the hospital fewer than 48 hours after birth. Babies discharged fewer than 72 hours after birth may also be at risk, and they should be closely monitored as well. Other risk factors warranting additional vigilance may include unexplained family history of neonatal hyperbilirubinemia, near-term gestation, low birth weight, excessive bruising or hematomata, and ethnicity at risk for exaggerated hyperbilirubinemia.

  Parents should be informed of the importance of keeping these appointments, as well as be familiarized with the symptoms of poor feeding in breastfed babies and how to seek help.

| MISCELLANEOUS	Section 9 of 11

Medical/Legal Pitfalls:

- Theoretically, most cases of kernicterus may be completely prevented by initiation of phototherapy in every baby shortly after birth. Therefore, this devastating neurologic disease could be prevented most of the time. As such, a significant component of medicolegal liability is introduced into the management of hyperbilirubinemia. Clinical reports of kernicterus in the absence of profound hyperbilirubinemia, coupled with the lack of definitive standards of care for the initiation of phototherapy, further complicate this exposure. As with all medical care, conformity with published clinical guidelines, rationale for departure from accepted clinical norms, and good documentation are the best defenses.

- The numerous areas of uncertainty surrounding the diagnosis and treatment of hyperbilirubinemia in the infant, coupled with the infrequency of sequelae, foster a cavalier attitude about the evaluation of a jaundiced infant. However, remembering that physiologic hyperbilirubinemia is a diagnosis of exclusion is important, and kernicterus, when it occurs, is devastating. Therefore, failure to evaluate or provide reasonable follow-up of infants at risk for the development of severe hyperbilirubinemia may place the clinician in a position that could be difficult to defend.

  Sepsis must always be excluded in the jaundiced infant. Uncommon, but treatable, metabolic causes of jaundice include hypothyroidism and galactosemia. The first sign of occult immune or nonimmune hemolytic disease may be hyperbilirubinemia. Failure by the clinician to diagnose an underlying etiology results in considerable medicolegal exposure.

Picture 1. Kernicterus. Typical patterns of total serum bilirubin levels in neonates of different racial origins. Used with the permission of the Academy of Pediatrics.
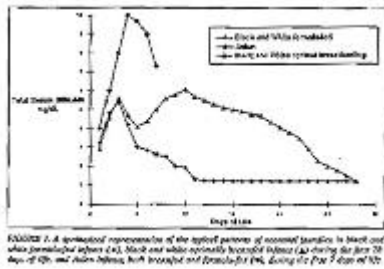
Picture 2. Kernicterus. Overview of bilirubin metabolism.
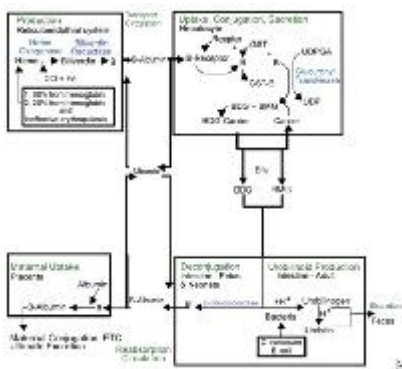
Picture 3. Kernicterus. Hour-specific nomogram for total serum bilirubin and attendant risk of subsequent severe disease in term and preterm infants. Used with the permission of the Academy of Pediatrics.
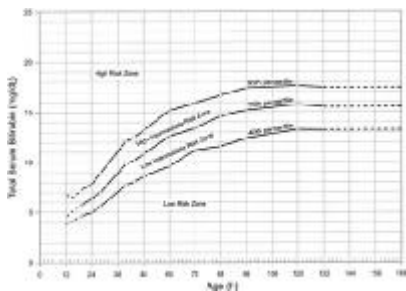
Picture 4. Magnetic resonance image of 21-month-old with kernicterus. Area of abnormality is the symmetric high-intensity signal in the area of the globus pallidus (arrows). Courtesy of M.J. Maisels.

Picture 5. Kernicterus. Neuronal changes observed in kernicterus. Courtesy of J.J. Volpe.

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Kernicterus excerpt

Meconium Aspiration Syndrome

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INTRODUCTION	Section 2 of 11

Background: The first intestinal discharge from newborns is meconium, which is a viscous, dark green substance composed of intestinal epithelial cells, lanugo, mucus, and intestinal secretions, such as bile. Intestinal secretions, mucosal cells, and solid elements of swallowed amniotic fluid are the 3 major solid constituents of meconium. Water is the major liquid constituent, making up 85-95% of meconium. Intrauterine distress can cause passage into the amniotic fluid. Factors that promote the passage in utero include placental insufficiency, maternal hypertension, preeclampsia, oligohydramnios, and maternal drug abuse, especially of tobacco and cocaine. Meconium-stained amniotic fluid may be aspirated during labor and delivery, causing neonatal respiratory distress. Because meconium is rarely found in the amniotic fluid prior to 34 weeks' gestation, meconium aspiration chiefly affects infants at term and postterm.

Pathophysiology: Meconium may be passed in utero secondary to a hypoxic stress; alternatively, evidence exists suggesting that meconium passage results from neural stimulation of a mature GI tract. As the fetus approaches term, the GI tract matures, and vagal stimulation from head or cord compression may cause peristalsis and relaxation of the rectal sphincter leading to meconium passage.

Although the etiology is not well understood, effects of meconium are well documented. Meconium directly alters the amniotic fluid, reducing antibacterial activity and subsequently increasing the risk of perinatal bacterial infection. Additionally, meconium is irritating to fetal skin, thus increasing the incidence of erythema toxicum. However, the most severe complication of meconium passage in utero is aspiration of stained amniotic fluid before, during, and after birth. Aspiration induces 3 major pulmonary effects, which are airway obstruction, surfactant dysfunction, and chemical pneumonitis.

Airway obstruction

Complete obstruction of the airways results in atelectasis. Partial obstruction causes air trapping and hyperdistention of the alveoli. Hyperdistention of the alveoli occurs from airway expansion during inhalation and airway collapse around inspissated meconium in the airway, causing increased resistance during exhalation. The gas that is trapped, hyperinflating the lung, may rupture into the pleura (pneumothorax), mediastinum (pneumomediastinum), or pericardium (pneumopericardium).

Surfactant dysfunction

Several constituents of meconium, especially the free fatty acids (eg, palmitic, stearic, oleic), have a higher minimal surface tension than surfactant and strip it from the alveolar surface, resulting in diffuse atelectasis.

Chemical pneumonitis

Enzymes, bile salts, and fats in meconium irritate the airways and parenchyma, causing a diffuse pneumonia that may begin within a few hours of aspiration.

All of these pulmonary effects can produce gross ventilation-perfusion (V-Q) mismatch. To complicate matters further, many infants with meconium aspiration syndrome (MAS) have primary or secondary persistent pulmonary hypertension of the newborn (PPHN) as a result of chronic in utero stress and thickening of the pulmonary vessels. Finally, though meconium is sterile, its presence in the air passages can predispose the infant to pulmonary infection.

Frequency:

- **In the US:** In the industrialized world, meconium in the amniotic fluid can be detected in 8-20% of all births after 34 weeks' gestation. Of those newborns with meconium-stained amniotic fluid, 1-9% may develop MAS.

- **Internationally:** In developing countries with less availability of prenatal care and where home births are common, incidence of MAS is thought to be higher and is associated with a greater mortality rate.

Mortality/Morbidity:

- The mortality rate for MAS resulting from severe parenchymal pulmonary disease and pulmonary hypertension is as high as 20%.

- Other complications include air block syndromes (eg, pneumothorax, pneumomediastinum, pneumopericardium) and pulmonary interstitial emphysema.

Race: No racial predilection exists.

Sex: MAS affects both sexes equally.

Age: MAS is exclusively a disease of newborns.

History:

- Severe respiratory distress may be present. Symptoms include the following:

  o Cyanosis
  o End-expiratory grunting
  o Alar flaring
  o Intercostal retractions
  o Tachypnea
  o Barrel chest in the presence of air trapping

- Green urine may be observed in newborns with meconium aspiration syndrome (MAS) less than 24 hours after birth. Meconium pigments can be absorbed by the lung and excreted in urine.

Physical:

- Presence of meconium in amniotic fluid is essential to the initiation of the pathogenesis.

Causes:

- Factors that promote the passage of meconium in utero include the following:

  o Placental insufficiency
  o Maternal hypertension
  o Preeclampsia
  o Oligohydramnios
  o Maternal drug abuse, especially of tobacco and cocaine

Aspiration Syndromes
Congenital Diaphragmatic Hernia
Pneumonia
Pulmonary Hypertension, Persistent-Newborn
Pulmonary Hypoplasia
Transient Tachypnea of the Newborn
Transposition of the Great Arteries

Other Problems to be Considered:

Sepsis
Surfactant deficiency
Pulmonary hypertension, congenital heart disease

Lab Studies:

- Acid-base status

    - Because V-Q mismatch and perinatal stress are prevalent, assessment of acid-base status is crucial.
    - Metabolic acidosis from perinatal stress is complicated by respiratory acidosis from parenchymal disease and PPHN.
    - Arterial blood gases that measure pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), and continuous measurement of oxygenation by pulse oximetry are necessary for appropriate management.

- Serum electrolytes: Obtain sodium, potassium, and calcium concentrations when the infant with MAS is aged 24 hours because the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and acute renal failure are frequent complications of perinatal stress.
- CBC

    - In utero or perinatal blood loss may contribute to perinatal stress, and infection also may be the source of the stress.
    - Hemoglobin and hematocrit levels must be sufficient to ensure adequate oxygen-carrying capacity.
    - Thrombocytopenia increases the risk for neonatal hemorrhage.
    - Neutropenia or neutrophilia with left shift of the differential may indicate perinatal bacterial infection.

Imaging Studies:

- A chest radiograph is essential to do the following:

    - Determine the extent of intrathoracic pathology
    - Identify areas of atelectasis and air block syndromes
    - Assure appropriate positioning of an endotracheal tube and umbilical arterial catheter

- Later in the course of MAS when the infant is stable, imaging procedures of the brain, such as MRI, CT scan, or cranial ultrasound, are indicated if findings of the infant's neurologic examination are abnormal.

Other Tests: An echocardiogram ensures normal cardiac structure and assesses the severity of pulmonary hypertension and right-to-left shunting.

Medical Care:

- Prevention

    - Prevention is paramount.
    - Obstetricians should monitor fetal status in an attempt to prevent and assuage fetal stress.
    - When meconium is detected, administering amnioinfusion with warm sterile saline may be beneficial. This procedure dilutes meconium in the amniotic fluid; therefore, the severity of aspiration may be minimized.

- o Upon delivery of the head of the baby, careful suctioning of the posterior pharynx decreases the potential for aspiration of meconium. When aspiration occurs, intubation and immediate suctioning of the airway can remove much of the aspirated meconium.
  - o No clinical trials justify suctioning based on the consistency of meconium. Do not perform the following harmful techniques to prevent aspiration of meconium-stained amniotic fluid:
    - Squeezing the chest of the baby
    - Inserting a finger into the mouth of the baby
    - Externally occluding the airway of the baby
  - o The American Academy of Pediatrics Neonatal Resuscitation Program Steering Committee has promulgated the following guidelines for management of the baby exposed to meconium:
    - If the baby is not vigorous (Apgar 1-3): Suction the trachea soon after delivery (ie, before many respirations have occurred). Suction for no longer than 5 seconds. If no meconium is retrieved, do not repeat intubation and suction. If meconium is retrieved and no bradycardia is present, reintubate and suction. If the heart rate is low, administer positive pressure ventilation and consider suctioning again later.
    - If the baby is vigorous (Apgar >5): Clear secretions and meconium from the mouth and nose with a bulb syringe or a large-bore suction catheter. In either case, the remainder of the initial resuscitation steps should ensue: dry, stimulate, reposition, and administer oxygen as necessary.

- Intervention

  - o Maintain an optimal thermal environment and minimal handling because these infants are agitated easily and quickly become hypoxemic and acidotic.
  - o Continue respiratory care. Oxygen therapy via hood or positive pressure is crucial in maintaining adequate arterial oxygenation. If mechanical ventilation is required, make concerted efforts to minimize the mean airway pressure and to use as short an inspiratory time as possible. Use of surfactant has not yet been proven to be efficacious in this setting and is under investigation.
  - o Although conventional ventilation commonly is used initially, oscillatory, high-frequency, and jet ventilation are alternative effective therapies. Hyperventilation to induce hypocapnia and respiratory alkalosis is used as primary therapy for pulmonary hypertension. Inhaled nitric oxide has displaced the use of most intravenous pulmonary vasodilators.
  - o Pay careful attention to systemic blood volume and BP. Volume expansion, transfusion therapy, and systemic vasopressors are critical in maintaining systemic BP greater than pulmonary BP, thereby decreasing the right-to-left shunt through the patent ductus arteriosus.
  - o Extracorporeal membrane oxygenation (ECMO) is employed if all other therapeutic options have been exhausted.

Surgical Care: Although primary management of air block syndromes is achieved by thoracic drainage tubes inserted by a neonatologist, a pediatric surgical consultation may be necessary in severe cases.

Consultations: A pediatric cardiology evaluation is necessary to perform an echocardiogram. This imaging technique ensures normal cardiac structure and assesses the severity of pulmonary hypertension and right-to-left shunting. A pediatric neurology evaluation is essential in the presence of neonatal encephalopathy or seizure activity.

Diet:

- Perinatal distress and severe respiratory distress preclude feeding.
- Intravenous fluid therapy begins with adequate dextrose infusion to prevent hypoglycemia.
- Progressively add electrolytes, protein, lipids, and vitamins to ensure adequate nutrition and prevent essential amino acid and essential fatty acid deficiencies.

In addition to the treatments listed below, surfactant replacement therapy is prescribed frequently. Natural bovine lung extract is administered to replace the surfactant that has been stripped. Surfactant also acts as a detergent to break up residual meconium, thereby decreasing the severity of lung disease. Although 4 different commercial surfactant preparations are available, the FDA has not yet approved surfactant for this indication. However, surfactant commonly is used in patients with MAS, even though its efficacy, dosage regimen, and most effective product still are not established clinically.

Drug Category: *Pulmonary vasodilating agents --* Decreases pulmonary vascular resistance. Administer directly into the main pulmonary artery because the major complication is systemic hypotension without significant effects on pulmonary hypertension. Because of the severe systemic hypotensive effects of tolazoline and nitroprusside, inhaled nitric oxide is used more commonly.

Drug Name	Tolazoline (Priscoline) -- Competitively blocks alpha-adrenergic receptors to antagonize circulating epinephrine and norepinephrine. Produces direct smooth muscle relaxation. Results in decreased blood pressure, peripheral vasodilation, and decreased peripheral resistance.
Pediatric Dose	1-2 mg/kg IV infused over 10 min into a vein that drains via the superior vena cava; if arterial pO_2 increases, follow with continuous IV infusion of 1-2 mg/kg/h
Contraindications	Documented hypersensitivity (rare in neonates); hypotension
Interactions	Incompatible with indomethacin (forms precipitant); disulfiramlike reaction with concomitant alcohol administration (avoid IV diluents with alcohol); H2-antagonists (eg, ranitidine) may decrease effects
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Major adverse effect is systemic hypotension without significant effect on pulmonary pressure; gastric bleeding; ulceration, and gastric perforation has been reported; acidosis may decrease response
Drug Name	Nitroprusside (Nitropress) -- Causes peripheral vasodilatation by direct action on venous and arteriolar smooth muscle. Increases inotropic activity of the heart. At higher dosages, it may exacerbate myocardial ischemia by increasing the heart rate.
Pediatric Dose	0.25-0.5 mcg/kg/min continuous IV infusion; titrate to effect
Contraindications	Documented hypersensitivity (rare in neonates); arteriovenous shunt; coarctation of the aorta
Interactions	Produces vasodilation and increases inotropic activity of the heart. At higher dosages, it may exacerbate myocardial ischemia by increasing the heart rate
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Major adverse effects include severe systemic hypotension and tachycardia; thiocyanate and cyanide toxicity with long-term therapy; exercise caution in patients with elevated ICP and/or severe renal and hepatic failure; use only in 5% dextrose-containing solutions; wrap the solution in opaque material to protect it from light Caution in increased intracranial pressure, hepatic failure, severe renal impairment, and hypothyroidism; caution in renal or hepatic insufficiency

Drug Category: *Respiratory gases --* Inhaled nitric oxide (NO) has the direct effect of pulmonary vasodilatation without the adverse effect of systemic hypotension. Approved for use if concomitant hypoxemic respiratory failure occurs.

Drug Name	Nitric oxide, inhaled (INOmax) -- Produced endogenously from the action of the enzyme NO synthetase on arginine. Exogenously inhaled NO is used in an attempt to decrease pulmonary vascular resistance and improve lung blood flow. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cGMP, which then leads to vasodilation.
Pediatric Dose	20 ppm inhaled via respirator initially; not to exceed 80 ppm; most children respond at 20 ppm and can be weaned to lower doses; effect of pulmonary vasodilatation may still be observed at 5 ppm Must be delivered by a system that measures concentrations of NO in the breathing gas, with a constant concentration throughout the respiratory cycle and that does not cause generation of excessive inhaled nitrogen dioxide
Contraindications	Right to left shunting of blood; methemoglobin reductase deficiency
Interactions	Nitric oxide donor compounds (eg, nitroprusside, nitroglycerin) may increase risk of developing methemoglobinemia
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Toxic effects include methemoglobinemia and pulmonary inflammation resulting from reactive nitrogen intermediates; caution in thrombocytopenia, anemia, leukopenia, or bleeding disorders; monitor for PaO_2, methemoglobin, and NO_2; abrupt withdrawal causes rebound pulmonary hypertension

Drug Category: *Systemic vasoconstrictors* -- Used to prevent right-to-left shunting by raising systemic pressure above pulmonary pressure. Systemic vasoconstrictors include dopamine, dobutamine, and epinephrine. Dopamine is the most commonly used.

Drug Name	Dopamine (Intropin) -- At lower doses, dopamine stimulates beta1-adrenergic and dopaminergic receptors (renal vasodilation, positive inotropism); at higher doses, it stimulates alpha-adrenergic receptors (renal vasoconstriction).
Pediatric Dose	5-20 mcg/kg/min IV
Contraindications	Documented hypersensitivity (rare in neonatal population); outflow tract obstructions such as subaortic stenosis
Interactions	Incompatible when admixed with acyclovir, amphotericin B, indomethacin, insulin, and sodium bicarbonate Phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong effects of dopamine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Adverse effects include tachycardia and arrhythmia; treat hypovolemia before infusion; promptly treat extravasation with SC phentolamine; administration through a central vein is recommended; do not use a systemic or umbilical artery for infusion; if dosages >20 mcg/kg/min are required, consider a different agent (eg, epinephrine, dobutamine) Monitor closely urine flow, cardiac output, pulmonary wedge pressure, and blood pressure during the infusion; before infusion, correct hypovolemia as indicated; monitoring central venous pressure or left ventricular filling pressure may be helpful in detecting and treating hypovolemia

Drug Category: *Sedatives* -- Maximizes efficiency of mechanical ventilation and minimizes oxygen consumption.

Drug Name	Morphine -- Used for analgesia and sedation.
Pediatric Dose	0.05-0.2 mg/kg/dose IV over 5 min q2-4h prn
Contraindications	Documented hypersensitivity (rare in neonates); severe respiratory depression
Interactions	Any CNS depressant; phenothiazines may antagonize analgesic effects of opiate agonists; tricyclic antidepressants, MAOIs, and other CNS depressants may potentiate adverse effects of morphine; incompatible when admixed with furosemide, pentobarbital, phenobarbital, or phenytoin (forms precipitant)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in hypotension, respiratory depression, nausea, emesis, constipation, urinary retention, atrial flutter, and other supraventricular tachycardias; has vagolytic action and may increase ventricular response rate; may cause histamine release
Drug Name	Fentanyl (Sublimaze) -- Potent opioid used for analgesia, sedation, and anesthesia. Has a shorter duration of action than morphine.
Pediatric Dose	1-4 mcg/kg/dose IV slow push Infusion rate: 1-5 mcg/kg/h IV
Contraindications	Documented hypersensitivity (rare in neonates); hypotension or potentially compromised airway where it would be difficult to establish rapid airway control
Interactions	Barbiturates (eg, pentobarbital, thiopental) or other CNS depressants may have additive effects; phenothiazines may antagonize analgesic effects of opiate agonists; tricyclic antidepressants may potentiate adverse effects of fentanyl when both drugs are used concurrently
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May cause marked respiratory depression and hypotension; exercise caution with patients diagnosed with emesis, constipation, or urinary retention; idiosyncratic reaction (ie, chest wall rigidity syndrome) may require neuromuscular blockade to increase ventilation
Drug Name	Phenobarbital (Luminal) -- An anticonvulsant that may be used as a sedative. Suppresses the CNS from the reticular activating system (ie, presynaptic, postsynaptic).
Pediatric Dose	20 mg/kg IV as a single dose, administer slowly over 10-15 min
Contraindications	Documented hypersensitivity (rare in neonates); severe uncontrolled pain
Interactions	Incompatible when admixed with clindamycin, hydralazine, insulin, methadone, midazolam, morphine, ranitidine, and vancomycin; may cause respiratory depression if concurrently on CNS depressants (eg, benzodiazepines); decreases effectiveness of corticosteroids, theophylline, and beta-blockers
Pregnancy	D - Unsafe in pregnancy
Precautions	Rarely causes respiratory depression at this dose; do not administer IV administration faster than 50 mg/min; carefully monitor upon administration for hypotension, bradycardia, and arrhythmias because parental product contains 68% propylene glycol; paradoxical excitement and delirium may occur in infants experiencing pain

Drug Name	Pentobarbital (Nembutal) -- CNS sedative and hypnotic that acts primarily on the cerebral cortex and reticular formation through decreased neuronal synaptic activity.
Pediatric Dose	2-6 mg/kg IV slow push
Contraindications	Documented hypersensitivity (rare in neonates); severe uncontrolled pain
Interactions	Incompatible when admixed with cefazolin, cimetidine, clindamycin, fentanyl, hydrocortisone, insulin, midazolam, morphine, pancuronium bromide, phenytoin, ranitidine, or vancomycin; may cause respiratory depression with concurrent use of CNS depressants (eg, benzodiazepines); increased toxicity with CNS depressants and possibly phenobarbital
Pregnancy	D - Unsafe in pregnancy
Precautions	Caution with hypovolemic shock, CHF, hepatic impairment, chronic or acute pain, or renal dysfunction; may cause respiratory and cardiovascular depression; carefully monitor upon administration for hypotension, bradycardia, and arrhythmias because parental product contains 68% propylene glycol; paradoxical excitement and delirium may occur in infants experiencing pain

Drug Category: *Neuromuscular blocking agents* -- Used for skeletal muscle paralysis to maximize ventilation by improving oxygenation and ventilation. Also used to reduce barotrauma and minimize oxygen consumption.

Drug Name	Pancuronium (Pavulon) -- Neuromuscular blocker whose effects are reversed by neostigmine and atropine.
Pediatric Dose	Initial dose: 0.1 mg/kg (0.04-0.15 mg/kg) IV push Maintenance dose: 0.02-0.1 mg/kg/dose q30min to q3h prn
Contraindications	Documented hypersensitivity (rare in neonates)
Interactions	Dose-dependent increased toxicity with magnesium sulfate and furosemide (increase or decrease neuromuscular blockade); caution with coadministration with drugs that increase neuromuscular blockade (eg, aminoglycosides, inhaled anesthetics); avoid drugs that antagonize neuromuscular blockade or prolong muscular weakness (eg, corticosteroids, amphotericin B, phenytoin, verapamil)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May cause hypoxemia (unlikely in a ventilated patient), tachycardia, BP changes, and excessive salivation; exercise caution in patients with preexisting pulmonary, hepatic, or renal disease; prolonged use may result in muscle delayed recovery of paralysis

FOLLOW-UP	Section 8 of 11

Further Inpatient Care:

- Thorough cardiac examination is necessary to eliminate the possibility of cyanotic heart disease.
- Confirming the degree of pulmonary hypertension, prior to instituting therapy, is extremely important.

Transfer:

- Although stabilization is possible at community hospitals, infants with MAS frequently require high-frequency ventilation, inhaled nitric oxide, or ECMO. Therefore, in the event of significant aspiration, transfer these infants in community hospitals to regional NICUs.

Complications:

- A few infants with MAS have increased incidence of infections in the first year of life because the lungs are still recovering.
- Children with MAS may develop chronic lung disease as a result of intense pulmonary intervention.

Prognosis:

- Nearly all infants with MAS have complete recovery of pulmonary function.
- Events initiating the meconium passage may cause the infant to have long-term neurologic deficits, including CNS damage, seizures, mental retardation, and cerebral palsy.

MISCELLANEOUS	Section 9 of 11

Medical/Legal Pitfalls:

- Many infants who have experienced MAS have had prenatal and postnatal periods of hypoxia and acidosis; therefore, these individuals are at increased risk of significant CNS damage.
- Typically, medicolegal action is initiated by parents whose newborn develops long-term sequelae from significant perinatal hypoxia. Although the delivering physician is the primary focus of such a lawsuit, additional liability to other healthcare professionals may ensue from a poorly planned and executed resuscitation.
- Commonly, the providers of the tertiary intensive care are included in these lawsuits, which are usually due to complications of necessary complex and aggressive care. Although other organ systems may be damaged by the initial insult and subsequent therapy, they rarely are the basis of legal action.

PICTURES	Section 10 of 11

Picture 1. Air trapping and hyperexpansion from airway obstruction

Picture 2. Acute atelectasis

Picture 3. Pneumomediastinum from gas trapping and air leak

Picture 4. Left pneumothorax with depressed diaphragm and minimal mediastinal shift because of noncompliant lungs

Picture 5. Diffuse chemical pneumonitis from constituents of meconium

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Meconium Aspiration Syndrome excerpt

Multiple Births

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INTRODUCTION	Section 2 of 9

Background: The term multiple births is defined as more than one fetus being born of a pregnant woman. Since 1970, prevalence of multiple births has been increasing because of more widespread use of assisted reproductive technologies to treat infertility. Multifetal pregnancies are high-risk pregnancies with a number of associated fetal and neonatal complications. Researchers have studied twins in an attempt to separate the influence of genetic and environmental factors on both fetal and postpartum development.

Pathophysiology: Multiple births include twins and higher order multiples (eg, triplets, quadruplets). The 2 types of twins are monozygotic and dizygotic.

Two sperm fertilizing 2 ova produce dizygotic twins, which sometimes are called fraternal twins. Separate amnions, chorions, and placentas are formed in dizygotic twins (see Image 1). The placentas in dizygotic twins may fuse if the implantation sites are proximate. The fused placentas can be separated easily after birth.

Monozygotic twins develop when a single fertilized ovum splits during the first 2 weeks after conception. Monozygotic twins also are called identical twins. An early splitting (ie, within the first 2 days after fertilization) of monozygotic twins produces separate chorions and amnions (see Image 1). These dichorionic twins have different placentas that can be separate or fused. Approximately 30% of monozygotic twins have dichorionic/diamniotic placentas.

Later splitting (ie, during days 3-8 after fertilization) results in monochorionic/diamniotic placentation (see Image 2). Approximately 70% of monozygotic twins are monochorionic/diamniotic. If splitting

occurs even later (ie, during days 9-12 after fertilization), then monochorionic/monoamniotic placentation occurs (see Image 3). Monochorionic/monoamniotic twins are rare; only 1% of monozygotic twins have this form of placentation. Monochorionic/monoamniotic twins have a common placenta with vascular communications between the 2 circulations. These twins can develop twin-to-twin transfusion syndrome (TTTS). If twinning occurs beyond 12 days after fertilization, then the monozygotic pair only partially split, resulting in conjoined twins.

Triplets can be monozygotic, dizygotic, or trizygotic. Trizygotic triplets occur when 3 sperm fertilize 3 ova. Dizygotic triplets develop from one set of monozygotic cotriplets and a third cotriplet derived from a different zygote. Finally, 2 consecutive zygotic splittings with 1 split result in a vanished fetus and monozygotic triplets.

It is important to evaluate the placenta(s) after the birth of all multifetal pregnancies in order to determine zygosity.

Frequency:

- **In the US:** The birth rate of monozygotic twins is constant worldwide (approximately 4 per 1000 births). In contrast, dizygotic twinning is associated with multiple ovulation, and its frequency varies among races within countries and is affected by maternal age (increases from 3 in 1000 in women younger than 20 years to 14 in 1000 in women aged 35-40 years, declining thereafter) and parity. In the United States, the overall prevalence of twins is approximately 12 per 1000, and two thirds are dizygotic. The birth rate of dizygotic twinning is highest for African Americans (10-40 per 1000 births), followed by Caucasians (7-10 per 1000 births) and Asian Americans (3 per 1000 births). The rate of higher order multiple births has also increased recently, which has been attributed to in vitro fertilization and embryo transfer. Naturally occurring triplet births occur in approximately 1 per 7000-10,000 births; naturally occurring quadruplet births occur in 1 per 600,000 births.

- **Internationally:** The birth rate of monozygotic twins is constant worldwide (approximately 4 per 1000 births). Birth rates of dizygotic twins vary by race. The highest birth rate of dizygotic twinning occurs in African nations, and the lowest birth rate of dizygotic twinning occurs in Asia. The Yorubas of Western Nigeria have a frequency of 45 twins per 1000 live births, and approximately 90 percent are dizygotic.

Mortality/Morbidity: Multifetal pregnancies are high-risk pregnancies. The fetal mortality rate for twins is 4 times the fetal mortality rate for single births. The neonatal mortality rate for twins is 6 times more than the neonatal mortality rate for single births. Higher order multiple births have even greater mortality rates in comparison to twin and single births.

A high prevalence of low-birth weight infants, due to prematurity and intrauterine growth retardation (IUGR) and their associated complications, contribute to this problem. Twins have increased frequency of congenital anomalies, placenta previa, abruptio placenta, preeclampsia, cord accidents, and malpresentations, as well as asphyxia/perinatal depression, group B streptococcal (GBS) infections, hyaline membrane disease, and TTTS.

Race: The frequency of naturally occurring twin births varies by race. Black women have the highest birth rate of twins, followed by Caucasian and Hispanic women. Asian women have the lowest birth rate of twins. There is a racial disparity in the United States between black and Caucasian twin stillbirths. Risk of stillbirth is elevated in black fetuses compared with white fetuses among twins but not triplets.

Age: Maternal age has no effect on monozygotic twin births. Advanced maternal age (>35 y) is associated with increased risk of dizygotic twins. Prevalence of naturally occurring twin births has increased recently because of the trend to delay childbearing to later years.

History: Most multifetal pregnancies are diagnosed prenatally. Maternal complaints of excessive weight gain, hyperemesis gravidarum, and/or sensation of more than one moving fetus; use of ovulation-inducing drugs; or family history of dizygotic twins should alert caregivers to the possibility of a multifetal pregnancy.

Physical: Women with multifetal pregnancies may have a uterine size inconsistently large for dates and may experience accelerated weight gain. On auscultation, more than one fetal heart rate may be heard.

Causes: Risk factors for multifetal pregnancy can be divided into natural and induced. Risk factors for natural multifetal pregnancy include advanced maternal age, family history of dizygotic twins, and race. Induced multifetal pregnancies occur following infertility treatment via the use of ovulation-inducing agents or gamete/zygote transfer.

Lab Studies:

- CBC: In TTTS the donor twin is frequently anemic at birth. The recipient twin is polycythemic at birth.
- Calcium: Hypocalcemia is common in premature infants, especially the donor twin in TTTS.
- Glucose: Hypoglycemia is common in premature infants, especially if TTTS is present.
- Bilirubin: Hyperbilirubinemia may develop in polycythemic infants from TTTS.

Imaging Studies:

- Maternal ultrasonography confirms most multiple gestation pregnancies.
- Neonatal head ultrasound: Premature infants from multifetal pregnancies are susceptible to intraventricular hemorrhage and periventricular leukomalacia.

Medical Care: Medical care of the woman with multiple gestation pregnancy is beyond the scope of this chapter.

- Medical care of infants from multiple gestation births depends on complications.
- The usual method of delivery for higher order multiple births (eg, triplets, quadruplets) is cesarean delivery. Cesarean delivery is also the usual method of delivery for twins in the following situations:

    o Breech/vertex presentation with the possibility of interlocking twins
    o Monoamniotic twins
    o Conjoined twins
    o Congenital anomalies that threaten increased neonatal morbidity in a twin
    o Delayed interval delivery of remaining fetuses in multifetal pregnancy at the border of viability is becoming more common. Before 30 weeks of gestation, delayed delivery for 2 or more days is associated with improved survival in the second twin.

- Delivery room management of infants from multifetal pregnancies requires adequate personnel skilled in neonatal resuscitation. Infants from multifetal pregnancies are at increased risk of birth asphyxia and respiratory distress syndrome (RDS). Such infants may require bag mask ventilation and endotracheal intubation in the delivery room.
- Partial exchange transfusion may be necessary in donor or recipient twins from TTTS.

  - Partial exchange transfusions are used to increase hemoglobin concentrations in anemic donor twins while maintaining euvolemia. Small aliquots (5-15 cc) of packed red blood cells (RBCs) are infused (usually via an umbilical venous catheter) following removal of an equal volume of the infant's blood until a desired hemoglobin is attained. The transfused packed RBCs should be appropriately cross-matched, cytomegalovirus (CMV) negative, and irradiated.
  - Partial exchange transfusions are used to decrease hemoglobin concentrations in polycythemic recipient twins while maintaining euvolemia. Small aliquots (5-10 cc) of fresh frozen plasma are infused (usually via an umbilical venous catheter) following removal of an equal volume of the infant's blood until a desired hemoglobin is attained.

A woman with multiple gestation pregnancy may benefit from a consultation with a perinatologist. A neonatologist may be involved in the postnatal care of multiple birth infants, particularly if the births are premature or if congenital anomalies are present.

Complications:

- Prematurity: Infants from multifetal pregnancies are more likely to be born prematurely and to require neonatal intensive care. Approximately 50% of twin deliveries occur before 37 weeks' gestation. The length of gestation decreases inversely with the number of fetuses present. Infants from multifetal pregnancies represent 20% of very low birth weight infants.
- Hyaline membrane disease: Twins born at fewer than 35 weeks' gestation are twice as likely to develop hyaline membrane disease (HMD) as single birth infants born at fewer than 35 weeks' gestation are. Prevalence of HMD is greater in monozygotic than in dizygotic twins. Concordance rate for HMD (ie, both twins have HMD) is greater in monozygotic than in dizygotic twins. If the twins are discordant for HMD, then the second twin is more likely to develop HMD than the first twin.
- Birth asphyxia/perinatal depression: Newborns from multiple gestation pregnancies have an increased frequency of perinatal depression and birth asphyxia from a variety of causes. Umbilical cord entanglement, locked twins, a prolapsed umbilical cord, placenta previa, and uterine rupture can occur and result in asphyxiation of an infant. Occurrence of cerebral palsy is 6 times more common in twin births and 30 times more common in triplet births than in single births. Monochorionic/monoamniotic twins are at highest risk for cord entanglement. The second-born twin is at greatest risk for birth asphyxia/perinatal depression.
- GBS infections: Early onset GBS infections in low birth weight infants are nearly 5-fold greater than in average weight singletons.
- Vanishing twin syndrome: Early ultrasound diagnosis has revealed that as many as one half of all twin pregnancies result in the delivery of only a single fetus. The second twin vanishes. Intrauterine demise of one twin can result in neurologic sequelae in the surviving twin. Acute exsanguination of the surviving twin into the relaxed circulation of the deceased twin can result in intrauterine CNS ischemia.
- Congenital anomalies/acardia/twin reversed arterial perfusion sequence: Congenital anomalies more commonly develop in twins than in a single fetus. CNS, cardiovascular, and GI defects occur with increased frequency. Monozygotic twins have increased prevalence of deformations secondary to intrauterine space constraints. Common deformations in twins include limb defects, plagiocephaly, facial asymmetry, and torticollis. Acardia is a rare anomaly unique to multiple gestation. In this condition, one twin has an absent or rudimentary

heart. Twin reversed arterial perfusion (TRAP) sequence occurs when an acardiac twin receives all of the blood supply from the normal "pump" twin. This only occurs in monochorionic twins. Blood enters the acardiac twin in a reversed perfusion manner. Blood enters this fetus via an umbilical artery and exits via the umbilical vein. The excessive demands on the normal "pump" twin can cause cardiac failure in that twin.

- Twin-to-twin transfusion syndrome: This syndrome occurs in monochorionic/monoamniotic or monochorionic/diamniotic twins. Vascular anastomoses in the monochorionic placenta result in transfusion of blood from one twin (ie, donor) to the other twin (ie, recipient). One classification scheme separates TTTS into severe, moderate, and mild forms.

  o Severe TTTS presents early in the second trimester (16-18 weeks' gestation). A difference of more than 1.5 weeks' gestational size between twins occurs. Severe TTTS has a 60-100% mortality rate. Polyhydramnios develops in the sac of the recipient twin because of volume overload and increased fetal urine output. Oligohydramnios develops in the sac of the donor twin because of hypovolemia and decreased urine output. Severe oligohydramnios can result in the stuck twin phenomena in which the twin appears in a fixed position against the uterine wall.
  o Moderate TTTS develops later at 24-30 weeks' gestation. Although a fetal size discrepancy of more than 1.5 weeks' gestation occurs, polyhydramnios and oligohydramnios do not develop. The donor twin becomes anemic, hypovolemic, and growth retarded. The recipient twin becomes plethoric, hypervolemic, and macrosomic. Either twin can develop hydrops fetalis.
  o Mild TTTS develops slowly in the third trimester. Polyhydramnios and oligohydramnios usually do not develop. Hemoglobin concentrations differ by more than 5g/dL. Twin sizes differ by more than 20%. Polycythemic twins can develop hyperviscosity syndrome and hyperbilirubinemia after birth.

- Conjoined twins: Incomplete late division of monozygotic twins produces conjoined twins. Conjoined twins are connected at identical points and are classified according to site of union.

  o Thoracopagus - Joined at chest (40%)
  o Xiphopagus/omphalopagus - Joined at abdomen (34%)
  o Pygopagus - Joined at buttocks (18%)
  o Ischiopagus - Joined at ischium (6%)
  o Craniopagus - Joined at head (2%)

- Intrauterine growth retardation: Birth weights of twins, triplets, etc. are smaller than weights of corresponding singletons. However, when combined, birth weights of twins are greater than weights of corresponding singletons. Most of the deficit of birth weight occurs in the final 8-11 weeks of pregnancy. Average birth weights are similar between twins and singletons until 32 weeks of gestation. Average birth weights are similar between triplets and singletons until 29 weeks of gestation. Birth weight discrepancies of more than 20-25% are considered discordant. Discordant birth weights occur in 10% of twins. The cause of discordant birth weights among twins is the difference between each twin's placental surface area or TTTS. Discordant birth weights among triplets are more common than discordant birth weights between twins. Approximately 30% of pregnancies with triplets have a birth weight discordance of more than 25%.

Prognosis:

- The prognosis of infants born from multiple gestations depends upon the complications that develop. Some studies have reported that the risks of death, chronic lung disease, and grade III/IV intracranial hemorrhage were similar in twins and singletons. Other studies have reported a higher prevalence of complications such as necrotizing enterocolitis, retinopathy of prematurity, and patent ductus arteriosus in infants from multiple gestation versus singletons.

Medical/Legal Pitfalls: Most problems that could result in medical legal action against the health professional involve prenatal and intrapartum care issues.

Special Concerns: Multiple births have significant economic implications. Twins and triplets have more frequent and longer duration hospitalizations than singletons. Multiple births contribute disproportionately to inpatient hospital costs in the first 5 years of life.

Picture 1. Diamniotic, dichorionic placentation.
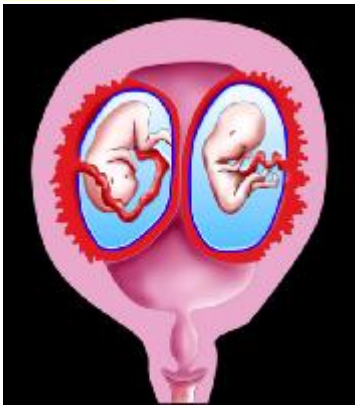
Picture 2. Diamniotic, monochorionic placentation.
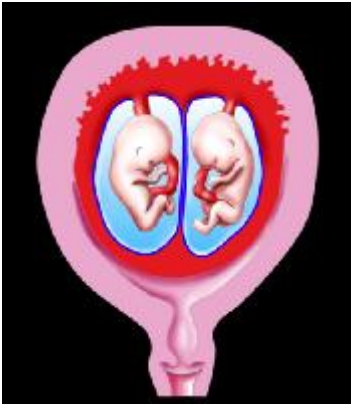
Picture 3. Monoamniotic, monoamniotic placentation.

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Multiple Births excerpt

Necrotizing Enterocolitis

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==Synonyms and related keywords:==NEC,inflammation of the intestinal tissue, enteral feeding, sepsis

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INTRODUCTION	Section 2 of 10

==Background:== Necrotizing enterocolitis (NEC) is the most common gastrointestinal medical and/or surgical emergency occurring in neonates. With mortality rates approaching 50% in infants who weigh less than 1500 g, NEC represents a significant clinical problem. Although, it is more common in premature infants, it can also be observed in term babies. Despite intensive study over the past 30 years, its etiology remains elusive.

==Pathophysiology:== NEC affects the gastrointestinal tract and, in severe cases, can have profound systemic impact.

Initial symptoms may be subtle and can include the following:

- Feeding intolerance
- Delayed gastric emptying
- Abdominal distention and/or tenderness
- Ileus/decreased bowel sounds
- Abdominal wall erythema (advanced stages)
- Hematochezia

Systemic signs can include the following:

- Apnea
- Lethargy
- Decreased peripheral perfusion
- Shock (in advanced stages)
- Cardiovascular collapse
- Bleeding diathesis (consumption coagulopathy)

Nonspecific laboratory abnormalities can include the following:

- Hyponatremia
- Metabolic acidosis
- Thrombocytopenia
- Leukopenia and leukocytosis with left shift
- Neutropenia
- Prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), decreasing fibrinogen, rising fibrin split products (in cases of consumption coagulopathy)

Although the exact etiology is still unknown, research suggests that it is multifactorial; ischemia and/or reperfusion injury may play a role. Cases that cluster in epidemics suggest an infectious etiology; however, a single causative organism has not been identified. Organisms isolated from stool cultures from affected babies are also isolated from healthy babies. Therefore, no single organism has been identified as the culprit responsible for triggering the disease. Some experimental work suggests that translocation of intestinal flora across an incompetent mucosa may play a role in spreading disease and systemic involvement. Such a mechanism would account for the apparent protection breastfed infants have against fulminant NEC.

Animal model research studies have shed light on the pathogenesis of this disease. Regardless of the triggering mechanisms, the resultant outcome is significant inflammation of the intestinal tissues and the release of inflammatory mediators (eg, leukotrienes, tumor necrosis factor, platelet-activating factor), which lead to variable degrees of intestinal damage.

Frequency: **In the US:** Frequency varies from nursery to nursery without correlation with season or geographic location. Outbreaks of NEC seem to follow an epidemic pattern within nurseries, suggesting an infectious etiology even though a specific causative organism is unknown. Population studies conducted in the United States over the past 25 years indicate a relatively stable incidence, ranging from 0.3-2.4 cases per 1000 live births. Because more premature babies are surviving, expecting an increase in the overall incidence of NEC is reasonable.

Internationally: Population-based studies from other countries suggest an attack rate similar to the United States.

Mortality/Morbidity:

- The mortality rate ranges from 10-44% in infants weighing less than 1500 g, compared to 0-20% mortality rate for babies weighing more than 2500 g. Extremely premature infants (1000 g) are particularly vulnerable, with reported mortality rates of 40-100%. One study compared mortality rates for term versus preterm infants and reported rates of 4.7% for term infants and 11.9% for premature babies.
- Survivors can have significant short-term and long-term morbidities. Patients with medical NEC (see Bell stage II under Medical Care) must remain on nothing by mouth (NPO) for protracted periods, compromising the nutrition that is essential for a premature infant. Many of these babies have difficult IV access; the need for prolonged parenteral nutrition requires placing central venous catheters, which have attendant risks and complications of their own. Prolonged hyperalimentation and the absence of enteral nutrition can cause cholestasis and direct hyperbilirubinemia.
- Patients with significant disease can develop strictures, which require surgical intervention and further compromise successful enteral feeding. Patients who are severely affected require intestinal resection. In rare cases, the entire intestine can be involved, precluding surgical intervention. Depending on the location and extent of the bowel removed, long-term morbidities can include the need for colostomy, repeated surgical procedures, prolonged parenteral nutrition, poor nutrition, malabsorption syndromes, failure to thrive, and multiple hospitalizations.

Race: Some studies indicate higher frequency in black babies than in white babies, but other studies show no difference based on race.

Sex: Most studies indicate that male and female babies are affected equally. However, the higher incidence of neonatal sepsis and meningitis reported for male infants suggests otherwise.

Age:

- NEC clearly predominates in premature infants, with incidence inversely related to birth weight and gestational age. Although specific numbers range from 4% to more than 40%, infants weighing less than 1000 g at birth have the highest attack rates. This rate drops dramatically to 3.8 per 1000 live births for infants weighing 1501-2500 g at birth. Similarly, rates decrease profoundly for infants born after 35-36 weeks' postconceptional age.
- Average age at onset in premature infants seems to be related to postconceptional age, with babies born earlier developing NEC at a later chronologic age. One study reported the average age of onset as 20.2 days for babies born less than 30 weeks' estimated gestational age (EGA), 13.8 days for babies born at 31-33 weeks' EGA, and 5.4 days for babies born after 34 weeks' gestation.
- Term infants develop NEC much earlier, with the average age of onset occurring within the first week of life or sometimes occurring within the first 1-2 days of life.

History:

- NEC is more common in preterm infants.
- Epidemiologic studies demonstrate that antecedent history is usually the same for term as well as preterm babies. However, demographics, risk factors, typical patient characteristics, and clinical course differ significantly.

- Term baby

  - Typically the term baby is much younger than the afflicted preterm baby, with published series reporting median age of onset from 1-3 days of life
  - The affected term neonate is usually systemically ill with other conditions, such as birth asphyxia, respiratory distress, congenital heart disease, metabolic abnormalities, or has a history of abnormal fetal growth pattern.
  - Maternal risk factors that reduce fetal gut flow, such as placental insufficiency from chronic disease or maternal cocaine abuse, can increase the baby's risk.

- Premature baby

  - Premature babies are at risk for several weeks, with the age of onset inversely related to gestational age at birth.
  - Patients are typically advancing on enteral feedings or may have achieved full-volume feeds when symptoms develop.
  - Presenting symptoms may include subtle signs of feeding intolerance that progress over several days, subtle systemic signs that may be reported enigmatically by the nursing staff as "acting different," and fulminant systemic collapse.
  - Symptoms of feeding intolerance can include abdominal distention/tenderness, delayed gastric emptying as evidenced by gastric residuals, and vomiting (occasionally).
  - Systemic symptoms can progress insidiously to include increased apnea and bradycardia, lethargy, and temperature instability representing the primary manifestation(s).

- o Patients with fulminant NEC present with profound apnea, rapid cardiovascular and hemodynamic collapse, and shock.
- o The baby's feeding history can help increase the index of suspicion for early NEC. Babies who are breastfed have a lower incidence of NEC than formula-fed babies.
- o Rapid advancement of formula feeding has been associated with an increased risk of NEC (McKeown, 1992).

Physical:

- The pertinent physical findings in patients who develop NEC can be primarily gastrointestinal, primarily systemic, indolent, fulminant, or any combination of these. A high index of clinical suspicion is essential to minimize potentially significant morbidity or mortality.
- Gastrointestinal signs can include any or all of the following:

  - o Increased abdominal girth
  - o Visible intestinal loops
  - o Obvious abdominal distention and decreased bowel sounds
  - o Change in stool pattern
  - o Hematochezia
  - o A palpable abdominal mass
  - o Erythema of the abdominal wall

- Systemic signs can include any of the following:

  - o Respiratory failure
  - o Decreased peripheral perfusion
  - o Circulatory collapse
  - o With insidious onset, the severity of derangement may be mild, whereas patients with fulminant disease can present with severe clinical abnormalities.

- Several characteristic laboratory findings occur (see Lab Studies).
- If abdominal signs are present, surgical consultation may be advisable. Disease progression ranges from indolent to fulminant, and early involvement of surgical colleagues can be helpful, especially if appropriate surgical care requires transfer to another facility.

DIFFERENTIALS	Section 4 of 10

Acidosis, Metabolic   Acidosis, Respiratory
Apnea of Prematurity   Bacteremia
Candidiasis   Coarctation of the Aorta
Enteroviral Infections   Gastroesophageal Reflux
Hirschsprung Disease   Hospital-Acquired Infections
Hypoplastic Left Heart Syndrome Intestinal Malrotation
Intestinal Volvulus   Meningitis, Bacterial
Neonatal Sepsis   Omphalitis
Prematurity   Urinary Tract Infection   Volvulus

Other Problems to be Considered:

Spontaneous intestinal perforation (SIP): Not infrequently, free air is noted on an abdominal radiograph of a premature infant, either as an incidental finding on imaging performed for other reasons or during an initial evaluation for abdominal pathology. SIP can be distinguished from NEC by its lack of systemic involvement, absence of other clinical signs common to bowel perforation, and higher rate of survival (Shorter, 1999). SIP is further distinguished by its earlier onset in babies of smaller birthweight and more extreme prematurity (Adderson, 1998). Associations have been identified between SIP and indomethacin (Shorter, 1999), dexamethasone (Stark, 2001), and systemic candidiasis (Adderson, 1998).

Lab Studies:

- Initial presentation usually includes subtle signs of feeding intolerance, such as gastric residuals, abdominal distention, and/or grossly bloody stools. Abdominal imaging studies are crucial at this stage. Laboratory studies are pursued if the abdominal studies are worrisome or the baby is manifesting any systemic signs.
- Complete blood count with manual differential to look for signs of infection, anemia, and thrombocytopenia is usually repeated at least every 6 hours if the patient continues to deteriorate.

  - White blood cell count: Marked elevation may be worrisome ($\leq$20,000 depending on whether treatment includes systemic steroids for lung disease), but leukopenia (<5000) is even more concerning. Although elevated mature and/or immature neutrophil counts may not be good indicators of neonatal sepsis after the first 3 days of life, moderate neutropenia (absolute neutrophil count [ANC] <1500) strongly suggests evolving sepsis.
  - Red blood cell count: Premature infants are prone to anemia from iatrogenic blood draws as well as anemia of prematurity; however, blood loss from hematochezia and/or a developing consumptive coagulopathy can manifest as an acute decrease in hematocrit.
  - Platelet count: Platelets are an acute phase reactant, and thrombocytosis can represent physiologic stress to an infant, but acute NEC is more commonly associated with thrombocytopenia (<100,000). Thrombocytopenia may become more profound and alarming in severe cases that become complicated with consumption coagulopathy. Consumption coagulopathy is characterized by prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (aPTT), and decreasing fibrinogen and increasing fibrin degradation products concentrations
  - Blood culture: Drawing a blood culture is recommended before beginning antibiotics in any patient presenting with any signs/symptoms of sepsis or NEC. Although blood cultures do not grow any organisms in most cases of NEC, sepsis is one of the major conditions that mimic NEC and it should be considered in the differential diagnosis. Therefore, identification of a specific organism can aid and guide further therapy.

- Serum electrolytes can show some characteristic abnormalities. Obtain a panel of basic electrolytes during the initial evaluation, followed serially at least every 6 hours depending on the acuity of the patient's condition.

  - Serum sodium: Hyponatremia is a worrisome sign that can suggest the initial stages of a developing capillary leak. Depending on the baby's age and feeding regimen, baseline sodium levels may be low-normal or subnormal, but an acute decrease (<130 mEq/dL) is alarming and heightened vigilance is warranted.
  - Metabolic acidosis: Low serum bicarbonate (<20) in a baby with a previously normal acid-base status also is concerning.

- Arterial blood gasses

  - Depending on presentation acuity and the baby's respiratory status, an arterial blood gas can reveal whether the baby needs respiratory support and the developing acid-base status.
  - Acute acidosis with baseline carbon dioxide pressure is worrisome (as is apnea). Metabolic acidosis results from decreased cardiac output (as in cardiovascular collapse and shock), leading to poor perfusion of peripheral tissues and lactic acidosis.

- An arterial blood sample is a convenient way to simultaneously obtain a blood culture, CBC, serum electrolytes, and ABG for the initial evaluation (note that arterial blood has a lower yield for demonstrating bacteremia than venous blood). Depending on presentation acuity, inserting

a peripheral arterial line while peripheral perfusion and intravascular volume is still good may be prudent. This peripheral arterial line facilitates serial blood sampling and invasive blood pressure monitoring that is essential if the baby's condition deteriorates.

Imaging Studies:

- The mainstay of diagnostic imaging is abdominal radiography. An anteroposterior (AP) abdominal radiograph and a left lateral decubitus radiograph (left side down) are essential for initially evaluating any baby with abdominal signs. Perform these abdominal radiographs serially at 6-hour or greater intervals, depending on presentation acuity and the preferences of the attending medical team, including any involved surgeons.

  o Characteristic findings on an AP abdominal radiograph include an abnormal gas pattern, dilated loops, and thickened bowel walls (suggesting edema/inflammation). Serial radiographs help assess disease progression. A fixed and dilated loop that persists over several examinations is especially worrisome.
  o Radiographs can sometimes reveal scarce or absent intestinal gas, which is more worrisome than diffuse distention that changes over time.
  o Pneumatosis intestinalis is a radiologic sign pathognomonic of NEC. It appears as a characteristic train-track lucency configuration within the bowel wall. Intramural air bubbles represent extravasated air from within the intestinal lumen. Analysis of gas aspirated from these air bubbles reveals that it consists primarily of hydrogen, suggesting that these are caused by bacterial fermentation of undigested intraluminal substrates. Carbohydrate (often lactose) fermentation by intestinal flora yields hydrogen and carbon dioxide and a series of short-chain organic acids, which can promote inflammation.
  o Abdominal free air is ominous and usually requires emergency surgical intervention (see Spontaneous intestinal perforation under Other Problems to be Considered). The presence of abdominal free air can be difficult to discern on a flat radiograph, which is why decubitus radiographs are recommended at every evaluation. The football sign is characteristic of intraperitoneal air on a flat plate and manifests as a subtle oblong lucency over the liver shadow. It represents the air bubble that has risen to the most anterior aspect of the abdomen in a baby lying in a supine position and can be demonstrated by left lateral decubitus imaging.
  o Portal gas is a subtle and transient finding that was originally thought to be ominous when detected but is now considered less ominous. Portal gas, which is not usually captured in serial radiographs, appears as linear branching areas of decreased density over the liver shadow and represents air present in the portal venous system. Portal gas is much more dramatically observed on ultrasonography (see below).
  o Ascites is a late finding that usually develops some time after perforation when peritonitis is present. Ascites is observed on an AP radiograph as centralized bowel loops that appear to be floating on a background of density. It is better appreciated on ultrasonography.
  o Left side down (left lateral) decubitus radiography allows the detection of intraperitoneal air, which rises above the liver shadow (right side up) and can be visualized easier than on other views. Obtain this view with every AP examination until progressive disease is no longer a concern.

- Abdominal ultrasonography is a relatively new technology for evaluating suspected NEC in neonates.

  o Advantages
    ▪ Available at bedside
    ▪ Noninvasive imagery of intra-abdominal structures

  o Disadvantages
    ▪ Limited availability at some medical centers
    ▪ Requires extensive training to discern subtle ultrasonographic appearance of some pathologies

- With abdominal ultrasonography, a skilled physician can identify a larger amount of diagnostic information faster and with less risk to the baby than with the current
- tandard evaluation methods.
- Abdominal air (easily observed on ultrasonography and in grossly distended patients) can interfere with assessing intra-abdominal structures.
- Ultrasonography can be used to identify areas of loculation and/or abscess consistent with a walled-off perforation when patients with indolent NEC have scarce gas or a fixed area of radiographic density.
- Ultrasonography is excellent for distinguishing fluid from air, so ascites can be identified and quantified. Serial examinations can be used to monitor the progression of ascites as a marker for the disease course.
- Portal air can be easily observed as bubbles present in the venous system. This finding has been termed informally the "champagne sign" because of its similar appearance to a champagne flute.
- Recent data suggest that ultrasonographic assessment of major splanchnic vasculature can help in the differential diagnosis of NEC from other more benign and emergent disorders.

- The orientation of the superior mesenteric artery in relationship to the superior mesenteric vein can provide information regarding the possibility of a malrotation with a subsequent volvulus. If a volvulus is present, the artery and vein are twisted and, at some point in their courses, their orientation switches. This abnormality can be detected, even if the rotation is 360 degrees, if the full path of the vessels can be observed.
- Doppler study of the splanchnic arteries early in the course of NEC can help distinguish developing NEC from benign feeding intolerance in a mildly symptomatic baby.
- A clinical study from Europe and a recent small series in the United States demonstrate markedly increased peak flow velocity (>1.00) of arterial blood flow in the celiac and superior mesenteric arteries in early NEC. Such a finding at the presentation of symptoms can further aid in diagnosis and therapy, potentially sparing those individuals at low risk for NEC from unnecessary interventions.

<mark>Procedures:</mark>

- Upper GI (with or without) small bowel follow-through

  - This procedure is a definitive way to diagnose the presence or absence of intestinal volvulus.
  - Always consider intestinal volvulus if bilious vomiting is present, especially in the term infant.
  - Because the presence of volvulus is a surgical emergency, it is an important diagnosis to exclude in a neonate with abdominal symptoms.
  - Perform before contrast enema because the presence of contrast in the colon can obscure pertinent findings.

- Contrast enema

  - This procedure is a definitive way to diagnose a distal obstruction.
  - Always use a water-soluble contrast agent because of the risk of perforation. Contrast enemas are contraindicated in the presence of perforation. Consider carefully the clinical risks and benefits before undertaking this evaluation in the unstable and/or acutely ill infant.
  - Contrast enema findings are important for the differential diagnosis of intestinal abnormalities because distal obstructions, such as meconium plug, small left colon syndrome, and Hirschsprung disease, may cause symptoms in the baby without fulminant systemic collapse.

- Rectal biopsy

  - This procedure is the criterion standard for diagnosing Hirschsprung disease.
  - This biopsy is a pediatric surgical procedure that is performed either as a bedside suction biopsy or as an open biopsy.
  - Ganglion cells in the biopsied specimen definitively rule out the diagnosis. The absence of cells, while suspicious for disease, merely may be the result found in the particular specimen obtained and is not 100% conclusive.

- Placement of a peripheral arterial line may be helpful at the beginning of the patient's evaluation to facilitate serial arterial blood sampling and invasive monitoring.
- If the baby is deteriorating rapidly, with apnea and/or signs of impending circulatory and respiratory collapse, airway control and initiation of mechanical ventilation is indicated.
- Abdominal decompression

  - Decompression is essential at the first sign of abdominal pathology.
  - If possible, use a large-bore catheter with multiple side holes to prevent vacuum attachment to the stomach mucosa.
  - Set the catheter for low continuous suction and monitor output.
  - If copious amounts of gastric/intestinal secretions are removed, consider IV replacement with a physiologically similar solution, such as lactated Ringer solution.

- Paracentesis
  - Ascites can develop during fulminant NEC and can compromise respiratory function. Remove ascites using intermittent paracentesis.
  - Ultrasonographic guidance can facilitate paracentesis.
  - After completing the procedure, significant fluid shifts between the intravascular and extravascular spaces are possible, so avoid removing large amounts of fluid at one time.

- Place an intra-abdominal drain as an alternative to laparotomy if the baby is not a surgical candidate.

Histologic Findings: Inspecting the affected bowel reveals mucosal ischemia, progressing to cell death and sloughing. Necrosis can be limited to the mucosal layer, observed radiographically as pneumatosis, or it can affect the full wall, resulting in perforation with subsequent peritonitis. Necrotic and/or perforated intestine must be resected.

TREATMENT	Section 6 of 10

Medical Care:

- Diagnosis of NEC is based on clinical suspicion supported by findings on radiologic as well as laboratory studies. Treatment of NEC depends on the degree of bowel involvement and severity of its presentation. Objective staging criteria developed by Bell have been widely adopted or modified to help tailor therapy according to disease severity.
- Bell stage I - Suspected disease

  - Stage IA
    - Mild nonspecific systemic signs such as apnea, bradycardia, and temperature instability are present.
    - Mild intestinal signs such as increased gastric residuals and mild abdominal distention are present.
    - Radiographic findings can be normal or can show some mild nonspecific distention.
    - Treatment is NPO with antibiotics for 3 days.

- o Stage IB
  - Diagnosis is the same as IA, with the addition of grossly bloody stool.
  - Treatment is NPO with antibiotics for 3 days.

- Bell stage II - Definite disease
  - o Stage IIA
    - Patient is mildly ill.
    - Diagnostic signs include the mild systemic signs present in stage IA.
    - Intestinal signs include all of the signs present in stage I, with the addition of absent bowel sounds and abdominal tenderness.
    - Radiographic findings show ileus and/or pneumatosis intestinalis. This diagnosis is sometimes referred to colloquially as medical NEC.
    - Treatment includes NPO and antibiotics for 7-10 days.
  - o Stage IIB
    - Patient is moderately ill.
    - Diagnosis requires all of stage I signs plus the systemic signs of moderate illness, such as mild metabolic acidosis and mild thrombocytopenia.
    - Abdominal examination reveals definite tenderness, perhaps some erythema or other discoloration, and/or right lower quadrant mass.
    - Radiographs show portal venous gas with or without ascites.
    - Treatment is NPO and antibiotics for 14 days.

- Bell stage III - Represents advanced NEC with severe illness that has a high likelihood of progressing to surgical intervention
  - o Stage IIIA
    - Patient has severe NEC with an intact bowel.
    - Diagnosis requires all of the above conditions, with the addition of hypotension, bradycardia, respiratory failure, severe metabolic acidosis, coagulopathy, and/or neutropenia.
    - Abdominal examination shows marked distention with signs of generalized peritonitis.
    - Radiographic examination reveals definitive evidence of ascites.
    - Treatment involves NPO for 14 days, fluid resuscitation, inotropic support, ventilator support, and paracentesis.
  - o Stage IIIB
    - This stage is reserved for the severely ill infant with perforated bowel observed on radiograph.
    - Free air visible on abdominal radiograph indicates surgery. Surgical treatment includes resecting the affected portion of the bowel, which may be extensive. Initially, an ileostomy with a mucous fistula is typically performed, with reanastomosis performed later. Strictures may occur, with or without a history of surgical intervention, which may require surgical treatment.
    - If the patient is extremely small and sick, he/she may not have the stability to tolerate laparotomy. If free air develops in such a patient, consider inserting a peritoneal drain under local anesthesia in the nursery. Two retrospective reviews of the use of peritoneal drains as initial therapy for perforated bowel concluded that, while most patients ultimately require open laparotomy, initial peritoneal drainage may allow systemic stabilization and recovery in the smallest, sickest infants until they become better surgical candidates (Ahmed, 1998; Rovin, 1999).

Surgical Care: Any patient requiring surgical intervention and many of those patients not progressing to surgery require protracted courses of parenteral nutrition and intravenous antibiotics.

- o Secure central venous access is optimal for ensuring uninterrupted delivery of antibiotics and nutrition as well as maximizing nourishment with central venous formulations.
- o Some units successfully use percutaneously inserted central venous catheters (PCVCs), while other units prefer surgically placed central lines such as Broviac catheters. Both types carry an increased risk of infection, particularly if they are used to administer lipids.

Consultations: Consult with a pediatric surgeon at the earliest suspicion of developing NEC. This may require transferring the patient to another facility where such services are available.

Diet:

- When NEC is suspected, enteral feedings are withheld and parenteral nutrition is initiated. Centrally delivered formulations with maximal nutritional components are preferred (see Surgical Care). Enteral feedings can be restarted 10-14 days after findings on abdominal radiographs normalize in the case of nonsurgical NEC. Reinitiating enteral feeds in postsurgical babies may take longer and may also depend on issues such as the extent of surgical resection, timing of reanastomosis, and preference of the consulting surgical team.
- Because of the high incidence of postsurgical strictures, some clinicians prefer to evaluate intestinal patency via contrast studies prior to initiating enteral feeds. When feeds are restarted, formulas containing casein hydrolysates, medium-chain triglycerides, and safflower/sunflower oils (Pregestimil/Nutramigen) may be better tolerated and absorbed than standard infant formulas.

<table>
<tr><td colspan="2" style="background:#3b3b8f;color:white">MEDICATION</td><td style="background:#3b3b8f;color:white">Section 7 of 10</td></tr>
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Pharmacologic therapy includes agents to treat the developing disease and those to provide supportive and symptomatic relief.

Drug Category: *Antimicrobial agents* -- Although no definitive infectious etiology is known to cause NEC, clinical consensus finds that antibiotic treatment is appropriate for the threat of sepsis. Broad-spectrum parenteral therapy is initiated at the onset of symptoms after collecting blood, spinal fluid, and urine for culture. Antibacterial coverage for gram-positive and gram-negative organisms is essential, with the addition of anaerobic coverage for infants older than 1 week who show radiologic disease progression. Antifungal therapy should be considered for premature infants with a history of recent or prolonged antibacterial therapy or for babies who continue to deteriorate clinically and/or hematologically despite adequate antibacterial coverage.

Although any combination of drugs can be employed, one frequently used regimen includes vancomycin, cefotaxime, and clindamycin or metronidazole. This combination provides broad gram-positive coverage (including staphylococcal species), excellent gram-negative coverage (with the exception of pseudomonads), and anaerobic coverage.

Drug Name	Vancomycin (Lyphocin, Vancocin, Vancoled) -- Provides excellent gram-positive coverage, including methicillin-resistant *Staphylococcus* species and *Streptococcus* species. Blocks bacterial cell wall synthesis. The parenteral formulation is widely bioavailable throughout all body tissues and fluids, including cerebrospinal fluid. Recommended for empiric use in patients with central lines, VP shunts, and for those with probable staphylococcal or streptococcal infection. Enteral administration for *Clostridium difficile* intoxication.
Adult Dose	Severe infections: 2-4 g/d IV Mild-to-moderate infections: 1-2 g/d IV
Pediatric Dose	Dosage depends on gestational age, postnatal age, and birthweight <7 days, <1200 g: 15 mg/kg/d IV qd >7 days, >2000 g: 60 mg/kg/d IV divided q6-8h
Contraindications	Documented hypersensitivity
Interactions	Concurrent administration with anesthetic agents can cause erythema, hypotension, and hypothermia; concurrent administration of other ototoxic or nephrotoxic drugs, including loop diuretics and aminoglycosides

Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Use caution with compromised renal function; monitor trough levels (5-10 mcg/mL) and adjust regimen to maintain safe and effective serum levels

Drug Name	Cefotaxime (Claforan) -- Broad-spectrum third-generation cephalosporin with excellent nonpseudomonal gram-negative coverage at the expense of gram-positive effects. Safety profile is more favorable than aminoglycosides. Penetrates cerebrospinal fluid to treat meningitis.
Adult Dose	1-2 g IV/IM q6-8h
Pediatric Dose	Varies with weight and postnatal age <1 month, <1200 g: 50 mg/kg/dose IV/IM q12h >7 days, >2000 g: 50 mg/kg/dose IV/IM q6h
Contraindications	Documented hypersensitivity
Interactions	Probenecid may increase cefotaxime levels; coadministration with furosemide and aminoglycosides may increase nephrotoxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Adjust dose in severe renal impairment; has been associated with severe colitis

Drug Name	Clindamycin (Cleocin) -- Inhibits bacterial protein synthesis and is bacteriostatic or bacteriocidal depending on drug concentration and organism. Coverage includes anaerobes commonly found in the intestinal tract and many staphylococcal and streptococcal species.
Adult Dose	600-1200 mg IV/IM q6-8h
Pediatric Dose	Dependent on weight and postnatal age Parenteral recommendation range: <7 days, <2000 g: 10 mg/kg/d IV divided q12h; not to exceed 4.8 g/d >7 days, >2000 g: 20 mg/kg/d IV divided q6h; not to exceed 4.8 g/d
Contraindications	Documented hypersensitivity; regional enteritis; ulcerative colitis; hepatic impairment; antibiotic-associated colitis
Interactions	Increases duration of neuromuscular blockade induced by tubocurarine and pancuronium; erythromycin may antagonize effects of clindamycin; antidiarrheals may delay absorption of clindamycin
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Dosage may require adjustment if patient has hepatic impairment; overgrowth of *Clostridium difficile* and associated development of pseudomembranous colitis can occur; *C difficile* infection has been associated with the development of postinflammatory adhesions and/or stricture (Freeman, 1999); metronidazole also has anaerobic coverage and may be an acceptable substitute

Drug Category: *Antifungal agents* -- Their mechanism of action may involve an alteration of RNA and DNA metabolism or an intracellular accumulation of peroxide, which is toxic to the fungal cell.
If antifungal therapy is warranted, fluconazole can be initiated. Fluconazole is less toxic than amphotericin B, which is substituted if no clinical response to fluconazole occurs or if evidence of microbiological resistance is present.

Drug Name	Fluconazole (Diflucan) -- Antifungal agent with good activity against *Candida albicans.* Associated with less toxicity and easier to administer than amphotericin B; however, fluconazole-resistant candidal species are being isolated with increasing frequency. Can be administered enterally or parenterally.
Adult Dose	200-800 mg PO/IV qd

Pediatric Dose	Dependent on EGA and postnatal age 29 weeks' EGA and <14 d postnatal: 5-6 mg/kg/dose PO/IV q72h Term and age >14 d: 3-6 mg/kg/d PO/IV qd
Contraindications	Documented hypersensitivity
Interactions	Levels may increase with hydrochlorothiazide; fluconazole levels may decrease with chronic coadministration of rifampin; coadministration of fluconazole may decrease phenytoin clearance; inhibits CYP2C19 and CYP3A4; may increase concentrations of theophylline, tolbutamide, glyburide, and glipizide; effects of anticoagulants may increase with fluconazole coadministration; increases in cyclosporine concentrations may occur when administered concurrently
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Use caution in impaired renal function, dosage may require adjustment; monitor liver enzymes and liver function tests during protracted therapy; discontinue use if clinical signs of hepatic failure develop

Drug Category: *Vasopressors* -- Babies with serious illness may progress to shock and require pharmacologic blood pressure support.

Drug Name	Dopamine (Intropin) -- An adrenergic agonist that increases blood pressure by stimulating alpha-adrenergic vascular receptors resulting in vasoconstriction. Has some inotropic effects via beta1 cardiac receptors and, at low doses, increases glomerular filtration via renal dopaminergic receptors. Useful for babies with hypotension not responsive to volume repletion. May be mixed in dextrose so that glucose delivery is not compromised.
Adult Dose	1-5 mcg/kg/min IV; not to exceed 30 mcg/kg/min
Pediatric Dose	1-20 mcg/kg/min IV; titrate to effect
Contraindications	Documented hypersensitivity; pheochromocytoma; ventricular fibrillation
Interactions	Phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong effects of dopamine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Extravasation can cause tissue necrosis, treat with phentolamine as quickly as possible after the event; correct hypovolemia before infusion
Drug Name	Dobutamine (Dobutrex) -- Adrenergic agonist with specific effects on beta1-receptors in the heart, resulting in increased contractility. Has minimal alpha-adrenergic activity. Can be used for babies in shock, usually adjunctively with dopamine, to increase cardiac output. May be mixed in dextrose so that glucose delivery is not compromised.
Adult Dose	1-20 mcg/kg/min IV
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; idiopathic hypertrophic subaortic stenosis; atrial fibrillation or flutter
Interactions	Beta-adrenergic blocking agents antagonize effects; general anesthetics may increase toxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Hypovolemic state should be corrected before using this drug

Drug Name	Epinephrine (Adrenaline) -- Nonspecific adrenergic agonist that stimulates alpha-, beta1-, and beta2-receptors. Can be used to support blood pressure in severe hypotension refractory to other treatment modalities.
Pediatric Dose	0.1-1 mcg/kg/min IV
Contraindications	Documented hypersensitivity; cardiac arrhythmias or angle-closure glaucoma; local anesthesia in areas such as fingers or toes because vasoconstriction may produce sloughing of tissue; do not use during labor (may delay second stage of labor)
Interactions	Increases toxicity of beta- and alpha-blocking agents and that of halogenated inhalational anesthetics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in hypertension, hyperthyroidism, and cerebrovascular insufficiency; rapid IV infusions may cause death from cerebrovascular hemorrhage or cardiac arrhythmias

Drug Name	Naloxone (Narcan) -- Opioid receptor blocker. Experimental evidence suggests that it may increase blood pressure for babies in shock, perhaps by blocking the binding of endogenously produced endorphins released in sepsis, particularly from gram-negative organisms.
Pediatric Dose	Bolus dose: 0.1 mg/kg IV For continuous IV infusion, administer a test dose as above, observe for magnitude and duration of effect, and calculate continuous dose appropriately Reported dosage range 2.5-160 mcg/kg/h IV
Contraindications	Documented hypersensitivity; opioid addiction in baby or mother if baby is <7 d
Interactions	Blocks the effects of narcotic analgesics and those of endogenous endorphins that may be involved in intrinsic pain relief pathways
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in cardiovascular disease; naloxone may precipitate withdrawal symptoms in patients addicted to opiates

Drug Category: _Volume expanders --_ Patients with severe illness may experience fluid shifts to the extracellular space, resulting in intravascular depletion requiring expansion.

Drug Name	Albumin (5% and 25%) -- Used to increase intravascular oncotic pressure in hypovolemia and helps mobilize fluids from the interstitial to the intravascular space. Concentration can be either 5% (5 g/100 mL) or 25% (25 g/100 mL), depending on the desired effect.
Pediatric Dose	Typical dose: 0.5-1 g/kg Use 5% to replete the intravascular space Use 25% to move fluid from the extravascular to the intravascular space
Contraindications	Documented hypersensitivity; severe anemia; cardiac failure
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	If the patient has an ongoing capillary leak, exogenous albumin also moves into the interstitium;administer IV slowly, rapid administration can cause fluid shifts, exacerbating the risk of intraventricular hemorrhage in premature neonates; carries all of the risks and restrictions associated with administering blood products; protein load may exacerbate renal insufficiency, a potential complication of septic shock

Drug Name	Sodium chloride 0.9% (Normal saline, NS, Isotonic saline) -- Can be used as a volume expander and be as effective as albumin in acute hypovolemia.
Pediatric Dose	10-20 mL/kg IV infused over 30 min
Contraindications	Fluid retention; hypernatremia; cardiac failure
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in congestive heart failure, hypertension, edema, liver cirrhosis, renal insufficiency, and sodium toxicity

Drug Name	Fresh frozen plasma -- Used as a volume expander, especially helpful for patients with concomitant coagulopathy.
Pediatric Dose	10-15 mL/kg IV infused over 1 h
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Carries all of the risks and restrictions associated with administering blood products

Drug Category: *Opioid analgesics --* Although difficult to assess, premature infants presumably experience pain with severe illness and invasive procedures. Narcotic analgesics are safe and effective in premature infants and have a long history of clinical experience.

Drug Name	Morphine sulfate (Duramorph, Astramorph) -- Opioid analgesic with a long history of safe and effective use in neonates. Inhibits ascending pain pathways by binding to the opiate receptors in the CNS. Causes generalized CNS depression. It is used for sedation and analgesia.
Adult Dose	Starting dose: 0.1 mg/kg IV/IM/SC Maintenance dose: 5-20 mg/70 kg IV/IM/SC q4h; titrate to control pain and to tolerable adverse effects
Pediatric Dose	Administer as a bolus or a continuous infusion Bolus: Start >0.01 mg/kg IV q2-4h prn; not to exceed 0.1 mg/kg q1h Continuous infusion: >0.01 mg/kg/h IV; titrate upward until desired effect is achieved
Contraindications	Documented hypersensitivity; hypotension; potentially compromised airway when establishing rapid airway control would be difficult
Interactions	Other CNS depressants (eg, drugs typically not used in neonates) can potentiate the adverse effects of morphine; naloxone reverses morphine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Causes respiratory depression/apnea at higher doses; use only preservative-free preparations in neonates; may cause systemic hypotension secondary to histamine release; prolonged use causes physiologic dependence and abrupt cessation can cause severe neonatal abstinence syndrome
Drug Name	Fentanyl (Sublimaze) -- Opioid analgesic 50-100 times more potent than morphine; mechanism of action and indications for use are similar; has less hypotensive effects than morphine because of minimal-to-no associated histamine release. Administered bolus IV or as a continuous infusion. Because of small volumes used in neonates for bolus administration, it is not usually cost-effective to administer bolus.

Pediatric Dose	Bolus dose: 1-4 mcg/kg/dose slow IV push Continuous infusion: 0.5-1 mcg/kg/h IV; titrate to desired effect If used during ECMO, higher doses can be anticipated, typically 1-5 mcg/kg/h initially Because of tachyphylaxis, dose may need to be increased during the ECMO run, with doses as high as 20 mcg/kg/h reported by day 7 of treatment
Contraindications	Documented hypersensitivity; hypotension; potentially compromised airway when establishing rapid airway control would be difficult
Interactions	Other CNS depressants (eg, drugs not typically used in neonates) and MAOIs may potentiate adverse effects; naloxone reverses fentanyl
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Rapid IV administration may result in chest wall rigidity, severely compromising ability to ventilate the baby; higher doses are associated with respiratory depression/apnea; should be administered by qualified health care professionals trained in the use of general anesthetic agents; patient should be closely monitored, dose should be titrated, and lowest effective dose should be used; prolonged use (>5 d continuous infusion) results in physiologic dependence and abrupt cessation precipitates neonatal abstinence syndrome

FOLLOW-UP Section 8 of 10

Further Inpatient Care:

- Prolonged parenteral nutrition is essential to optimize the baby's nutrition while the gastrointestinal tract is allowed enough time for recovery and return to normal functioning. Central venous access is essential to facilitate parenteral delivery of adequate calories and nutrients to the recovering premature baby to minimize catabolism and promote growth.
- Prolonged central venous access may be associated with an increased incidence of nosocomial infection, predominately with skin flora such as coagulase-negative *Staphylococcus* species. A high degree of clinical suspicion must be maintained to detect the subtle signs of such infection as early as possible.
- Parenteral administration of lipid formulations via central venous catheters is also associated with an increased incidence of catheter-related sepsis.

  - Lipids coat the catheter's interior, allowing ingress of skin flora through the catheter lumen. A high degree of clinical suspicion is required for early detection of such an infection.
  - If line infection is suspected, obtain a blood culture through the central line. Antibiotics effective against skin flora (eg, vancomycin) should be administered through the line. Obtain another central line blood culture if the results of the first culture are positive. Persistently positive line cultures require removing the central line.

- Prolonged parenteral nutrition may be associated with cholestasis and direct hyperbilirubinemia. This condition resolves gradually following initiation of enteral feeds.
- Prolonged broad-spectrum antibacterial therapy increases the premature infant's risk for fungal sepsis.

  - Almost all premature infants demonstrate fungal colonization of the intestinal tract. Antibacterial therapy inhibits normal gut flora and allows fungal overgrowth caused by the absence of normal bacterial inhibition. Although prophylactic antifungal therapy reduces the incidence of fungal colonization in premature infants, it does not reduce the incidence of fungal sepsis. Therefore, it is not a recommended standard practice in the management of the preterm neonates

- As with other systemic infections in this patient population, clinical signs of fungal sepsis can be subtle and nonspecific. Delay in detection and treatment of fungal sepsis can allow the formation of fungal balls intraocularly, in the kidney, and/or in the heart. This complication carries a high mortality rate and morbidity including blindness, obstructive renal failure, and endocarditis. A high index of suspicion for fungal infection must be maintained when a baby on broad-spectrum antibacterials develops signs of systemic infec

- If a baby goes home with a colostomy, parents need thorough instruction regarding the baby's care. Having the parent(s) room with the baby at the hospital for several days prior to discharge is advisable so that they can learn and demonstrate adequate caregiving skills.
- Babies who have undergone intestinal resection may experience short-gut syndrome (see Short-gut syndrome under Complications). These babies require vigilant nutritional regimens to maintain adequate calories and vitamins for optimum growth and healing.

Transfer: In the acute phase, patients with progressive NEC require pediatric surgical consultation. During refeeding, patients with or without previous surgical history may demonstrate signs of obstruction requiring surgical evaluation and/or intervention. Transfer the patient to a facility offering pediatric surgical expertise, if it is not available at the current location.

Deterrence/Prevention:

- Breastfed babies have a lower incidence of NEC than formula-fed babies (Lucas, 1990; Eyal, 1982).
- Much anecdotal evidence exists about the role of feeding regimens in the etiology of NEC. Clinical research does not demonstrate definitive evidence for either causation or prevention. Although conventional wisdom recommends slow initiation and advancement of enteral feeds for premature infants, random trials do not show an increased incidence for babies in whom feeds have been started early in life versus after 2 weeks' chronologic age (Berseth, 1992; Meetze, 1992). In 1992, McKeown et al reported that rapid increase in feeding volume (>20 mL/kg/d) was associated with higher risk of NEC. However, in 1999, Rayyis et al showed no difference in NEC Bell stage greater than or equal to II in patients advanced at 15 mL/kg/d compared with those advanced at 35 mL/kg/d. Systematic review published by the Cochrane Collaboration in 1999 reported no effect on NEC of rapid feeding advancement for low–birth weight infants.
- Because early presentation of NEC can be subtle, high clinical suspicion is important when evaluating any infant with signs of feeding intolerance or other abdominal pathology. In general, continuing to feed a baby with developing NEC worsens the disease.

Complications:

- Approximately 75% of all patients survive. Of those patients who survive, 50% develop a long-term complication. The 2 most common complications are intestinal stricture and short-gut syndrome.
- Intestinal strictures

  - This complication can develop in infants with or without a preceding perforation.
  - Incidence is 25-33%.
  - Although the most likely location for acute disease is the terminal ileum, strictures most commonly involve the left side of the colon.
  - Symptoms of feeding intolerance and bowel obstruction typically occur 2-3 weeks after recovery from the initial event.
  - The presence and location of the obstruction is diagnosed using barium enema; surgical resection of the affected area is required. Many surgeons routinely perform barium enemas in their patients before bowel reanastomosis so that all necessary surgical intervention can be performed at one time.

- Short-gut syndrome

    o This is a malabsorption syndrome resulting from removal of excessive or critical portions of small bowel necessary for absorption essential nutrients from intestinal lumen.
    o Symptoms are most profound in babies who either have lost most of their small bowel or have lost a smaller portion that includes the ileocecal valve.
    o Loss of small bowel can result in malabsorption of nutrients as well as fluids and electrolytes.
    o The neonatal gut will grow and adapt over time, but long-term studies suggest that this growth may take as long as 2 years to occur. During that time, maintenance of an anabolic and complete nutritional state is essential for the growth and development of the baby. This is achieved by parenteral provision of adequate vitamins, minerals, and calories; appropriate management of gastric acid hypersecretion; and monitoring for bacterial overgrowth. The addition of appropriate enteral feedings during this time is important for gut nourishment and remodeling.

Medical/Legal Pitfalls:

- Following hospital discharge, caring for premature infants has shifted away from neonatologists at regionalized centers to general pediatricians and other health care providers in the community. Adequate interaction between subspecialists and community physicians and formulation of well-communicated health care plans for these vulnerable babies are crucial to serve their best interest, to optimize their health outcome, and to minimize the opportunities for malpractice law suits.

- Failure to recognize signs of NEC early enough to effect timely transfer to a tertiary care facility offering pediatric surgery could expose the clinician to medicolegal liability if the baby has a poor outcome as a result. Timely communication with parents and education are crucial to prevent lawsuits in case of unfortunate outcome.

Special Concerns:

- As with all neonatal care, the risks and benefits of various clinical approaches must be considered carefully. As many as 50% of all premature infants manifest feeding intolerance during their hospital course, but less than one fourth of those infants develop NEC.

- Cessation of feeding and initiation of broad-spectrum antibiotics in every baby with feeding intolerance impedes proper nutrition and exposes the baby to unnecessary antibacterials that may predispose to fungemia. On the other hand, failure to intervene appropriately for the baby with early NEC may exacerbate the disease and worsen the outcome. Clearly, managing this population requires a high degree of clinical suspicion for possible untoward events, tempered by cautious watching and waiting.

Picture 1. Necrotizing enterocolitis. Pneumatosis intestinalis. Photo courtesy of Loren G Yamamoto, MD, MPH, Kapiolani Medical Center for Women & Children, University of Hawaii, with permission.
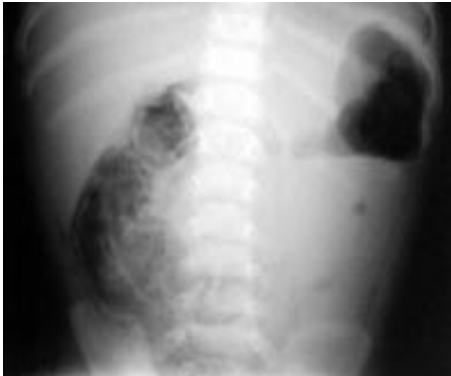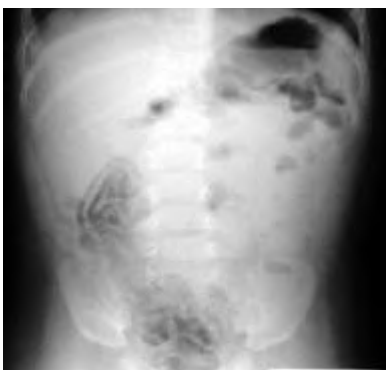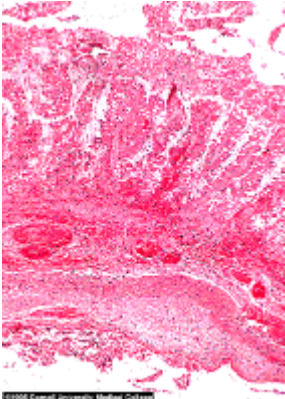

Picture 2. Necrotizing enterocolitis. Pneumatosis intestinalis. Photo courtesy of Loren G Yamamoto, MD, MPH, Kapiolani Medical Center for Women & Children, University of Hawaii.

Picture 3. Necrotizing enterocolitis. Pneumatosis intestinalis. Photo courtesy of Loren G Yamamoto, MD, MPH, Kapiolani Medical Center for Women & Children, University of Hawaii.

Picture 4. Necrotizing enterocolitis. Pneumatosis intestinalis. Photo courtesy of Loren G Yamamoto, MD, MPH, Kapiolani Medical Center for Women & Children, University of Hawaii.

Picture 5. Necrotizing enterocolitis. Pneumoperitoneum. Photo courtesy of the Department of Pathology, Cornell University Medical College.

Picture 6. Necrotizing enterocolitis. Resected portion of necrotic bowel.
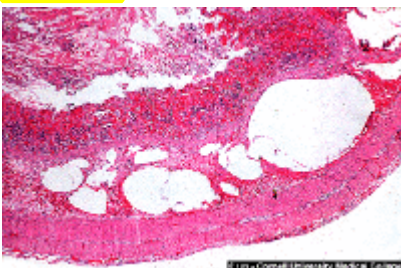

Picture 7. Necrotizing enterocolitis. Micrograph of mucosal section showing transmural necrosis. Photo courtesy of the Department of Pathology, Cornell University Medical College.


Picture 8. Necrotizing enterocolitis. Normal (top) versus necrotic section of bowel.
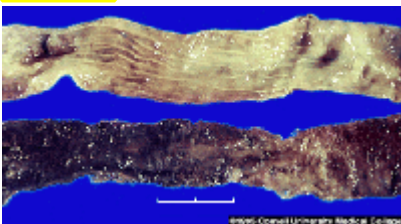
Picture 9. Necrotizing enterocolitis. Histologic section of mucosal wall demonstrating pneumatosis.

Picture 10. Necrotizing enterocolitis. Histologic section of bowel mucosa showing regeneration of normal cellular architecture. Department of Pathology, Cornell University Medical.
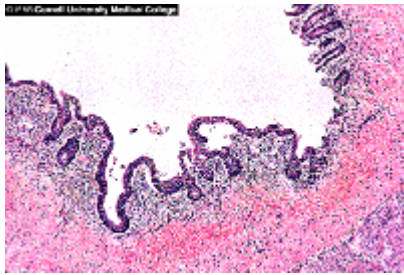
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Neonatal Hypertension

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INTRODUCTION	Section 2 of 10

Background: Recent advances in the ability to identify, evaluate, and care for hypertensive infants, coupled with advances in the practice of neonatology in general, have led to an increased awareness of hypertension in modern neonatal intensive care units (NICUs) since its first description in the 1970s. This article discusses an overview of the differential diagnosis of hypertension in the neonate, the optimal diagnostic evaluation, and both immediate and long-term antihypertensive therapy.

Pathophysiology: Hypertension in newborn infants primarily is of renal origin, although cardiac, endocrine, and pulmonary causes have been described as well. Therefore, the pathophysiology depends on the organ system involved. For example, hypertension related to renal emboli primarily is a high renin form of hypertension, whereas the hypertension associated with bronchopulmonary dysplasia (BPD) is likely related to hypoxia. Such differences in pathophysiology are very important because they can guide the clinician with respect to evaluation and treatment.

Frequency: In the US: Although precise figures are difficult to obtain, available data suggest that the incidence of hypertension in newborns is low, with published figures ranging from 0.2-3%. Hypertension is so unusual in otherwise healthy term infants that routine blood pressure (BP) determination is not advocated for these patients. In 1992, Singh and colleagues found that in a group of over 3000 infants admitted to a Chicago area NICU, the overall incidence of hypertension was found to be 0.81%. Hypertension was considerably more common in infants with BPD, patent ductus arteriosus, or intraventricular hemorrhage or in those who had indwelling umbilical arterial catheters. Approximately 9% of the infants who had indwelling umbilical arterial catheters developed hypertension.

Hypertension may also be detected following discharge from the NICU. In 1987, Friedman and Hustead diagnosed hypertension (defined as a systolic BP >113 mm Hg on 3 consecutive visits over 6 wk) in 2.6% of infants discharged from a teaching hospital NICU. The diagnosis of hypertension was made in these infants at a mean corrected age of approximately 2 months. Infants in this study who developed hypertension tended to have lower initial Apgar scores and slightly longer NICU stays than infants who remained normotensive, indicating that sicker babies have a somewhat greater likelihood of developing hypertension. Although the number of babies affected is likely to be relatively small, include screening for hypertension in the follow-up of NICU graduates, especially those with more complicated NICU courses.

History:

- Defining hypertension in the newborn

  - In determining the level of BP that should be considered hypertensive for a newborn infant, keep in mind that just as BP in older children has been demonstrated to increase with increasing age and body size, numerous studies have demonstrated that BP in newborns increases with both gestational and postconceptual age as well as with birthweight.
  - The most recent study demonstrating this principle is a 1995 study by Zubrow and associates, who prospectively obtained serial BP measurements from nearly 700 infants admitted to several NICUs in a large metropolitan area over a period of 3 months. They used these data to define the mean plus upper and lower 95% confidence limits for BP for the infants who were studied; their data clearly demonstrated increases in BP with increasing gestational age, birthweight, and postconceptual age. Based on these data, an infant's BP is considered elevated if it falls above the upper limit of the 95% confidence interval for infants of similar gestational or postconceptual age and size. The curves generated by Zubrow's study have been widely published and should be consulted in assessing whether a newborn has hypertension.
  - For older infants found to be hypertensive following discharge from the nursery, the percentile curves generated by the Second Task Force on Blood Pressure Control in Childhood appear to be the most useful. These curves, which can be found in many reference texts and handbooks, allow BP to be characterized as normal or elevated not only by age and sex but also by size, albeit to a somewhat limited extent. Hypertension in this age group is defined as BP elevation higher than the 95th percentile for infants of similar age, size, and sex.

- Clinical presentation: In most newborns, hypertension is discovered on routine monitoring of vital signs. Other presentations of neonatal hypertension to be aware of in acutely ill infants include congestive heart failure (CHF) and cardiogenic shock, which are potentially life threatening. Fortunately, these consequences of hypertension gradually resolve with appropriate BP reduction. In the less acutely ill infant, feeding difficulties, unexplained tachypnea, apnea, lethargy, irritability, or seizures may constitute symptoms of unsuspected hypertension. In older infants who have been discharged from the nursery, unexplained irritability or failure to thrive may be the only manifestations of hypertension.

- Patient history: Focus the history on discovering any pertinent prenatal exposures, as well as to the particulars of the infant's nursery course and any concurrent conditions. Review the procedures that the infant has undergone, especially umbilical catheter placement, and analyze the baby's current medication list. If the infant has been discharged from the nursery, the history should also cover symptoms related to possible underlying causes of hypertension.

Physical: Issues pertinent to the physical examination in neonates with hypertension can be divided into two categories, the first being proper blood pressure measurement, and the second being other components of the physical examination.

- Blood pressure measurement

  - Proper identification of hypertension in the newborn requires accurate BP measurement. Fortunately, in most acutely ill infants, BP is usually monitored directly via an indwelling arterial catheter, either in the radial or umbilical artery. This method provides the most accurate BP readings and is clearly preferable to other methods. In infants who do not have indwelling umbilical lines, automated oscillometric devices are an acceptable alternative method of BP measurement.

- Although BP readings obtained using such devices may differ slightly from intra-arterial readings, they are easy to use and facilitate monitoring BP trends over time. BP readings obtained using such devices also are useful for infants who require BP monitoring after discharge from the NICU. Pay attention to the size of the cuff and also to the extremity used. Most normative BP data, not only in infants but also in older children, have been collected using BP measurements obtained in the right arm. Because BP measurements obtained in the leg are typically higher than those obtained in the arm, the use of other extremities for routine BP determination may complicate the evaluation of hypertension. The nursing staff should document the extremity used for BP determinations and try to use the same extremity for all BP measurements.

- Physical examination: The physical examination should begin with 4-extremity BP measurements in order to rule out aortic coarctation. Assess the general appearance of the infant and pay particular attention to the presence of dysmorphic features that may indicate an underlying genetic syndrome. Perform careful cardiac and abdominal examinations to rule out CHF or renal anomalies. Examine the genitalia to rule out congenital adrenal hyperplasia (CAH).

<mark>Causes:</mark> As in older infants and children, most cases of neonatal hypertension are of renal origin, with the 2 largest categories being renovascular and other renal parenchymal diseases (see Differentials).

- With respect to renovascular disease, umbilical artery catheter–associated thromboembolism affecting the aorta, the renal arteries, or both probably is the most common cause observed in the typical NICU. In 1972, Neal et al were the first investigators to demonstrate an association between the use of umbilical arterial catheters and development of arterial thrombi. Using aortography at the time of umbilical artery removal as well as autopsy data, they demonstrated thrombus formation in 25 out of 31 infants studied (81%).
- Following Neal's report, the association between umbilical arterial catheter–associated thrombi and the development of hypertension was confirmed by several other groups of investigators. Although potential predisposing factors such as duration of line placement and line position (low versus high) have been studied, these studies have not been conclusive, leading to the assumption that the cause of hypertension in such cases is related to thrombus formation at the time of line placement, which is probably related to disruption of the vascular endothelium of the umbilical artery. Such thrombi may then embolize into the kidneys, causing areas of infarction and increased renin release.
- Other renovascular problems that may lead to neonatal hypertension include renal venous thrombosis (RVT) and renal artery stenosis secondary to fibromuscular dysplasia (FMD). Many infants with FMD may have main renal arteries that appear fairly normal on angiography but demonstrate significant branch vessel disease that can cause severe hypertension.
- Other vascular abnormalities may also lead to hypertension in the newborn, including idiopathic arterial calcification and renal artery stenosis secondary to congenital rubella infection.
- Finally, mechanical compression of one or both renal arteries by tumors, hydronephrotic kidneys, or other abdominal masses may also lead to hypertension.
- Numerous congenital renal parenchymal abnormalities can lead to hypertension in the newborn period. For example, patients with autosomal dominant or autosomal recessive polycystic kidney disease (PKD) may present in the newborn period with severe nephromegaly and hypertension. The most severely affected infants with PKD are at risk for development of CHF due to severe malignant hypertension. Although much less common than in PKD, hypertension has also been reported in infants with unilateral multicystic dysplastic kidneys. Renal obstruction may be accompanied by hypertension, even in the absence of renal arterial compression. This has been observed, for example, in infants with congenital ureteropelvic junction obstruction and in infants with ureteral obstruction by other intra-abdominal masses. The mechanism of hypertension in such instances is unclear, although the renin-angiotensin system (RAS) may be involved.
- Other renal parenchymal causes of hypertension in the newborn period include severe acute tubular necrosis, interstitial nephritis, and cortical necrosis. Hemolytic uremic syndrome,

although rare in the newborn period, is usually accompanied by hypertension that can be quite difficult to control, frequently requiring multiple agents.

- The most important nonrenal cause of neonatal hypertension is BPD. This association was first described in 1984 by Abman et al, who studied 65 infants discharged from a NICU. Abman et al reported that the incidence of hypertension in infants with BPD was 43% versus an incidence of 4.5% in infants without BPD. More than half of the infants with BPD who developed hypertension did not manifest it until following discharge from the NICU, highlighting the need for measurement of BP in NICU graduates. Investigators were unable to identify a clear cause of hypertension, but postulated that hypoxemia may be involved.

- These findings have subsequently been reproduced by several other investigators, most recently in 1998 by Alagappan, who found that hypertension was twice as common in very low birthweight infants with BPD compared to the incidence in all very low birthweight infants. As in Abman's report, the development of hypertension appeared to be correlated with the severity of pulmonary disease because all of the hypertensive infants were receiving supplemental oxygen and aminophylline. These observations reinforce the impression that infants with severe lung disease are clearly at increased risk of developing hypertension and need close monitoring for this problem.

- Numerous other causes of hypertension in newborns exist, a comprehensive listing of which can be found in Differentials. Of these, hypertension associated with coarctation of the thoracic aorta deserves further comment. This is perhaps one of the most easily detected forms of hypertension in the newborn period and has been included in the differential diagnosis of this problem since the earliest reported case series of neonatal hypertension.

- Repair early in infancy seems to lead to an improved long-term outcome compared to delayed repair, which may be followed by persistent hypertension. Endocrinologic disorders that may produce hypertension in the newborn period include CAH, hyperaldosteronism, and hyperthyroidism.

- Iatrogenic hypertension can be the result of medications administered to infants for treatment of pulmonary disease, such as dexamethasone and aminophylline, high doses of adrenergic agents, prolonged use of pancuronium, or administration of phenylephrine ophthalmic drops. Hypertension in such cases typically resolves when the offending agent is discontinued or its dose is reduced.

- For infants receiving prolonged total parenteral nutrition (TPN), hypertension may result from salt and water overload or from hypercalcemia. Patients with certain tumors, including neuroblastoma, Wilms tumor, and mesoblastic nephroma, may present in the neonatal period, and the tumors may produce hypertension either because of compression of the renal vessels or ureters or because of production of vasoactive substances such as catecholamines. Neurologic problems, such as seizures, intracranial hypertension, and pain, constitute fairly common causes of episodic hypertension. Finally, illicit substances ingested by the mother during pregnancy, most notably cocaine and heroin, may also lead to significant problems with hypertension in the newborn either because of direct effects on the developing kidney or because of drug withdrawal.

DIFFERENTIALS	Section 4 of 10

Acute Tubular Necrosis
Coarctation of the Aorta
Fluid, Electrolyte, and Nutrition Management of the Newborn
Graves Disease
Hyperaldosteronism
Hypertension
Infantile Polyarteritis Nodosa
Neonatal Hypertension
Noonan Syndrome
Posterior Urethral Valves
Renal Cortical Necrosis   Respiratory Distress Syndrome   Thromboembolism
Tuberous Sclerosis   Turner Syndrome   Ureteropelvic Junction Obstruction
Williams Syndrome

Bronchopulmonary Dysplasia
Extremely Low Birth Weight Infant
Follow-up of the NICU Patient
Hematuria
Hypercalcemia
Hyperthyroidism
Multicystic Renal Dysplasia
Neuroblastoma
Polycystic Kidney Disease
Prematurity
Wilms Tumor

Other Problems to be Considered:

Renovascular conditions

Thromboembolism
Renal artery stenosis
Midabdominal aortic
Renal venous thrombosis
Compression of renal artery
Idiopathic arterial calcification
Congenital rubella syndrome

Renal parenchymal disease

Polycystic kidney disease
Multicystic-dysplastic kidney disease
 coarctation Tuberous sclerosis
Ureteropelvic junction obstruction
Acute tubular necrosis
 Cortical necrosis
Interstitial nephritis
 Hemolytic-uremic syndrome

Pulmonary conditions

BPD
Pneumothorax

Cardiac conditions

 Thoracic aortic coarctation

Endocrine conditions

Congenital adrenal hyperplasia
Hyperaldosteronism
Hyperthyroidism
Pseudohypoaldosteronism type II

Medications/Intoxications

Dexamethasone
Adrenergic agents
Vitamin D intoxication
 Theophylline
 Caffeine
 Pancuronium
 Phenylephrine
Maternal cocaine or heroin use

Tumors

Neoplasia
Wilms tumor
Mesoblastic nephroma
Neuroblastoma
Pheochromocytoma

Miscellaneous conditions

Closure of abdominal wall defect
Adrenal hemorrhage
Hypercalcemia
Traction
Extracorporeal membrane oxygenation (ECMO)
 Birth asphyxia
Urological neoplasms

Neurologic conditions

Pain
Intracranial hypertension
Seizures
Familial dysautonomia
Subdural hematoma

Lab Studies:

- Usually only a limited set of laboratory data is needed in the evaluation of neonatal hypertension. Obtain serum electrolytes, creatinine, BUN, and a urinalysis in order to look for renal parenchymal disease. Obtain endocrinologic studies, such as cortisol, aldosterone, or thyroxine, when pertinent history exists.

- Measurement of plasma renin activity is usually recommended as part of the laboratory assessment of hypertensive newborns, although an elevated peripheral renin may not

signify the presence of underlying pathology because renin values are typically quite high in infancy. In addition, plasma renin may be elevated falsely by medications that are commonly used in the NICU, such as aminophylline. Keep these factors in mind when interpreting renin values.

- Chest radiography may be helpful in infants with CHF or in those with a murmur on physical examination.

- Obtain renal ultrasonography in all hypertensive infants. Accurate renal ultrasonography may help uncover potentially correctable causes of hypertension (eg, RVT); it may detect aortic thrombi, renal arterial thrombi, or both; and it can reveal anatomic renal abnormalities or other congenital renal parenchymal disease. Ultrasonography is fast, noninvasive, and relatively inexpensive. Ultrasonography has largely replaced intravenous pyelography, which has little, if any, use in the routine assessment of neonatal hypertension.

- For infants with extremely severe BP elevation, angiography may be necessary. Although some investigators have used aortography via the umbilical artery catheter, a formal angiography using the traditional femoral venous approach is much more accurate for diagnosing renal arterial stenosis, primarily because of the high incidence of intrarenal branch vessel abnormalities observed in children with FMD.

- Nuclear scanning may demonstrate abnormalities of renal perfusion caused by thromboembolic phenomenon, although obtaining good studies in infants is difficult because of their immature renal function.

- Obtain other studies, including echocardiography and voiding cystourethrography, as indicated.

TREATMENT	Section 6 of 10

Medical Care: Numerous medications are available that may be used in the treatment of neonatal hypertension. Assess the clinical status of the infant and correct any easily correctable iatrogenic causes of hypertension (eg, infusions of inotropic agents, volume overload, pain) prior to instituting drug therapy. Next, choose an antihypertensive agent that is most appropriate for the specific clinical situation.

- Intravenous antihypertensive infusions

  - Usually, continuous intravenous infusions are the most appropriate initial therapy, especially in acutely ill infants with severe hypertension. The advantages of intravenous infusions are numerous, most importantly including the ability to quickly increase or decrease the rate of infusion to achieve the desired BP. As in patients of any age with malignant hypertension, take care to avoid too rapid a reduction in BP in order to avoid cerebral ischemia and hemorrhage; premature infants in particular are already at an increased risk because of the immaturity of their periventricular circulation. Because of the paucity of available data regarding the use of these agents in newborns, the choice of agent depends on the individual clinician's experience.

  - Currently available drugs for continuous infusion include nitroprusside, labetalol, esmolol, and nicardipine (see Table 1). Nicardipine, which is a dihydropyridine calcium channel blocker, appears to have some advantages over older drugs, such

as nitroprusside, that may make it the drug of choice in this population. Regardless of the drug chosen, monitor BP continuously via an indwelling arterial catheter or by frequently repeated (q10-15min) cuff readings so that the rate of infusion can be titrated to achieve the desired degree of BP control.

Table 1. Intravenous Drugs for Severe Hypertension in Neonates

Drug	Class	Dosage	Comments
Diazoxide	Vasodilator (arteriolar)	2-5 mg/kg/dose rapid IV bolus	Slow IV injection ineffective; duration unpredictable; use with caution, may cause rapid hypotension
Esmolol	Beta-blocker	100-300 mcg/kg/min IV infusion	Very short-acting; constant IV infusion necessary
Hydralazine	Vasodilator (arteriolar)	0.15-0.6 mg/kg/dose or 0.75-5 mcg/kg/min IV bolus or constant infusion	Tachycardia is frequent adverse effect; must administer q4h with IV bolus
Labetalol	Alpha- and beta-blocker	0.2-1 mg/kg/dose or 0.25-3 mg/kg/h IV bolus or constant infusion	Heart failure, BPD relative contraindications
Nicardipine	Calcium channel blocker	1-3 mcg/kg/min IV constant infusion	May cause reflex tachycardia
Sodium nitroprusside	Vasodilator (arteriolar and venous)	0.5-10 mcg/kg/min IV constant infusion	Thiocyanate toxicity can occur with prolonged (>72 h) use or in renal failure; usual maintenance dose <2 mcg/kg/min, may use 10 mcg/kg/min for short duration (ie, <10-15 min)

- Intermittently administered intravenous antihypertensive agents: For some infants, intermittently administered intravenous agents have a role in therapy (see Table 1). Hydralazine and labetalol, in particular, may be useful in infants with mild-to-moderate hypertension who are not yet candidates for oral therapy because of GI dysfunction. Enalaprilat, the intravenous ACE inhibitor, has also been reported to be useful in the treatment of neonatal renovascular hypertension, but it should be used with great caution. Even doses at the lower end of published ranges may lead to significant prolonged hypotension and oliguric acute renal failure.

- Oral antihypertensive agents

  o Oral antihypertensive agents (see Table 2) are best reserved for infants with less severe hypertension or infants whose acute hypertension has been controlled with intravenous drugs and who are ready to be converted to long-term therapy. Captopril, in particular, is a useful agent for many causes of neonatal hypertension and is considered by many authorities to be the oral drug of choice for neonatal hypertension. The initial dose of captopril recommended for premature infants is lower than that used in older infants because it may produce a rapid exaggerated fall in BP in preterm infants. For BP that cannot be controlled by captopril alone, a diuretic should be used as the second agent.

o Beta-blockers may need to be avoided in long-term antihypertensive therapy in infants with BPD. In such infants, diuretics may have a beneficial effect not only in controlling BP but also in improving pulmonary function. Other drugs, which may be useful in some infants, include vasodilators, such as hydralazine and minoxidil (because it can be compounded into a stable suspension) and the calcium channel blocker isradipine, which may be superior to the older agents. Nifedipine is a poor choice for long-term therapy because of the difficulty in administering small doses and because of the rapid, profound, and short-lived drops in BP that are typically produced by this agent.

Table 2. Oral Antihypertensive Agents Useful for Treatment of Neonatal Hypertension

Drug	Class	Dosage	Comments
Captopril	ACE inhibitor	<3 months: 0.01-0.5 mg/kg/dose tid; not to exceed 2 mg/kg/d >3 months: 0.15-0.3 mg/kg/dose tid; not to exceed 6 mg/kg/d	Drug of choice for most cases of neonatal hypertension; monitor serum creatinine and potassium
Clonidine	Central agonist	0.05-0.1 mg/dose bid-tid	Adverse effects include dry mouth and sedation; rebound hypertension with abrupt discontinuation
Hydralazine	Vasodilator (arteriolar)	0.25-1 mg/kg/dose tid-qid; not to exceed 7.5 mg/kg/d	Suspension stable up to 1 wk; tachycardia and fluid retention are common adverse effects; lupuslike syndrome may develop in slow acetylators
Isradipine	Calcium channel blocker	0.05-0.15 mg/kg/dose qid; not to exceed 0.8 mg/kg/d or 20 mg/d	Suspension may be compounded; useful for both acute and chronic hypertension
Amlodipine	Calcium channel blocker	0.1-0.3 mg/kg/dose bid; not to exceed 0.6 mg/k/d or 20 mg/d	Less likely to cause sudden hypotension than isradipine
Minoxidil	Vasodilator (arteriolar)	0.1-0.2 mg/kg/dose bid-tid	Most potent oral vasodilator; excellent for refractory hypertension
Propranolol	Beta-blocker	0.5-1 mg/kg/dose tid	Maximal dose depends on heart rate; may administer as much as 8-10 mg/kg/d if no bradycardia; avoid in infants with BPD
Labetalol	Alpha- and beta-blocker	1 mg/kg/dose bid-tid, up to 12 mg/kg/d	Monitor heart rate; avoid in infants with BPD
Spironolactone	Aldosterone antagonist	0.5-1.5 mg/kg/dose bid	Potassium-sparing diuretic; monitor electrolytes; several days necessary to observe maximum effectiveness
Hydrochlorothiazide	Thiazide diuretic	1-3 mg/kg/dose qd	Monitor electrolytes
Chlorothiazide	Thiazide diuretic	5-15 mg/kg/dose bid	Monitor electrolytes

Surgical Care: Surgery is rarely indicated for treatment of neonatal hypertension, except for specific diagnoses, such as ureteral obstruction, aortic coarctation, or certain tumors. Unilateral RVT is commonly treated with nephrectomy to avoid the need for long-term drug therapy. For infants with renal arterial stenosis, managing the infant medically may be necessary until growth is sufficient to undergo definitive repair of the vascular abnormalities. Infants with malignant hypertension secondary to PKD may require bilateral nephrectomy. Fortunately, such severely affected infants are quite rare.

Consultations: Consultation with a cardiologist may be indicated for performance of echocardiography or evaluation of CHF or both. Consultation with an interventional radiologist may also be needed in some cases for performance of renal angiography.

Diet: A low-sodium diet may assist in treatment of infants with persistent hypertension; however, because most infant formula is relatively low in sodium content, no special dietary modifications are usually necessary in the neonatal period.

Understand that most of the medications discussed in this article have not been studied specifically in newborns; however, through empiric use of these medications, a reasonable clinical experience has been accumulated. The information below has been summarized in Table 1 and Table 2; the tables also contain information on several other drugs, which are not included in this section because of space limitations.

Drug Category: *Vasodilators* -- Relax blood vessels; thus, they decrease peripheral vascular resistance.

Drug Name	Hydralazine (Apresoline) -- Decreases systemic resistance through direct vasodilation of arterioles.
Adult Dose	10-20 mg/dose IV q4-6h prn initially; increase to 40 mg/dose prn; change to PO as soon as possible
Pediatric Dose	0.15-0.6 mg/kg/dose IV q4h 0.25-1 mg/kg/dose PO q6h
Contraindications	Documented hypersensitivity; mitral valve rheumatic heart disease
Interactions	MAOIs and beta-blockers may increase hydralazine toxicity; pharmacologic effects of hydralazine may be decreased by indomethacin
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Tachycardia may develop; lupuslike syndrome may occur in nonacetylators
Drug Name	Sodium nitroprusside (Nitropress) -- Produces vasodilation and increases inotropic activity of the heart.
Adult Dose	0.3-0.5 mcg/kg/min IV infusion initially, titrate by increments of 0.5 mcg/kg/min to desired effect; average effective dose is 1-6 mcg/kg/min
Pediatric Dose	0.5-10 mcg/kg/min continuous IV infusion; initiate at lower dose, may titrate as in adults
Contraindications	Documented hypersensitivity; subaortic stenosis; idiopathic hypertrophic and atrial fibrillation or flutter

Interactions	Effects are additive when administered with other hypotensive agents
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in increased intracranial pressure, hepatic failure, severe renal impairment, and hypothyroidism; in renal or hepatic insufficiency, nitroprusside levels may increase and can cause cyanide toxicity

Drug Name	Diazoxide (Hyperstat) -- Produces direct smooth muscle relaxation of peripheral arterioles, which decreases blood pressure.
Adult Dose	1-3 mg/kg IV push as a single injection; not to exceed 150 mg/dose Repeat dose in 5-15 min prn until blood pressure is reduced adequately
Pediatric Dose	2-5 mg/kg/dose IV push as a single injection
Contraindications	Documented hypersensitivity; aortic coarctation; pheochromocytoma; arteriovenous shunts; aortic aneurysm
Interactions	May decrease serum hydantoins, possibly resulting in decreased anticonvulsant effects; thiazide diuretics may potentiate hyperuricemic and antihypertensive effects of diazoxide
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Inject rapidly; magnitude and duration of effect may be variable; patients with diabetes mellitus may require treatment for hyperglycemia; when administered before delivery, may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and other adverse reactions

Drug Category: _Calcium channel blockers_ -- Blockade of calcium channels in vascular smooth muscle, which leads to vasodilatation.

Drug Name	Amlodipine (Norvasc) -- Relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery. Good choice for long-term outpatient treatment; may be compounded into a stable suspension (1 mg/mL).
Adult Dose	2.5-10 mg PO qd
Pediatric Dose	0.1-0.3 mg/kg/dose PO bid; not to exceed 0.6 mg/kg/d
Contraindications	Documented hypersensitivity
Interactions	Coadministration with amiodarone can cause bradycardia and a decrease in cardiac output; triazole antifungals may increase levels
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Slow onset of action; caution in hepatic insufficiency
Drug Name	Isradipine (DynaCirc) -- Dihydropyridine calcium channel blocker. It binds to calcium channels with high affinity and specificity and inhibits calcium flux into cardiac and smooth muscle. The resultant effect is arteriole dilation, which reduces systemic resistance and blood pressure, with a small increase in resting heart rate. Rapid onset of action. May be compounded into a stable suspension.
Adult Dose	2.5-10 mg PO bid
Pediatric Dose	0.05-0.15 mg/kg/dose PO q6-8h; not to exceed 0.8 mg/kg/d
Contraindications	Documented hypersensitivity
Interactions	Coadministration with amiodarone can cause bradycardia and a

	decrease in cardiac output; triazole antifungals or cimetidine may increase levels
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May cause tachycardia and flushing; caution in aortic stenosis or hepatic insufficiency; may cause dizziness or syncope upon treatment initiation

Drug Name	Nicardipine (Cardene) -- Relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery and reduces myocardial oxygen consumption. Intravenous nicardipine is the DOC for initial management of severe neonatal hypertension.
Adult Dose	20-40 mg PO tid 1-15 mg/h IV
Pediatric Dose	1-3 mcg/kg/min continuous IV infusion
Contraindications	Documented hypersensitivity
Interactions	When administered concurrently with beta-blockers, may increase cardiac depression; triazole antifungals may increase levels; increases cyclosporine levels
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Have arterial line in place for continuous BP monitoring; tachycardia may develop

Drug Category: *Beta-adrenergic blockers --* Decrease heart rate and cardiac output.

Drug Name	Labetalol (Normodyne, Trandate) -- Blocks beta1-, alpha-, and beta2-adrenergic receptor sites, decreasing blood pressure.
Adult Dose	20-30 mg IV over 2 min, followed by 40-80 mg at 10-min intervals; not to exceed 300 mg/dose
Pediatric Dose	0.2-1 mg/kg/dose IV q6-8h; or 0.25-3 mg/kg/h continuous IV infusion 1 mg/kg/dose PO q8; not to exceed 12 mg/kg/d
Contraindications	Documented hypersensitivity; cardiogenic shock; pulmonary edema; bradycardia; atrioventricular block; uncompensated congestive heart failure; reactive airway disease
Interactions	Labetalol decreases effect of diuretics and increases toxicity of methotrexate, lithium, and salicylates; may diminish reflex tachycardia resulting from nitroglycerin use without interfering with hypotensive effects; cimetidine may increase labetalol blood levels; glutethimide may decrease labetalol effects by inducing microsomal enzymes
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Caution in impaired hepatic function; discontinue therapy if signs of liver dysfunction are present
Drug Name	Propranolol (Inderal) -- Has membrane-stabilizing activity and decreases automaticity of contractions. Not suitable for emergency treatment of hypertension. Do not administer IV in hypertensive emergencies.
Adult Dose	40-80 mg PO bid initially; increase to 160-320 mg/d (some patients require up to 640 mg/d)
Pediatric Dose	0.5-1 mg/kg/dose PO q8h; not to exceed 10 mg/kg/d

Contraindications	Documented hypersensitivity; uncompensated congestive heart failure; bradycardia; cardiogenic shock; AV conduction abnormalities
Interactions	Coadministration with aluminum salts, barbiturates, NSAIDs, penicillins, calcium salts, cholestyramine, and rifampin may decrease propranolol effects; calcium channel blockers, cimetidine, loop diuretics, and MAOIs may increase toxicity of propranolol; toxicity of hydralazine, haloperidol, benzodiazepines, and phenothiazines may increase with propranolol
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Beta-adrenergic blockade may decrease signs of acute hypoglycemia and hyperthyroidism; abrupt withdrawal may exacerbate symptoms of hyperthyroidism, including thyroid storm; withdraw drug slowly and monitor closely
Drug Name	Esmolol (Brevibloc) -- Excellent drug for use in patients at risk for experiencing complications from beta-blockade, particularly those with reactive airway disease, mild-to-moderate LV dysfunction, and/or peripheral vascular disease. Short half-life of 8 min allows for titration to desired effect and quick discontinuation if needed.
Adult Dose	Loading dose: 250-500 mcg/kg/min IV for 1 min, followed by 4-min maintenance infusion of 50 mcg/kg/min; if satisfactory response is not obtained, the bolus is repeated before each sequential upward titration in infusion rate through 100, 150, 200, 250, and 300 mcg/kg/min
Pediatric Dose	100-300 mcg/kg/min continuous IV infusion
Contraindications	Documented hypersensitivity; uncompensated congestive heart failure; bradycardia; cardiogenic shock; AV conduction abnormalities
Interactions	Aluminum salts, barbiturates, NSAIDs, penicillins, calcium salts, cholestyramine, and rifampin may decrease bioavailability and plasma levels of esmolol, possibly resulting in decreased pharmacologic effect; cardiotoxicity of esmolol may increase when administered concurrently with sparfloxacin, astemizole, calcium channel blockers, quinidine, flecainide, and contraceptives; toxicity of esmolol increases when administered concurrently with digoxin, flecainide, acetaminophen, clonidine, epinephrine, nifedipine, prazosin, haloperidol, phenothiazines, and catecholamine-depleting agents
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Beta-adrenergic blockers may mask signs and symptoms of acute hypoglycemia and clinical signs of hyperthyroidism; symptoms of hyperthyroidism, including thyroid storm, may worsen when medication is abruptly withdrawn; withdraw drug slowly and monitor patient closely

Drug Category: *Angiotensin-converting enzyme (ACE) inhibitors --* Inhibit conversion of I to II.

Drug Name	Captopril (Capoten) -- DOC for long-term treatment of neonatal hypertension. Prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, resulting in lower aldosterone secretion.
Adult Dose	12.5-25 mg PO bid-tid; may increase by 12.5-25 mg/dose at 1- to 2-wk intervals up to 50 mg tid
Pediatric Dose	<3 months: 0.01-0.5 mg/kg/dose PO tid; not to exceed 2 mg/kg/d >3 months: 0.15-0.3 mg/kg/dose PO tid; not to exceed 6 mg/kg/d

Contraindications	Documented hypersensitivity; renal impairment
Interactions	NSAIDs may reduce hypotensive effects of captopril; ACE inhibitors may increase digoxin, lithium, and allopurinol levels; rifampin decreases captopril levels; probenecid may increase captopril levels; the hypotensive effects of ACE inhibitors may be enhanced when administered concurrently with diuretics
Pregnancy	D - Unsafe in pregnancy
Precautions	Pregnancy category D in second and third trimester, pregnancy category C in first trimester; caution in renal impairment, valvular stenosis, or severe congestive heart failure
Drug Name	Enalapril (Vasotec) -- Competitive inhibitor of ACE. Reduces angiotensin II levels, decreasing aldosterone secretion.
Adult Dose	1.25 mg (as enalaprilat)/dose IV over 5 min q6h; not to exceed 5 mg/dose 5-20 mg/d PO; not to exceed 40 mg/d
Pediatric Dose	IV: Not recommended (see precautions) PO: Not FDA approved for neonates; limited data exist, 0.08 mg/kg/d PO qd initially; may increase gradually, not to exceed 0.6 mg/kg/d
Contraindications	Documented hypersensitivity
Interactions	NSAIDs may reduce hypotensive effects of enalapril; ACE inhibitors may increase digoxin, lithium, and allopurinol levels; rifampin decreases enalapril levels; probenecid may increase enalapril levels; the hypotensive effects of ACE inhibitors may be enhanced when administered concurrently with diuretics
Pregnancy	D - Unsafe in pregnancy
Precautions	Pregnancy category D in second or third trimester, pregnancy category C in first trimester; the IV formulation is not recommended in managing neonatal hypertension due to risk of acute renal failure and oliguria; PO administration may be useful in the neonatal hypertension long-term management

Drug Category: *Diuretic agents* -- Decrease plasma volume. Promote excretion of water and electrolytes by the kidneys. May be used as monotherapy or combination therapy to treat hypertension.

Drug Name	Chlorothiazide (Diuril) -- Inhibits reabsorption of sodium in distal tubules, causing increased excretion of sodium and water as well as potassium and hydrogen ions.
Adult Dose	0.5-1 g PO divided qd/bid
Pediatric Dose	5-15 mg/kg/dose PO bid
Contraindications	Documented hypersensitivity; anuria
Interactions	Thiazides may decrease effects of anticoagulants, antigout agents, and sulfonylureas; thiazides may increase toxicity of allopurinol, anesthetics, antineoplastics, calcium salts, loop diuretics, lithium, diazoxide, digitalis, amphotericin B, and nondepolarizing muscle relaxants
Pregnancy	D - Unsafe in pregnancy
Precautions	Caution in renal disease, hepatic disease, gout, diabetes mellitus, and erythematosus

Drug Name	Hydrochlorothiazide (Esidrix, HydroDIURIL) -- Inhibits reabsorption of sodium in distal tubules, causing increased excretion of sodium and water as well as potassium and hydrogen ions. Good second agent to add to ACE inhibitor or vasodilator therapy.
Adult Dose	25-100 mg PO qd; not to exceed 200 mg/kg/d
Pediatric Dose	2-3 mg/kg/d PO divided bid
Contraindications	Documented hypersensitivity; anuria; renal decompensation
Interactions	Thiazides may decrease effects of anticoagulants, antigout agents, and sulfonylureas; thiazides may increase toxicity of allopurinol, anesthetics, antineoplastics, calcium salts, loop diuretics, lithium, diazoxide, digitalis, amphotericin B, and nondepolarizing muscle relaxants
Pregnancy	D - Unsafe in pregnancy
Precautions	Caution in renal disease, hepatic disease, gout, diabetes mellitus, and erythematosus

Drug Name	Spironolactone (Aldactone) -- Potassium-sparing diuretic. Used for management of hypertension. May block effects of aldosterone on arteriolar smooth muscles.
Adult Dose	25-200 mg/d PO in 1-2 divided doses
Pediatric Dose	0.5-1.5 mg/kg/dose PO bid; not to exceed 3.3 mg/kg/d
Contraindications	Documented hypersensitivity; anuria; renal failure; hyperkalemia
Interactions	May decrease effect of anticoagulants; potassium and potassium-sparing diuretics may increase toxicity of spironolactone
Pregnancy	D - Unsafe in pregnancy
Precautions	Caution in renal and hepatic impairment

Drug Category: *Central agonists --* Decrease central adrenergic output.

Drug Name	Clonidine (Catapres) -- Stimulates alpha2-adrenoreceptors in brain stem, activating an inhibitory neuron, which, in turn, results in reduced sympathetic outflow. These effects result in a decrease in vasomotor tone and heart rate.
Adult Dose	Initial: 0.1 mg PO bid Maintenance: 0.2-1.2 mg/d in 2-4 divided doses; not to exceed 2.4 mg/d
Pediatric Dose	Not established for neonates, limited data suggest 0.05-0.1 mg/dose PO bid/tid
Contraindications	Documented hypersensitivity
Interactions	Tricyclic antidepressants inhibit hypotensive effects of clonidine; coadministration of clonidine with beta-blockers may potentiate bradycardia; tricyclic antidepressants may enhance hypertensive response associated with abrupt clonidine withdrawal; hypotensive effects of clonidine are enhanced by narcotic analgesics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Adverse effects include dry mouth and sedation; rebound hypertension with abrupt discontinuation; caution in cerebrovascular disease, coronary insufficiency, sinus node dysfunction, and renal impairment

Further Inpatient Care:

- Monitor BP regularly until the infant is ready for discharge from the NICU. Infants treated with ACE inhibitors or diuretics should have their renal function monitored periodically until discharge.

- Arrangements for home BP monitoring should be part of the discharge plan for any infant sent home on antihypertensive therapy. The optimal device for home BP measurements in an infant is a Dinamap or similar oscillometric device. A second choice is a Doppler device (only measures systolic BP).

Further Outpatient Care: Include BP measurement at all follow-up visits for infants with neonatal hypertension. In addition, monitor infants with BPD at discharge and those who had complicated NICU courses for the development of hypertension following discharge.

In/Out Patient Meds: Refer to preceding sections.

Transfer: Occasionally, infants may need to be transferred to specialized centers for advanced diagnostic or therapeutic procedures, such as angiography or vascular surgery.

Deterrence/Prevention: Although several studies have examined the role of placement of umbilical artery catheters (ie, low versus high lines), no definitive proof has emerged that changes in catheter placement can prevent thromboembolism and the subsequent development of hypertension.

Complications: As mentioned above, the long-term sequelae of neonatal hypertension on renal growth, renal function, and future BP are unknown at this time. Long-term effects related to certain antihypertensive medications (eg, ACE inhibitors, calcium channel blockers) are also unknown. These infants may need to be monitored closely even after their hypertension has resolved, particularly with respect to renal growth and the redevelopment of hypertension in later childhood.

Prognosis:

- The long-term prognosis for most infants with hypertension is quite good. For infants with hypertension related to an umbilical arterial catheter, the hypertension usually resolves over time. These infants may require increases in their antihypertensive medications in the first several months following discharge from the nursery as they undergo rapid growth. Following this, weaning the patient off antihypertensive therapy is usually possible by making no further dose increases as the infant continues to grow. Home BP monitoring by the parents is a crucially important component of this process. Provide proper equipment, either a Doppler or oscillometric device, for all infants discharged from the NICU on long-term antihypertensive medications. Such infants may benefit from referral to a comprehensive pediatric hypertension clinic if their primary care physicians are inexperienced in managing hypertension.

- Other forms of neonatal hypertension may persist beyond infancy. In particular, PKD and other forms of renal parenchymal disease may continue to cause hypertension throughout childhood. Infants with RVT may also remain hypertensive, and some of these children ultimately benefit from nephrectomy. Persistent or recurrent hypertension may also be observed in children who have undergone repair of renal arterial stenosis or coarctation of the aorta. Reappearance of hypertension in these situations should prompt a search for restenosis using the appropriate imaging studies.

- BP in newborns depends on a variety of factors, including gestational age, postnatal age, and birth weight. Hypertension can be observed in a variety of situations in the modern NICU and is especially common in infants who have undergone umbilical arterial catheterization. A careful diagnostic evaluation should lead to determination of the underlying cause of hypertension in most infants. Tailor treatment decisions, which may include intravenous therapy, oral therapy, or both, to the severity of the hypertension. Hypertension resolves in most infants over time, although a small number of infants may have persistent BP elevation throughout childhood.

<mark>Patient Education:</mark> Educate the parents of infants who develop hypertension requiring drug therapy about the expected effects and side effects of their infant's antihypertensive medications. In addition, arrange home BP monitoring equipment and educate the parents in its use prior to the infant's discharge from the NICU. Parents must monitor the BP of all infants discharged on antihypertensive medications on a regular basis (ie, usually daily); parents should call the physician if the infant's BP exceeds or falls below the target range.

MISCELLANEOUS	Section 9 of 10

<mark>Medical/Legal Pitfalls:</mark> Failure to diagnose or treat neonatal hypertension; major concern would be missing an underlying cause of hypertension such as renal disease that might require specific therapy.

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Neonatal Hypertension excerpt

Neonatal Resuscitation

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INTRODUCTION	Section 2 of 10

Neonatal resuscitation skills are essential for all health care providers who are involved in the delivery of newborns. The transition from fetus to newborn requires intervention by a skilled individual or team in approximately 10% of all deliveries. This figure is concerning because 81% of all babies in the United States are born in nonteaching nonaffiliated level I or II hospitals. In such hospitals, the volume of delivery service may not be perceived to economically justify the continuous in-hospital presence of personnel with high-risk delivery room experience as recommended by the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) in *Guidelines for Perinatal Care.*

Perinatal asphyxia and extreme prematurity are the 2 complications of pregnancy that most frequently require a complex resuscitation by skilled personnel. However, only 60% of asphyxiated newborns can be predicted antepartum. The remaining newborns are not identified until the time of birth. Additionally, approximately 80% of low birth weight infants require resuscitation and stabilization at delivery. Nearly one half of newborn deaths (many of which are extremely premature infants) occur during the first 24 hours following birth. A number of these early deaths also have a component of asphyxia and/or respiratory depression as an etiology. For the surviving infants, effective management of asphyxia in the first few minutes of life may influence long-term outcome.

Even though prenatal care is able to identify many potential fetal difficulties antepartum, allowing maternal transfer of care to the referral center, many women who experience preterm labor are not identified prospectively, therefore not allowing the appropriate maternal transfer to a tertiary perinatal center. Consequently, many deliveries of extremely premature infants occur in smaller hospitals. For this reason, all personnel involved in delivery room care of the newborn should be trained adequately in all aspects of neonatal resuscitation.

This chapter reviews the adaptation to extrauterine life and the steps necessary to optimally resuscitate neonates. Along with the necessary skills, the practitioner should approach any resuscitation with a good comprehension of transitional physiology and adaptation, as well as an understanding of the infant's response to resuscitation. Resuscitation involves knowing much more than an ordered list of skills and having a resuscitation team; it requires excellent assessment skills and a grounded understanding of physiology.

To decrease neonatal morbidity and mortality, the practitioner must be able to rapidly identify infants whose transition from an intrauterine to extrauterine physiology is delayed. Neonatal transition requires spontaneous breathing and successful cardiopulmonary changes, as well as other changes to independent organ system functions. A thorough understanding of normal transitional physiology leads to a better understanding of the needs of the infant who is experiencing difficulties and, therefore, should result in a more effective resuscitative effort.

Respiratory adaptation

Following birth, for the lungs to operate as a functional respiratory unit providing adequate gas exchange, the airways and the alveoli must be cleared of fetal lung fluid; an increase in pulmonary blood flow also must occur. In utero, most of the blood flow is shunted away from the lungs and directed to the placenta where fetoplacental gas exchange occurs. Fetal pulmonary vascular resistance is high, and the fetal systemic vascular resistance is low. Within minutes of delivery, the newborn's pulmonary vascular resistance may decrease by 8- to 10-fold, causing a corresponding increase in neonatal pulmonary blood flow. At birth, the lungs must transition rapidly to become the site for gas exchange, or cyanosis and hypoxia rapidly develop.

An understanding of the structure and function of the fetal pulmonary vascularity and the subsequent transition to neonatal physiology is important to assist with adaptation effectively during resuscitation. In utero, the lungs develop steadily from early in gestation. Respiratory development is classified into 4 stages (see Table 1). Based on this information, it is easy to see why infants neonates born before approximately 23-24 weeks' gestational age often do not have sufficient lung development for survival because of the absence of a capillary network adjacent to the immature ventilatory units.

Table 1. The Embryologic Stages of Lung Development

Stage	Gestational Age	Structure Development
Embryonic	5 wk	Bronchi develop and airway branching occurs. Pulmonary veins return to the left atrium.
Pseudoglandular	5-17 wk	Lungs take on a glandular appearance, and there is continual branching of the tracheal bronchial tree (ending at 18-19 wk gestation). Blood vessels and lymphatics begin to form. The diaphragm develops.
Canalicular	13-25 wk	Rich vascular supply develops and capillaries are brought closer to the airways. Primitive respiratory bronchioles begin to form.
Terminal air sac	24-40 wk	Alveoli appear and begin increasing in number. The blood-gas interface develops. Type II alveolar cells appear between 20-25 wk and start producing surfactant between 24-25 wk; however, normal intra-airway concentrations are not reached until approximately 34 wk.
Postnatal	40 wk to 8 y	Thinning of the alveolar sac linings and continued alveolar proliferation occur.

Fetal pulmonary physiology

The fetal lung is filled with approximately 20 mL fluid at term. Fetal airways, alveoli, and terminal saccules are open and stable at normal fetal lung volumes, distended by lung fluid. A constant flow of this fluid is secreted into the alveolar spaces throughout development, which contributes to the fetal amniotic fluid. Pulmonary and bronchial circulation also develops as the alveoli appear. Because of the compressive effect of the fetal lung fluid and the low partial pressure alveolar oxygen (paO_2) in utero, the pulmonary capillary bed and pulmonary blood vessels remain constricted. High vascular resistance and low pulmonary blood flow results.

The placenta provides the respiratory function for the fetus. Two major characteristics of placental circulation enable the placenta to maintain adequate oxygenation of the fetus. First, the placenta has a multivillous circulation that allows for maximum exposure of maternal and fetal blood. Second, several factors result in the lowering of maternal pH and increasing of fetal pH, which results in increased transfer of oxygen by the maternal and fetal hemoglobins.

Maternal blood, carrying oxygen on adult hemoglobin, releases oxygen to the fetal circulation and accepts both carbon dioxide and various byproducts of metabolism from the fetal circulation. These transfers result in a decrease in the maternal placental blood pH and a corresponding shift of the maternal oxygen-dissociation curve to the right, which results in a lower affinity of the hemoglobin for oxygen and the release of additional oxygen to the fetal hemoglobin. The corresponding shift in the fetal oxygen-dissociation curve to the left allows the fetal hemoglobin to bind more oxygen.

Fetal "breathing" begins at approximately 11 weeks and increases in strength and frequency throughout gestation. Fetal respirations are controlled by chemoreceptors located in the aorta and at the bifurcation of the common carotid. These areas sense both pH and partial pressure of carbon dioxide (pCO_2). A reflex response to altered pH and pCO_2 is present at approximately 18 weeks' gestation; however, the fetus is not able to regulate this response until approximately 24 weeks of gestation. Recent studies have indicated that this response cannot be elicited in utero even when the pH and pCO_2 are altered, leading researchers to believe that this response is suppressed in utero and is not activated until birth. Studies also suggest that the low paO_2 in utero may be the mechanism that inhibits continuous breathing, and when paO_2 is increased, continuous breathing is stimulated.

Neonatal pulmonary physiology

As discussed above, the fetal airways and alveoli are filled with lung fluid that needs to be removed before respiration. Only a portion of this fetal lung fluid is removed physically during delivery. During the thoracic squeeze, 25-33% of the fluid may be expressed from the oropharynx and upper airways, although this amount may be markedly less. Thoracic recoil allows for passive inspiration of air into the larger bronchioles. Effective transition requires that any remaining liquid be quickly absorbed to allow effective gas exchange.

A recent study showed that the decrease in lung fluid begins during labor. Using lamb fetuses, the researchers were able to show that the production of lung fluid is decreased on onset of labor. The subsequent reduction in lung fluid was associated with improved gas exchange and acid-base balance. In addition, labor is associated with an increase in catecholamine levels that stimulate lymphatic drainage of the lung fluid. These findings could account for the increased incidence of transient tachypnea of the newborn after a repeat cesarean section without labor. After birth, lung fluid is removed by several mechanisms, including evaporation, active ion transport, passive movement from Starling forces, and lymphatic drainage. Active sodium transport by energy-requiring sodium transporters, located at the basilar layer of the pulmonary epithelial cells, drive liquid from the lung lumen into the pulmonary interstitium where it is absorbed by the pulmonary circulation and lymphatics.

The first breath must overcome the viscosity of the lung fluid and the intraalveolar surface tension. This first breath must generate high transpulmonary pressure, which also helps drive the alveoli fluid across the alveolar epithelium. With subsequent lung aeration, the intraparenchymal structures stretch

and gasses enter the alveoli, resulting in increased paO_2 and pH. The increased paO_2 and pH result in pulmonary vasodilation and constriction of the ductus arteriosus.

Lung expansion and aeration also is a stimulus for surfactant release with the resultant establishment of an air-fluid interface and development of functional residual capacity (FRC). Normally, 80-90% of FRC is established within the first hour of birth in the term neonate with spontaneous respirations. The pulmonary vascularity is stimulated to dilate by chemical mediators, nitric oxide, and prostaglandins. Nitric oxide is released when pulmonary blood flow and oxygenation increases. The formation of certain prostaglandins, such as prostacyclin, is induced by the presence of increased oxygen tension. Prostacyclin acts on the pulmonary vascular smooth muscle bed to induce pulmonary vasodilation. Prostacyclin has a short half-life in the bloodstream and, therefore, does not affect the systemic circulation.

Two major physiologic responses have been described for the initial lung inflation in the neonate.

The first response is the "rejection response," in which the neonate responds to positive pressure lung inflation with a positive intraesophageal pressure to resist the inflation. That is to say, the infant actively resists attempts to inflate the lungs by generating an active exhalation. This response acts to not only reduce lung inflation, but also may cause high transient inflation pressures.

The second response is "Head's paradoxical response" in which the neonate responds to positive pressure lung inflation with an inspiratory effort, causing a negative intraesophageal pressure. This inspiratory effort, with the resultant negative, pressure produces a fall in inflation pressures but results in a transient increase in tidal volume.

Of course, the neonate may demonstrate no response to the inflation attempt, not generating any change in intraesophageal pressure during the positive pressure inflation, and passive inflation subsequently results. It is important to recognize that these physiologic responses to positive pressure inflation in the delivery room may cause large variability in the tidal volume and intrapulmonary pressures, despite constant delivery of inflation pressure.

Stimuli for the first breath may be multifactorial. The environmental changes that occur with birth (eg, tactile and thermal changes, increased noise and light) activate a number of sensory receptors that may help initiate and maintain breathing. Clamping of the cord removes the low resistance placenta, causing an increase in systemic vascular resistance and consequently causing an increase in both systemic blood pressure and pulmonary blood flow. Certain evidence also suggests that the increased arterial paO_2 following the initial breaths may be responsible for the development of continuous breathing via hormonal or chemical mediators that are still undefined.

When the newborn lungs fill with air, the paO_2 should rise gradually. In term infants with a persistent hypoxia, an initial increase in ventilation occurs, followed by a decrease in ventilation occurs. This effect is even more profound in premature infants whose CNS is not as mature. The carotid bodies and peripheral chemoreceptors located at the bifurcation of the common carotids are stimulated during hypoxia to increase minute ventilation. In asphyxiated infants who cannot increase minute ventilation (eg, because of extreme prematurity or sedation), profound bradycardia may result.

Cardiovascular adaptation

Fetal circulation

To understand the cardiovascular changes that occur in the neonate at birth, it is essential to have an understanding of normal fetal circulation. The umbilical vein carries the oxygenated blood from the placenta to the fetus. Blood flow in the umbilical vein divides at the porta hepatis, with 50-60% of the blood passing directly to the inferior vena cava and the remainder of the blood passing into the portal circulation. This portal blood flow perfuses the liver and then passes into the inferior vena cava.

Flow studies have revealed that relatively little mixing of the blood occurs in the inferior vena cava from these 2 sites. The more highly oxygenated blood, which has bypassed the liver, streams into the inferior vena cava to pass preferentially through the patent foramen ovale into the left atrium. The desaturated blood returning from the liver and lower body streams into the inferior vena cava to the right atrium. In the right atrium, it mixes with blood returning from the coronary sinus and superior vena cava and flows into the right ventricle. The more highly oxygenated blood that crosses the foramen ovale mixes with the small amount of pulmonary venous return and then crosses the mitral valve into the left ventricle.

The output from the left ventricle passes into the ascending aorta to the heart, brain, head, and upper torso. The less saturated blood from the right ventricle passes into the pulmonary arteries. Because the pulmonary vessels are constricted and highly resistant to flow, only about 12% of the blood enters the pulmonary veins. The remainder of the blood takes the path of least resistance through the patent ductus arteriosus into the descending aorta. Approximately one third of this blood is carried to the trunk, abdomen, and lower extremities, with the remainder entering the umbilical artery where it is returned to the placenta for reoxygenation.

Neonatal circulation

The aeration of the lung results in an increase in arterial oxygenation and pH, with a resulting dilation of the pulmonary vessels. Decompression of the capillary lung bed further decreases the pulmonary vascular resistance. There is also a corresponding decrease in right ventricular and pulmonary artery pressures. The decrease in pulmonary vascular resistance leads to an increase in blood flow to the lungs and in pulmonary venous return. Clamping of the umbilical cord removes the low resistance placental vascular circuit and causes a resultant increase in the total systemic vascular resistance with a resultant increase in left ventricular and aortic pressures. The increased systemic vascular resistance, combined with the decreased pulmonary vascular resistance, reverses the shunt through the ductus arteriosus (from right-to-left shunting to left-to-right shunting) until the ductus completely closes.

All of these peripartum events result in closure of the other fetal shunts. With the decrease in right atrial pressure and the increase in left atrial pressure, the "flap-valve" foramen ovale is pushed closed against the atrial septum. This functional closure at birth is followed by anatomical closure that usually occurs at several months of age. The ductus venosus closes because of the clamping of the umbilical cord, which terminates umbilical venous return. Functional mechanical closure of the ductus venosus is accomplished by the collapse of the thin-walled vessels. Anatomical closure subsequently occurs at approximately 1-2 weeks. The constriction and closure of the patent ductus arteriosus is accomplished by contractile tissue within the walls of the ductus arteriosus. The contraction of this tissue is dependent on both the increase in arterial oxygen related to the onset of spontaneous respirations and a fall in circulating prostaglandin E_2 (PGE2).

The placenta is a major site of fetal PGE2 production, thus the removal of the placenta from the circulation causes circulating PGE2 concentration to decrease markedly. Further reduction occurs in the concentration of PGE2 because of increased blood flow to the lungs (the site of PGE2 metabolism). Functional closure of the ductus generally occurs within 72 hours of life, with anatomical closure by age 1-2 weeks. In summary, functional postnatal circulation generally is established within 60 seconds; however, completion of the transformation can take up to 6 weeks.

Response to asphyxia

The fetus or newborn that is subjected to asphyxia begins a "diving" reflex (so termed because of certain similarities to the physiology of diving seals) in an attempt maintain perfusion and oxygen delivery to vital organs. Pulmonary vascular resistance increases, leading to a decreased pulmonary blood flow and increased blood flow directly to the left atrium. Systemic cardiac output is redistributed, with increased flow to the heart, brain, and adrenal gland and decreased flow to the rest of the body. Early in asphyxia systemic blood pressure increases. However, with ongoing hypoxia and acidosis, the myocardium fails and the blood pressure begins to decrease, leading to tissue ischemia and hypoxia.

Infants who are undergoing asphyxia have an altered respiratory pattern. Initially, they have rapid respirations. These respiratory efforts eventually cease with continued asphyxia (termed primary apnea). During primary apnea, the infant responds to stimulation with reinstitution of breathing. However, if the asphyxia continues, the infant then begins irregular gasping efforts, which slowly decrease in frequency and eventually cease (termed secondary apnea).

Infants who experience secondary apnea do not respond to stimulation and require positive pressure ventilation to restore ventilation. Primary and secondary apnea cannot be clinically distinguished. Therefore, if an infant does not readily respond to stimulation, positive pressure ventilation should be instituted as outlined in the Neonatal Resuscitation Program guidelines. If an infant is experiencing primary apnea, the stimulation of the ventilatory efforts cause the infant to resume breathing. If the infant is in secondary apnea, positive pressure ventilation is required for a period. The longer the infant is asphyxiated, the longer the onset of spontaneous respirations is delayed following the initiation of effective ventilation through the use of positive pressure ventilation.

A number of sources of information concerning the training of skills and procedures that are needed for the delivery room resuscitation of the newborn are available. One highly respected source of information concerning the preparation and practice of neonatal resuscitation is the Neonatal Resuscitation Program, which has been codeveloped by the AAP and the American Heart Association. The following sections contain a review of resuscitation procedures in a format that is similar to the format used by the Neonatal Resuscitation Program. Completion of the Neonatal Resuscitation Program should be considered for all hospital personnel who may be involved in the stabilization and resuscitation of neonates in the delivery room. To develop true expertise, additional supervised time with skilled personnel is essential.

Although the current program for neonatal resuscitation is considered a highly respected reference, it is important that more research continue to evaluate the effectiveness of the techniques of neonatal resuscitation. The Neonatal Resuscitation Program has evolved and will continue to evolve with new data from clinical studies and basic physiologic research.

Anticipation

The goals of resuscitation are to assist with the initiation and maintenance of adequate ventilation and oxygenation, adequate cardiac output and tissue perfusion, and normal core temperature and serum glucose. These goals may be attained more readily when risk factors are identified early, neonatal problems are anticipated, equipment is available, personnel are qualified and available, and a care plan is formulated.

Causes of depression and asphyxia

A large number of antepartum and intrapartum maternal conditions carry an increased risk for intrapartum asphyxia. A number of excellent texts review the extensive medical and surgical problems of the obstetrical patient. It is not within the purview of this article to review this topic.

Equipment

The delivery room should be equipped with all the necessary tools to successfully resuscitate any gestational age newborn. The equipment should include a radiant warmer, warmed blankets, a source of oxygen, instruments for visualizing and establishing an airway, a source of regulated suction, instruments and supplies for establishing intravenous access, trays equipped for emergency procedures, and drugs that may be useful in resuscitation. The following table outlines the minimum equipment necessary for each of these categories.

Table 2. Equipment for Neonatal Resuscitation

Respiratory	Suction	Fluids	Drugs	Procedures
- Oxygen supply - Assorted masks - Neonatal Bag - Respiratory tubing - Manometer - Endotracheal tubes (2.5-4) - Tape and scissors - Laryngoscope (0 and 1 sized blades) - Extra bulbs and batteries	- Bulb syringe - Regulated mechanical suction - Suction catheters (6F, 8F, 10F) - Suction tubing - Suction canister - Replogle or Salem pump (10F catheter) - Feeding tube (8F catheter) - Syringe, catheter tipped, 20 mL -Meconium aspirator	- IV catheters (22 g) - Tape and sterile dressing material - D10W - Isotonic sodium chloride solution saline - T-connectors - Syringes, assorted (1-20 mL)	- Epinephrine (1:10,000) - Pediatric naloxone (0.4 mg/mL) - Sodium bicarbonate (0.5 mEq/mL)	- Umbilical catheters (2.5F, 5F) - Chest tube (10F catheter) - Sterile procedure trays (eg, scalpels, hemostats, forceps)

Trained personnel

For all deliveries, at least one person should be present who is skilled in neonatal resuscitation and has responsibility for only the infant. Personnel should be available who are capable of performing a complete resuscitation, including intubation, medication administration, and emergency procedures. If the delivery is identified as high risk, 2 or more skilled individuals should be assigned for the infant at delivery. Remember that staff trained in neonatal resuscitation need to apprentice with experienced personnel for some time before they can be independently responsible for an infant at a delivery.

NEONATAL RESUSCITATION

Thermoregulation

It is essential to prevent heat loss during the resuscitation. Intrauterine thermoregulation is passive, with no use of calories or oxygen by the fetus. This intrauterine thermoregulation allows for maximal intrauterine growth without fetal energy expenditure for thermal homeostasis. Brown fat storage begins during the third trimester. It is the brown fat that is used for heat production in the newborn period.

Several factors lead to increased heat losses in the newborn infant. The neonate has a large skin surface area–to–body weight ratio, which increases heat and fluid evaporative loss. The fluid loss from the skin (not due to sweating but caused by direct transdermal water loss) results in massive heat loss. The thin skin with blood vessels that are near the surface provides poor insulation, leading to further heat loss. Additionally, the newborn infant (especially if premature) has a limited capacity to change

body position for heat conservation. Animals ordinarily attempt to decrease heat loss by decreasing exposed surface area. This reduction in exposed surface area is accomplished by assuming a flexed position; however, premature, critically ill, and depressed infants are unable to accomplish flexed positioning.

Neonates have a very limited capacity for metabolic heat production. The newborn infant has limited energy stores, largely because of decreased subcutaneous fat and brown fat stores. This paucity of fat stores is more pronounced in premature and growth-retarded infants. Additionally, infants do not shiver effectively, which is a major source of heat production in the adult. The main source of heat production in the newborn is nonshivering thermogenesis.

Thermoreceptors in the face have a marked sensitivity to heat and cold. Stimulation by cold leads to norepinephrine production and thyroid hormone release causing brown fat to be metabolized. Brown fat is highly vascularized and stored in pockets around the neonate's body. When brown fat is metabolized, triglycerides are hydrolyzed to fatty acids and glycerol. Additionally, glycolysis is initiated and glycogen stores are used; both processes resulting in glucose production. Heat is produced as a byproduct of the increased metabolic rate and oxygen consumption.

Infants who experience heat loss have an increased metabolic rate and use more oxygen. Increased oxygen consumption can be dangerous in infants who are experiencing respiratory compromise. The addition of cold stress in infants who are poorly oxygenated potentially can lead to a change from aerobic to anaerobic metabolism. This change in metabolism may lead to tissue hypoxia and acidosis because of the buildup of metabolic byproducts such as lactate. Because of the inefficiency of anaerobic metabolism, the infant uses up glucose and glycogen reserves rapidly and still produces only a limited amount of energy for heat production. Therefore, cold stress can lead to both metabolic acidosis and hypoglycemia.

Based on this information, it is essential to prevent excessive heat loss in the delivery room. Newborns should be dried with prewarmed blankets or towels and placed on a prewarmed heat source. Open bed warmers, which use radiant heat, are used in most delivery rooms. They provide warmth during resuscitation and for any subsequent invasive procedures. It is important for the practitioner to keep in mind that this source of heat does not protect the infant from evaporative heat loss but, instead, encourages evaporative heat losses.

It is also necessary to consider the environmental temperature in relationship to controlling heat loss in the newborn. As a fetus, the thermal environment is regulated precisely by the mother's core temperature, and heat losses are nonexistent. Following delivery, even when drying and a radiant heat source are used, infants continue to lose large amounts of heat. This occurs by convective and evaporative heat loss. When the environmental air is less than the neutral thermal environment for the infant being resuscitated, this cooler air causes further thermal losses.

Heat losses are related to the differences both in water concentrations between the skin and the air as well as the absolute temperature gradient. The primary goal in neonatal thermoregulation is to prevent heat loss, compared to later rewarming a cold infant. Ideally, an area (eg, a stabilization room) should be separate from the operating room (OR) or labor room that allows special attention to the unusual thermal and environmental needs of the newborn high-risk infant. This stabilization area should be kept as warm as possible, balancing the requirements of the high-risk infant with the comfort of the adult staff in that area. Centers with such stabilization areas generally quote temperature goals in the range of 80-88°F.

Another common source of heat loss in the newborn infant undergoing resuscitation is the use of unheated nonhumidified oxygen sources for the bag-valve-mask device. Inspired gasses that are sent to the lungs are subsequently heated and humidified by the infant, thus resulting in massive heat exchange and insensible water loss. Therefore, whenever possible, warmed and humidified gasses should be provided in the resuscitation area. Alternatively, the intubated and ventilated infant should be placed on a heated ventilator circuit as soon as is feasible.

Airway management

Once the infant is placed in a heated environment, the infant should be positioned to open the airway, and the mouth and nose should be suctioned. A bulb syringe should be used for the initial suctioning. Infants have a vagal reflex response to sensory stimulation of the larynx, which may induce hypotension, bradycardia, swallowing, and apnea. Therefore, the act of suctioning the airway with a catheter because of extremely thick or meconium-stained fluids may cause profound central apnea, bradycardia, and laryngospasm. This reflex bradycardia may be profound. Therefore, deep suctioning of the trachea should be limited to infants who have thick mucous that cannot be removed by bulb syringe or used for the aspiration of aspirate stomach contents, when necessary.

The instillation of saline into the trachea also has been shown to stimulate the afferent sensory neurons leading to these sequelae and has no place in the immediate resuscitation period. Lung inflation has been shown to reverse the effects of vagal stimulation. Vigorous suctioning of the nares with a catheter can lead to edema with resulting respiratory distress after the infant leaves the delivery room. Wall suction should be set so that pressures do not exceed 100 mm Hg.

Stimulation

Drying and suctioning often is enough stimulation to initiate breathing; however, if more vigorous stimulation is necessary, slapping the soles of the feet or rubbing the back may be effective. The back should be visualized briefly for any obvious defect in the spine before beginning these maneuvers. If there is no response to stimulation, it may be assumed the infant is in secondary apnea, and positive pressure ventilation should be initiated. At this point, the infant's respiratory rate, heart rate, and color should be evaluated. Most infants do not require further intervention.

Supplemental oxygen

Infants who have a sustained heart rate more than 100 beats per minute (BPM) and adequate respiratory effort but who remain cyanotic should receive blow-by oxygen via oxygen tubing or a mask. It is arguably advantageous to provide heated, humidified oxygen if possible, but this is rarely available in the delivery room environment. Supplemental oxygen should be initially provided with a FiO_2 of 1 at a flow rate of 8-10 L/min. If supplemental oxygen is to be provided for a prolonged period, then heated humidified oxygen should be supplied via an oxy-hood with the FiO_2 adjusted to result in pulse-oximetry saturations of 92-96% in the term infant and 88-92% in the preterm infant.

Positive pressure ventilation

For a number of reasons (discussed above), it can be difficult for the infant to clear fluid from the airways and establish air-filled lungs. Initial respiratory efforts may need to be augmented by the addition of either continuous positive airway pressure (CPAP) or positive pressure ventilation. The addition of positive pressure aids in the development of functional residual capacity and is needed more commonly in premature infants. Mechanical lung inflation also is important to reverse persistent bradycardia in an apneic asphyxiated infant.

Infants with adequate respirations who are having respiratory distress manifested by tachypnea, grunting, flaring, retracting, or persistent central cyanosis may benefit from CPAP. If the infant is apneic, has inadequate respiratory efforts, or a heart rate less than 100 BPM, then positive pressure ventilation should be initiated immediately. The bag must be equipped to deliver positive end-expiratory pressure and the appropriately sized mask should be applied firmly to the face.

Some infants respond to brief mechanical ventilation and subsequently begin independent ventilation; others need continued ventilatory support. It is essential that sufficient, but not excessive, initial pressure be used to adequately inflate the lungs, or bradycardia and apnea will persist. A pressure manometer always should be used with a pressure release valve limiting the positive pressure to 30-35 cm H_2O. To provide adequate distending pressure, the infant must be positioned properly and the upper airway cleared of secretions; the mask must be the correct size and form a tight seal on the face.

While providing assisted breaths, look for a rise and fall in the chest and an immediate increase in heart rate. If no chest rise occurs, either the airway is blocked or insufficient pressure is being generated by the squeezing of the bag. Ventilatory rates of 40-60 breaths per minute should be provided initially, with proportionally fewer assisted breaths provided if the infant's spontaneous respiratory efforts increase. Although not studied extensively, it has been reported that the initial inflation of the newborn's lungs with either slow-rise or square wave inflation to 30 cm H_2O pressure for approximately 5 seconds results in more rapid formation of a functional residual capacity.

It should be remembered that, at the moment of delivery and first, breath the neonatal lung is converting from a fetal, nonaerated status to a neonatal status. The neonatal lung has a requirement for gas exchange, and this requires the development of a functional residual capacity because of the resorption of lung fluid and the resolution of most of the atelectasis. Therefore, it is logical to conclude that initial slow ventilation with more prolonged inspiratory times may be useful to assist in this task, balanced with the avoidance of inappropriate inspiratory pressures.

However, these observations are counterbalanced with data showing that an increased risk of chronic lung disease in infants with very low birth weight is associated with centers who initiate mechanical ventilation more frequently. Therefore, prospective, randomized clinical trials are urgently needed to resolve several issues related to the timing of surfactant administration, use of various forms of positive end-pressure (CPAP), and/or initiation of mechanical ventilation.

Intubation

Infants may require tracheal intubation if direct tracheal suctioning is required, effective bag-mask ventilation cannot be provided, congenital diaphragmatic hernia is suspected, or a prolonged need for assisted ventilation exists. An appropriate blade (Miller size 0-1) should be chosen depending on the size of the infant. Premature infants may be more easily intubated with a size 0 blade, and term infants require a size 1 blade. An appropriate size of endotracheal tube (ETT) should be chosen based on the weight of the infant (Table 3).

Upon insertion of the ETT, the tube should be advanced until the vocal cord guide mark near the distal tip of the tube is visualized to be slightly past the vocal cords. This guide mark is positioned a variable distance from the distal tip (depending on the ETT size) and is designed to result in the placement of the tube tip between the vocal cords and the carina at the bifurcation of the right and left mainstem bronchi. The ETT should then be secured and cut to an appropriate length to minimize dead space and flow resistance.

Another estimate of correct placement of the ETT is to use the weight of the infant in kilograms plus 6 to arrive at the number of centimeters at which the tube should be secured at the lip (Table 3). Before securing the ETT, the infant should be assessed for equal bilateral breath sounds with maintenance of oxygenation. ETT position is confirmed with a chest x-ray. Free flow oxygen should be provided throughout the procedure, and then effective ventilation via the bag or ventilator after the infant is intub

Table 3. ETT Size and Measurement at Lip According to Infant Weight

Weight	ETT size	ETT measurement at lip
<1000 g	2.5 ETT	7 cm at the lip
1000-2000 g	2.5-3 ETT	8 cm at the lip
2000-3000 g	3-3.5 ETT	9 cm at the lip
>3000 g	3.5-4 ETT	10 cm at the lip

Cardiovascular support and chest compressions

Most infants who present at delivery with a heart rate less than 100 BPM respond to effective ventilatory assistance with a rapid increase in heart rate to normal rates. In contrast, if an effective airway and effective ventilation is not established, further support is not effective. Chest compressions should be initiated following only 30 seconds of effective positive pressure ventilations if the heart rate remains less than 60 BPM.

An assessment of the heart rate can be obtained by palpating the umbilical stump at the level of insertion of the infant's abdomen or by direct auscultation of the precordium. Chest compressions should be discontinued as soon as the heart rate is higher than 60 BPM. Chest compressions may be performed either by circling the chest with both hands and using a thumb to compress the sternum or by supporting the infant's back with one hand and using the tips of the middle and index finger to compress the sternum. The thumb technique is preferred because of improved depth control during compressions, however the 2-finger technique can be used.

Pressure should be applied to the lower portion of the sternum depressing it 0.5-0.75 inches at a rate of 90 per minute. One ventilation should be interposed after every 3 chest compressions allowing for 30 breaths per minute. The recommended ratio of chest compressions to ventilations is 3:1. Evaluate the heart rate and color every 30 seconds. Infants who fail to respond may not be receiving effective ventilatory support, thus it is imperative to be evaluating the ventilation of the infant constantly.

Medications

Neonatal resuscitation drugs should be stocked in any area in which neonates may be resuscitated, including each delivery and stabilization area, as well as the emergency room. Personnel should be familiar with neonatal medications, concentrations, dosages, and routes of administration. Drugs currently recommended include epinephrine (1:10,000), sodium bicarbonate (0.5 mEq/mL), and isotonic sodium chloride solution (0.9%) as a volume expansion agent.

Epinephrine use should be considered only when ventilation has been established and provided for at least 30 seconds. The only exception to this rule may be in infants who are born without a detectable pulse or heart rate. The current recommended dose for epinephrine is 0.01-0.03 mg/kg (0.1-0.3 mL of the 1:10,000 solution) via IV or endotracheal route.

No studies are currently available that assess the use of higher dosages or repeated dosing in neonates. Epinephrine administered via the ETT either should be diluted into 1 mL of saline or should be followed immediately by 1-2 mL of saline to ensure the distribution and absorption of the small volume of drug. If an umbilical venous catheter is used for medication administration, the catheter should be inserted only until blood flow is obtained, usually 3-5 cm. Because the dosing recommendations for epinephrine have included the endotracheal route of administration, the need for emergent placement of umbilical venous catheters has been reduced markedly in the delivery room.

In an editor's note commenting on an article entitled *Cardiopulmonary Resuscitation in the Delivery Room,* Catherine DeAngelis writes, "....check the airway (optimize respiratory support) one more time before compressing the chest. More often than not, you and the infant can then take deep breaths, and you can beat your own chest instead of the infant's."

The article reported that approximately one third of infants in their study with neonatal depression at birth had associated fetal acidemia. However, in the remaining infants without fetal acidemia, chest compressions were initiated as a consequence of improper or inadequate ventilatory support at birth. In this population of infants without the initial acidemia, chest compressions and/or epinephrine therapy was ineffective. The heart rate only improved after either effective tracheal intubation established a patent airway and/or after incremental increases in positive-pressure ventilation exceeded the opening pressure of the lungs, establishing ventilation. This study and others continue to reinforce the primary importance of the establishment of effective ventilation—for without ventilation, other therapies, including medications, will not be effective in establishing adequate heart rate and perfusion.

Sodium bicarbonate has been recommended in the delivery room to reverse the effects of metabolic acidosis related to hypoxia and asphyxia. However, recent studies show that 0.9% saline provides better cardiac and blood pressure support to correct both the acidosis and the underlying etiology of the metabolic acidosis. Sodium bicarbonate should not be used until adequate ventilation is obtained because of the concomitant production of carbon dioxide following the use of this drug. If sodium bicarbonate is used in the face of a persistent respiratory acidosis and elevated pCO_2, the acidosis will not be corrected.

To correct a documented or presumed metabolic acidosis following the establishment of adequate ventilation, a dose of 2 mEq/kg IV may be administered. If the base deficit is known, then a more precise dose can be administered. Use of sodium bicarbonate in the delivery room has been associated with an increased incidence of intraventricular hemorrhage in very low birthweight infants; thus, caution is advised.

Volume expansion may be used in neonates with evidence of acute blood loss or with evidence of shock of any etiology. In general, the neonatal heart responds well to the increase in preload at the atrial level caused by the volume expansion. Hypovolemia may be masked in a newborn infant because of the significant peripheral vasoconstriction caused by the elevated catecholamines following delivery. Systolic blood pressure also may be elevated falsely with pain.

The current recommendations for volume expansion during resuscitation include isotonic sodium chloride solution or lactated ringers, 5% albumin, Plasmanate, or O-negative blood that has been cross matched with the mother. However, because of the advantages of long shelf life, low cost, ready availability, and the lack of evidence of the superiority of other agents, isotonic sodium chloride solution is the most frequently used agent for volume expansion. The currently recommended dosage for volume expansion is 10 mL/kg IV over 5-10 minutes, and it may be infused more cautiously in extremely preterm infants.

Naloxone is an opioid antagonist and should be used only in neonates exhibiting respiratory depression in the setting of a laboring mother who has received iatrogenically administered opioids within 4 hours of delivery. Naloxone should not be administered to neonates who are not in distress or to neonates with another predisposing perinatal complication to explain the distress.

The great majority of neonates born to mothers who receive opioids do not receive and do not require naloxone administration. The intramuscular administration of naloxone should not be used as a substitute for other forms of vigorous stimulation. Additionally, the administration of naloxone to a neonate who is born to a mother with long-term use of opiates or opioids (eg, heroin, methadone) may induce seizures secondary to acute withdrawal. Remember that some opioid agents have a longer half-life in the neonate than naloxone, which may lead to a later recurrence of respiratory depression in the nursery. Therefore, any infant who has received naloxone should be monitored for the recurrence of respiratory depression for 12 hours. Naloxone dosage is 0.1 mg/kg of the 0.4-mg/mL parenteral solution administered intravenously, endotracheally, or intramuscularly.

THE IMMEDIATE POSTRESUSCITATION PERIOD	Section 6 of 10

Maintenance of airway and ventilation

The goal of delivery room management is to stabilize the airway and assure effective oxygenation and ventilation. Once initial lung recruitment is obtained, it is essential to avoid overdistension. Breaths delivered by bag-mask ventilation may be difficult to control and may result in overdistension and consequent pneumothorax or pneumomediastinum. Additionally, the unheated nonhumidified oxygen can quickly cool the infant via the large surface area of the lungs, resulting in hypothermia. Therefore, mechanical ventilation should be initiated as soon as possible once the infant is stabilized.

Although the ideal mode of assisted ventilation is controversial, it is essential to provide adequate positive end-expiratory pressure to prevent atelectasis, while at the same time preventing overinflation.

Once the appropriate functional residual capacity is obtained, it is essential to use the lowest support possible to allow for adequate oxygenation and ventilation. Oxygen saturations should be monitored continually and arterial blood gas analyses performed as needed during the initial stabilization period. Saturations should be maintained in the 90-96% range for the term infant and 88-92% in the preterm infant after the initial stabilization.

Fluid and electrolyte management

In utero, nutrients are provided in their basic form. Glucose is the major energy substrate of the fetus. Fetal glucose uptake parallels maternal blood glucose concentration. The liver, heart, and brain receive the greatest cardiac output and, therefore, the greatest amount of glucose. The fetus uses glucose, lactate, and amino acids to store fuels that are used during transition. Neonates must develop a homeostatic balance between energy requirements and the supply of substrate as they move from the constant glucose supply of fetal life to the normal intermittent variations in the availability of glucose and other fuels. With the clamping of the cord, the maternal glucose supply is cut off. A fall in blood glucose during the first 2-6 hours of life occurs in healthy newborns. The blood glucose usually reaches a nadir and stabilizes at 50-60 mg/dL.

The immediate goal of fluid and electrolyte support following resuscitation is to maintain an appropriate intravascular volume and to provide glucose homeostasis and electrolyte balance. The neonatal cardiovascular system is very sensitive to preload, requiring adequate intravascular volume to maintain adequate cardiac output. Therefore, expansion of intravascular volume with appropriate solutions (eg, isotonic sodium chloride solution) often is considered in the neonate with inadequate blood pressure or perfusion.

Additionally, as discussed in previous sections, hypoglycemia may occur rapidly in critically ill or premature infants. Blood glucose determinations should be performed as soon as possible and a continuous infusion of glucose should be started at 4-6 mg/kg/min for those infants who are not able to tolerate enteral feedings. Dextrose boluses should be limited to symptomatic infants because they may result in transient hyperosmolarity and rebound hypoglycemia. Electrolytes, such as sodium, potassium, and chloride, should not be added initially because the fluid shifts from other body compartments allow for adequate electrolyte supply until adequate renal function is documented.

The practitioner should monitor the weight, clinical hydration status, urine output, and serum sodium concentrations closely because inappropriate fluid overload or restriction can lead to increased mortality and morbidity. Taking the infant's environment into account when calculating fluid requirements is very important. Fluid rates may be started at 60-80 mL/kg/d for the infant in a humidified incubator, while fluid rates may be much higher for the infant in a dry radiant warmer environment.

Preparation for transport

Preparation of the infant for transfer to a remote nursery for subsequent care requires several considerations. First, it is important to complete all the routine care that is required of newborn infants. These basics of care may be neglected in the rush to prepare the infant for transport, with potentially disastrous results. Following resuscitation, care must be taken to secure all lines, tubes, catheters, and leads for transport. Monitoring in the transport environment is only possible with functioning leads in place, which is frequently difficult. Rapid and complete documentation of the resuscitation and subsequent therapies also is required for future caretakers. Please refer to Transport of the Critically Ill Newborn for further information.

This section is devoted to congenital neonatal conditions that may present in the delivery room and that may alter the resuscitation. The presentation of the disease and the immediate resuscitative efforts are discussed. Please refer to other specific chapters for further information on these disease processes.

Extreme prematurity

Premature infants have special needs that must be considered during the critical period immediately following delivery if mortality and morbidity are to be decreased in this group. This population of infants is at increased risk for respiratory failure, insensible water losses, hypoglycemia, and intraventricular hemorrhages. It is impossible to adequately review the many difficulties of extreme prematurity in this section, but special concerns regarding the care of these infants during the resuscitation period is discussed.

Insensible water loss in the premature infant is increased secondary to the infant's poorly cornified epidermis and an immature stratum corneum, which presents little barrier to evaporative heat loss. The stratum corneum is not functionally mature until 32-34 weeks' gestation. Differences in skin maturity, prenatal nutritional status, ventilation requirements, and environmental conditions all may influence the magnitude of insensible water loss that occurs following birth.

The skin is the most important route for water depletion after delivery of the extremely immature infant. Transepidermal water loss (TEWL) is highest at birth in infants who are born before 28 weeks' gestation and decreases slowly with advancing gestational age. Despite declines in TEWL with advancing age, infants born before 28 weeks' gestation continue to have increased TEWL for 4-5 weeks following birth, compared to infants born at term. Because of high evaporative loss with the accompanying heat loss, the ability to achieve and maintain thermoregulation is compromised further. The skin barrier dysfunction increases the risk for infection, especially because of organisms that colonize the skin surface (eg, staphylococcal species). This thin skin barrier also places the extremely immature infant at risk for toxicities from topically applied substances. Additionally, skin integrity is disrupted easily by the use of adhesives, which should be limited in premature infants.

Premature infants need increased fluid administration rates initially if they are on radiant warmers for a prolonged period. With increased parenteral fluid administration using dextrose-containing fluids, the dextrose needs to be monitored closely to ensure euglycemia. Placing infants in a humidified environment decreases transepidermal water loss, improves the maintenance of body temperature, and does not delay skin maturation. Measures to decrease insensible water loss should be initiated at delivery. Because radiant warmers are used routinely at deliveries because of a need for maximal patient access, infants less than 1000 g should have a plastic blanket or other barrier applied to decrease evaporative water loss until they can be placed in a humidified environment. However, care should be taken to ensure that the barrier does not block the transmission of the radiant heat source.

Premature infants are at risk for intraventricular hemorrhages and periventricular leukomalacia (PVL) secondary to their immature cerebral vascular regulation and the persistence of the germinal matrix. Ventricular hemorrhage and periventricular leukomalacia often lead to serious permanent neurodevelopmental disabilities. Prevention or reduction of the severity of these disorders may begin in the delivery room. Mechanical ventilation and fluid administration must be managed cautiously in this group of infants. Volume expansion should only be administered in the face of true hypotension. It is essential to know normal blood pressure values for infants of various gestational ages. Volume expansion in the face of normal blood pressure increases the risk of IVH.

Additionally, when administering hyperosmolar medications (eg, sodium bicarbonate), slow administration is important. Mechanical ventilation may lead to harmful fluctuations in cerebral blood flow, especially when pCO_2 and pH are altered rapidly. Rapid alterations in pCO_2 and pH result in acute fluctuations in the cerebral blood flow of the premature infant with immature cerebral vascular autoregulation.

Premature infants are also at high risk for volutrauma caused by poor lung compliance and overventilation following the administration of exogenous surfactants if changes in lung compliance are not monitored carefully. Overventilation with excessive tidal volumes and hypocarbia are associated with chronic lung disease. Stabilization of the infant using the lowest possible peak inspiratory pressures that are required to oxygenate and ventilate adequately is essential. Hand ventilation of an intubated infant, especially by inexperienced personnel, often leads to inconsistent tidal volumes and pressures. Use of a mechanical ventilator designed for infants offers the advantages of more consistent tidal volumes and a reduction of the heat losses because of the use of unheated nonhumidified air with hand bagging.

Although artificial surfactant administration is associated with a reduction of adverse sequelae in infants, its administration may lead to hyperventilation and overdistension when not administered by experienced attentive personnel. Following the instillation of artificial surfactant, rapid reaction to changes in pulmonary compliance to prevent the onset of hypocarbia and alkalosis is essential. Following the institution of mechanical ventilation, care should be taken with airway suctioning because vigorous or frequent airway suctioning is associated with hypoxia, intraventricular hemorrhage, and periventricular leukomalacia. Prematurity with respiratory distress syndrome (RDS) is not associated with mucous production in the first 24 hours of life, thus suctioning protocols should be altered to provide minimal suctioning during this time.

Airway problems

Choanal atresia

Choanal atresia is caused by a failure of embryologic regression of nasal airway tissue, thereby resulting in a partial or complete occlusion of the nasal airway. These choanal defects may be bony or membranous, with most having a boney component. Complete bilateral stenosis usually results in a neonatal respiratory emergency at birth because infants generally are obligate nasal breathers during the first 6-8 weeks of life. At rest, these infants usually manifest severe apnea, retractions, and respiratory distress that may be relieved with crying.

Wheezing or stridor may be audible with inspiration, and collapse of the small airways with vigorous inspiratory effort can occur. The infant in respiratory distress should be stimulated to cry and an artificial oral airway may be used to avoid intubation. The clinical diagnosis is achieved by the inability to pass a small caliber catheter through the nasal passages. However, the act of passing catheters, especially with repeated attempts, causes nasal passage swelling in any infant with the subsequent iatrogenic occlusion mimicking the congenital condition.

An alternative noninvasive method of excluding the diagnosis of complete atresia is to place a glass slide under the nasal orifices and look for fogging with expiration. Supplemental oxygen should be administered to infants with choanal atresia, and an oral airway may be of assistance. If the infant remains in significant respiratory distress, intubation is necessary. Intubation relieves the obstruction so that minimal ventilation (if any) is required.

Pierre Robin syndrome

This syndrome presents with micrognathia and with a resultant displacement of the tongue into the posterior pharynx, which may occlude the upper airway. A central cleft of the soft palate usually is present. Respiratory distress and cyanosis are caused by the obstruction of the upper airway. In the delivery room, the infant should be given supplemental oxygen and placed in a prone position in an attempt to have the tongue move forward in a dependent fashion from the posterior pharynx, relieving the airway obstruction. If the infant continues to have persistent respiratory distress, an oral airway may be placed. Alternatively, an appropriately sized endotracheal tube may be passed through the nose into the hypopharynx. Tracheotomies are generally not necessary and should be avoided. Intubation of these infants often is not easy because visualization of the larynx is difficult.

Tracheal webbing

The pathogenesis of tracheal webbing originates in the tenth week of gestation when an arrest in the development of the larynx near the vocal cords results in a residual web of tissue persisting in the airway. Approximately 75% of tracheal webs occur at the level of the vocal cords. These lesions are critical if more than 50% of the airway diameter is occluded, but this is rare. These disorders may be relatively asymptomatic at birth, with the development of distress later when activity increases and the need for airway flow increases.

When attempting to intubate these infants, an obstructive covering may be observed over the larynx and may occlude the airway completely. If the web consists of a thin membrane, the ETT may be pushed beyond the obstruction. However, if the membrane is thick, the infant requires an emergency tracheotomy. If the infant is manifesting severe distress, a large bore needle or catheter may be placed into the trachea to allow for gas exchange while arranging for emergency treatment. Caution must be used because inexperienced personnel may confuse this rare disorder with simple inability to visualize the vocal cords.

Esophageal atresia with and without tracheoesophageal fistulae

This condition rarely is considered a life-threatening emergency; however, early diagnosis is essential to prevent further complication. The types of esophageal atresia are reviewed in Table 4.

Table 4. Types of Esophageal Atresia

Type	Description
I: Esophageal Atresia with a distal fistula	This is the most common type (85%). Air is present in the stomach. A blind end upper esophageal segment is present with the distal segment of the esophagus connected to the trachea via a fistula.
II: Esophageal atresia only	A blind upper and lower esophageal segment is present. Air is absent from the lower GI tract, but an air-filled blind upper pouch may be observed.
III: H-type esophageal atresia	An isolated fistula connects the esophagus and trachea, usually occurring at the upper portion of the trachea and esophagus.
IV: Esophageal atresia with a proximal fistula	This type is rare. An upper esophageal segment is present with a fistula to the trachea and a blind lower esophageal segment. Air is absent from the lower GI tract.
V: Esophageal atresia with a double fistula	This type is rare. An upper esophageal segment is present with a fistula to the trachea, and a second fistula connects the distal esophagus and trachea. Air is present in the stomach.

The most common clinical symptoms in types of esophageal atresia with an esophageal-tracheal fistula are coughing, choking, and cyanosis. Infants with isolated esophageal atresia usually do not demonstrate respiratory distress immediately in the delivery room but may have excess secretions. The atretic air-filled esophageal pouch occasionally may be observed on a chest radiograph, manifested by a midthoracic rounded lucency. This pouch is visualized more readily by the passage of a radiopaque catheter into the esophagus before the chest radiograph.

Because secretions or oral feedings are not capable of passage into the stomach, the contents of the esophageal pouch readily reflux, placing these infants at high risk for aspiration. A Replogle suction catheter should be inserted to reach the esophageal pouch and placed on low continuous suction as soon as possible. Infants with an associated distal fistula to the trachea are also at high risk for aspiration of gastric contents into the lungs via the gastrobronchial fistula, which most often empties into the airway near the carina.

If at all possible, positive pressure ventilation should be avoided in these infants. Any positive pressure applied to the airway results in inflation of the fistula, stomach, and bowel, which then results in abdominal distention. This distending pressure cannot be relieved by esophageal reflux through the atretic esophagus. Relief of the distending pressure occurs with reflux of gastric contents into the lungs via the fistula. The continued application of positive pressure ventilation also may lead to massive gastric distention and possible rupture. In rare emergency situations, percutaneous gastrotomy may be required to decompress the stomach; however, controlled surgical placement of a gastrostomy tube is preferable.

Cystic adenomatoid malformation

Cystic adenomatoid malformations of the lung are masses that may cause a spectrum of symptoms, from massive mediastinal shifts in the fetus (resulting in pulmonary hypoplasia) to isolated subsegmental lobar masses in the newborn (or adult) with minimal associated symptoms. Severe lesions also may cause fetal cardiac compromise and result in hydrops. If the infant requires positive pressure ventilation, extreme caution must be used because the distending pressure may inflate the cystic malformation. An inflated cystic malformation is capable of massive expansion, causing respiratory embarrassment because of the prevention of ventilation of other normal lung tissue.

Cystic hygromas

This condition is the result of a congenital deformity of the lymphatic channels. Lymph accumulates and may compress the airway, depending on the size and location of the lymph accumulation. Approximately 80% of these lymphatic cystic accumulations occur in the neck and may compress the trachea. These infants may present with significant respiratory distress and require immediate intubation with deep positioning of the ETT to relieve the obstruction by stinting open the airway. However, most of these lesions expand outward from the neck and do not cause significant airway compromise in the delivery room.

Pulmonary compression

~~Congenital diaphragmatic hernia~~

The pathogenesis of this disorder is caused by the incomplete formation of the diaphragm in the fetus, resulting in a migration of the abdominal viscera into the chest during development. If the defect is large and the abdominal viscera have caused long-standing compression of the developing lungs, pulmonary hypoplasia may develop.

The diagnosis of diaphragmatic hernia is established frequently by prenatal ultrasound, which allows the management to be transferred to a perinatal referral center where pediatric surgery and appropriate medical support are available, including extracorporeal bypass. In the delivery room, the infant often presents with respiratory distress. Physical signs may include a scaphoid abdomen and a shift in heart sounds to the right hemithorax.

Respiratory distress in the delivery room may be caused by either a pulmonary hypoplasia or may be secondary to an expansion of the bowel caused by swallowed air. The expansion of the bowel results in compression of the lung. Delivery room management includes immediate intubation and passage of a large catheter for gastric decompression. Intubation prevents distention of the stomach and bowel contents because of crying or bag-valve-mask ventilation. The gastric decompression should be achieved with a Replogle or Salem pump suction catheter connected to a low continuous drain.

Constant maintenance of the gastric suction during the preoperative and immediate postoperative period is essential.

New modes of ventilation such as high frequency oscillatory ventilation has decreased the use of extracorporeal membrane oxygenation (ECMO) in this population. However, the survival rate for infants with this anomaly has not changed over the past decade.

Pneumothorax

Air leak syndromes are disorders produced when a rupture of pulmonary tissue occurs with the resultant escape of air into spaces in which air would not be present normally. The incidence of pneumothorax varies with gestational age, severity of pulmonary disease, need for assisted ventilation, mode of ventilation, and expertise of delivery room personnel. Following the initial rupture of a small airway or an alveolus, air may enter the perivascular and peribronchial spaces and track along the lymphatic channels. Air that dissects into the hilum results in a pneumomediastinum. Air that tracks into the pleural space manifests as a pneumothorax. Spontaneous rupture of the lung directly into the pleural space is thought to occur rarely but may be caused iatrogenically with the percutaneous insertion of a chest tube. Caution is required.

Pneumomediastinum frequently is an isolated disorder that occurs spontaneously in infants with minimal pulmonary disease. These infants usually are asymptomatic or minimally symptomatic because air in the mediastinum is capable of escaping to the tissues of the neck. Intrathoracic tension is relieved and circulation is not compromised. Infants with a pneumomediastinum should be observed. Intervention usually is unnecessary.

Pneumothorax may occur immediately in the delivery room or later when significant pulmonary disease has developed. The occurrence of a pneumothorax often is associated with positive pressure ventilation, but it also may occur in infants who are not receiving assisted ventilation. Following the initial air leak, the subsequent expansion of intrathoracic spaces often rapidly results in an increase of intrathoracic pressure such that there is an inability to ventilate the lungs and an inability to return venous blood to the heart. This is termed a "tension pneumothorax."

The rapid clinical deterioration of such infants is caused by circulatory collapse and an inability to ventilate. Any infant who has a sudden precipitous change in ventilatory status associated with an abrupt fall in blood pressure should be evaluated immediately for a pneumothorax. Transillumination of the chest may be used for the rapid diagnosis of severe tension pneumothorax. In cases where the clinical situation allows, an x-ray should be used to make or confirm the diagnosis. Infants in acute distress should have a needle aspiration performed to relieve the tension while preparation is made to place a chest tube. Symptomatic pneumothorax is managed with the insertion of a chest tube until the pulmonary leak is resolved. A chest tube may not be required if the pneumothorax is small and does not involve an infant who is not receiving positive pressure ventilation. Supplemental oxygen ($FiO_2 = 1$) often is administered for 6-12 hours to hasten reabsorption of the trapped intrapleural air.

Miscellaneous

Multiple gestation

The delivery and subsequent resuscitation of multiple infants presents a considerable challenge to the labor and delivery team. The first consideration to be addressed with the initial prenatal diagnosis of multiple gestations is to ensure that the care of such a pregnancy is at an institution capable of providing such support for the mother and multiple infants at delivery. As for singleton births, a minimum of 2 experienced personnel should be available for each infant. Because multiple gestation infants often are born prematurely (especially with higher order gestation) more personnel may be required for each infant. Therefore, for higher order gestation involving triplets or more, preparation to ensure the presence of appropriate personnel and equipment must be planned well in advance of the delivery.

The team should be led and organized by a designated experienced leader, and the planning phase should involve a number of disciplines, including neonatologists, perinatologists, nurse practitioners, pediatricians, nursery and obstetrics nurses, respiratory therapists, and pharmacists. The delivery team should consist of other individuals who are prepared to make complex decisions, perform technical skills, and respond quickly to changing circumstances. Organization and teamwork is essential with adequate personnel prospectively identified to respond to each infant. These preparations are becoming more commonplace because an increasing number of multiple birth pregnancies are resulting from assisted conception.

Hydrops

When preparing for the resuscitation of a hydropic infant, it is essential to have a sufficient number of skilled personnel in the delivery room to ensure that the multiple needs of this significantly compromised neonate can be met. Equipment should be prepared before the delivery, and all personnel in the room should be assigned specific procedures, such as a paracentesis or thoracentesis, if required. These procedures may need to be performed immediately if the fluid accumulation is causing difficulties in ventilation. If the hydrops is caused by anemia, blood for transfusion should be available in the delivery room. Because of the excess fluid in the lungs, often using high pressures and oxygen are necessary initially. Artificial surfactant administration also has been attempted in the delivery room to treat any surfactant deficiency in an attempt to improve pulmonary function. Umbilical venous and arterial lines should be placed and central venous pressures monitored.

Omphalocele and gastroschisis

Gastroschisis is an abdominal wall defect lateral to the umbilicus that does not have a sac or membrane covering the bowel. In contrast, an omphalocele involves the bowel herniating through the umbilical opening, with the bowel covered by a thin membrane, unless the membrane has been ruptured intrapartum. For both omphalocele and gastroschisis, it is necessary to maintain adequate intravascular fluid volume, to maintain thermoregulation, and to prevent bowel ischemia. Preoperatively, these infants have increased fluid requirements unless the bowel is appropriately wrapped with an airtight material.

The bowel may be first wrapped with warmed saline-soaked gauze. Care should be taken to support the bowel and not compromise blood flow. Observe the bowel closely to ensure no areas are compromised from the bowel twisting. A 10F Replogle or Salem pump suction catheter should be placed at low continuous suction to decompress the bowel and prevent further ischemic injury. If the infant is diagnosed with an omphalocele, the blood glucose should be assessed because this defect may be associated with Beckwith-Wiedemann syndrome. Trisomy 18 is associated with this anomaly. Therefore, if the condition is recognized prenatally, amniocentesis for chromosomal analysis should be offered to the family.

If chromosomal information is not available at the time of delivery and there are other anomalies are consistent with Trisomy 18, surgery should be delayed until a complete genetic evaluation is complete.

Congenital anomalies

Severe malformations observed in the delivery room should not change the resuscitative management unless skilled and experienced care providers are able to determine that the condition is incompatible with life. The family should be involved in any decision in which no resuscitation is to occur. Infants with severe malformations should be resuscitated and stabilized until an accurate diagnosis can be made.

Neonatal resuscitation has been standardized with the development of a certification program. Evaluation and recommendations for changes in the current standards is an ongoing process. As new research is published, it is essential to evaluate the quality of the studies and make changes in practice based on evidence. This section outlines some of the current controversies and concerns in resuscitation.

Room air versus 100% oxygen

Oxygen is a drug with the potential for serious adverse effects that must be considered. Oxygen free radicals are capable of tissue injury and have been implicated in several disease states in the neonate. The use of lower oxygen concentrations when resuscitating the neonate may decrease the number of oxygen free radicals and their damaging adverse effects. In one study, resuscitation in room air was shown to be as effective as 100% oxygen at lowering pulmonary vascular resistance. Other investigations have shown that there are no benefits in raising the pO_2 higher than 50 mm Hg.

Although large controlled multicentered trials have been performed indicating room air (FiO_2= 0.21) is just as effective as 100% oxygen when resuscitating infants, long-term outcomes are still pending. The results of these studies do highlight that, in situations in which 100% oxygen is not available, the resuscitation should proceed with the use of room air and a self-inflating bag. However, recent animal model studies have shown that rats exposed to high oxygen concentrations have increased cellular sodium channel activity that assists in limiting pulmonary edema. Hypoxia has been shown to inhibit cellular sodium channel activity and increase lung fluid. Therefore, there may be a significant rationale for using high oxygen concentrations during resuscitation of the asphyxiated or hypoxic infant.

Timing of artificial surfactant administration

Surfactant deficiency, which leads to RDS, is the most likely cause for persistent and progressive respiratory distress in premature infants. Controlled randomized clinical studies have shown that the prophylactic use of exogenous surfactant administered to premature infants effectively reduces death secondary to RDS. Controlled randomized clinical studies also have shown that treatment of only those infants who develop RDS symptoms has a significant reduction of death secondary to RDS. Prophylactic dosing of artificial surfactant is performed in the delivery room before the first breath or within 30 minutes following birth.

Controversies related to the prophylactic treatment regiment are related to the interruption of the standard resuscitation paradigm for the administration, treatment, and attendant risks of a population of infants who would not develop RDS, as well as the additional costs related to this dosing scheme. The argument for prophylactic surfactant dosing is that treated infants who require surfactant replacement should have more uniform and effective drug distribution when the lungs are fluid-filled without air-fluid interfaces. Obviously, the treatment of only those infants with the diagnosis of RDS-established results in a smaller proportion of infants being treated. The proportion of infants given prophylactic artificial surfactant therapy who would not develop RDS depends on the entry criteria for prophylactic treatment and population characteristics.

Recent studies have demonstrated that early prophylactic dosing of surfactant is efficacious and associated with better outcomes in extremely premature infants. Researchers have recommended that, whenever possible, infants with surfactant deficiency be identified before delivery using lecithin-sphingomyelin ratio or testing for the presence of phosphatidylglycerol. Researchers also suggest that all infants delivered earlier than 28 weeks of gestation receive their first dose of surfactant in the delivery room within a few minutes of life, following cardiopulmonary stabilization. Infants born later than 28 weeks of gestation should receive rescue therapy as soon as they show clinical signs of RDS.

Intubation and suctioning for meconium

Meconium staining of amniotic fluid occurs in 5-12.5% of all deliveries and rarely is seen before 34 weeks of gestation. Of newborns born with meconium stained fluid, 60% require stabilization and/or resuscitation. Of these infants that require stabilization and/or resuscitation, 4-6% are diagnosed with meconium aspiration syndrome. Meconium aspiration in a newborn can lead to atelectasis, overdistension, pneumothorax, pneumonitis, surfactant deficiency, and persistent pulmonary hypertension. Trained personnel should be at all meconium stained deliveries. Suctioning of the oropharynx and nasal pharynx once the head is delivered is the current standard in obstetrics. Intubation and suctioning of infants beyond this point is still controversial.

In a recent, multicentered, prospective, randomized, controlled trial, it was shown that regardless of the type of meconium, vigorous infants do not have any increased risk for meconium aspiration syndrome if they are not intubated and suctioned. The study also indicated that depressed infants, regardless of the type of meconium, do benefit from intubation and suctioning before the initiation of positive pressure ventilation (PPV).

Depressed infants should be placed on a radiant heat source and no drying or stimulation provided until they are intubated and direct tracheal suctioning is performed. A meconium aspirator should be applied directly to the ETT, and continuous pressure should be applied using 120-150 mm Hg as the tube is removed. If meconium is obtained, it is necessary to evaluate the heart rate before a second intubation is performed. With the second intubation, the practitioner may want to consider providing PPV through the ETT once suctioning is performed. Once an infant has been stabilized, intubation and suctioning can be performed again. Researchers have stated that meconium can be suctioned from the trachea up to an hour or longer following birth. Note that infants who are vigorous at delivery and then develop respiratory distress or become depressed also should be intubated and suctioned before initiation of PPV, if meconium was present.

Preliminary studies show potential benefits in using dilute surfactant lavage in infants with meconium aspiration syndrome. New research has shown that infants who receive surfactant replacement therapy within 6 hours of delivery have improved oxygenation and a reduced incidence of air leaks, pulmonary morbidity, and length of stay; however, further studies still are necessary before this can be recommended as standard care.

SUMMARY	Section 9 of 10

This article reviews the adaptation process at delivery, outlines the steps necessary to resuscitate neonates, serves as a review for practitioners who already resuscitate infants, and highlights special problems and controversies. It is essential that new practitioners complete the Neonatal Resuscitation Program or some other program that introduces resuscitation material and allows for skill assessment. After reading the material and practicing the skills, it is essential to work with experienced personnel before providing resuscitation at deliveries.

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Neonatal Resuscitation excerpt

Neonatal Sepsis

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AUTHOR INFORMATION	Section 1 of 11

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INTRODUCTION	Section 2 of 11

Background: Neonatal sepsis may be categorized as early or late onset. Eighty-five percent of newborns with early-onset infection present within 24 hours, 5% present at 24-48 hours, and a smaller percentage of patients present between 48 hours and 6 days of life. Onset is most rapid in premature neonates. Early-onset sepsis syndrome is associated with acquisition of microorganisms from the mother. Transplacental infection or an ascending infection from the cervix may be caused by organisms that colonize in the mother's genitourinary tract. The infant may acquire the microbe by passage through a colonized birth canal at delivery. The microorganisms most commonly associated with early-onset infection include group B *Streptococcus* (GBS), *Escherichia coli, Haemophilus influenzae,* and *Listeria monocytogenes.*

Late-onset sepsis syndrome occurs at 7-90 days of life and is acquired from the caregiving environment. Organisms that have been implicated in causing late-onset sepsis syndrome include coagulase-negative staphylococci, *Staphylococcus aureus, E coli, Klebsiella, Pseudomonas, Enterobacter, Candida,* GBS, *Serratia, Acinetobacter,* and anaerobes. The infant's skin, respiratory tract, conjunctivae, gastrointestinal tract, and umbilicus may become colonized from the environment, leading to the possibility of late-onset sepsis from invasive microorganisms. Vectors for such colonization may include vascular or urinary catheters, other indwelling lines, or contact from caregivers with bacterial colonization.

Pneumonia is more common in early-onset sepsis, whereas meningitis and/or bacteremia are more common in late-onset sepsis. Premature and ill infants have an increased susceptibility to sepsis and subtle nonspecific initial presentations; therefore, they require much vigilance so that sepsis can be identified and treated effectively.

Pathophysiology: The infectious agents associated with neonatal sepsis have changed over the past 50 years. *S aureus* and *E coli* were the most common infectious hazards for neonates in the 1950s in the United States. GBS then replaced *S aureus* as the most common gram-positive agent, causing early-onset sepsis during the next decades. During the 1990s, GBS and *E coli* continued to be associated with neonatal infection; however, coagulase-negative *S aureus* is now observed more frequently. Additional organisms, such as *L monocytogenes, Chlamydia pneumonia, Haemophilus influenzae, Enterobacter aerogenes,* and species of *Bacteroides* and *Clostridium* have also been identified in neonatal sepsis.

Meningoencephalitis and neonatal sepsis syndrome can also be caused by infection with adenovirus, enterovirus, or coxsackievirus. Additionally, sexually transmitted diseases and viral diseases, such as gonorrhea, syphilis, herpes simplex virus (HSV), cytomegalovirus (CMV), hepatitis, HIV, rubella, toxoplasmosis, *Trichomonas vaginalis,* and *Candida* species, have all been implicated in neonatal infection. Bacterial organisms with increased antibiotic resistance have also emerged and have further complicated the management of neonatal sepsis. The colonization patterns in nurseries and personnel are reflected in the organisms currently associated with nosocomial infection. Infants with lower birth weight and infants who are less mature in today's neonatal intensive care units (NICUs) have increased susceptibility to these organisms.

Staphylococcus epidermidis, or coagulase-negative *Staphylococcus* is increasingly seen as a cause of nosocomial or late-onset sepsis, especially in the premature infant. It is considered the leading cause of late-onset infections for this population. Its prevalence is related to its preference for the plastic mediums found in cannulas and shunts, which increases its introduction via umbilical catheters and other indwelling lines. The bacterial capsule polysaccharide adheres well to the plastic polymers of the catheters. The adherence creates a capsule between microbe and catheter, which prevents C3 deposition and phagocytosis. Also, proteins found in the organism [AtlE and SSP-1] enhance attachment to the surface of the catheter.

Biofilms are formed at the site from the aggregation of organisms that have multiplied with the protection provided by the adherence to the catheter. Slimes are produced at the site from the extracellular material formed by the organism, which provides a barrier to the host defense, as well as antibiotic action. Therefore, it can be seen that slime production increases the difficulty to treat coagulase-negative staphylococcal septicemia. The toxins formed by this organism have been associated with necrotizing enterocolitis. Coagulase-negative *Staphylococcus* is a frequent contaminate of blood and cerebrospinal fluid (CSF) cultures; therefore, it can be a false indicator of coagulase-negative staphylococcal septicemia.

The neonate is unable to respond effectively to infectious hazards because of deficits in the physiological response to infectious agents. The neonatal neutrophil or polymorphonuclear (PMN) cell, which is vital for effective killing of bacteria, is defective in chemotaxis and killing capacity. Decreased adherence to the endothelial lining of blood vessels reduces their ability to marginate and leave the intravascular area to migrate into the tissues. Once in the tissues, they may fail to deaggregate in response to chemotactic factors. Also, neonatal PMNs are less deformable; therefore, they are less able to move through the extracellular matrix of tissues to reach the site of inflammation and infection. The limited ability of neonatal PMNs for phagocytosis and killing of bacteria is impaired when the infant is clinically ill. Lastly, neutrophil reserves are depleted easily because of the diminished response of the bone marrow, especially in the premature infant.

Neonatal monocyte concentration and function are at adult levels; however, macrophage chemotaxis is impaired and continues to exhibit decreased function into early childhood. Macrophages are decreased in the lungs and probably also in the liver and spleen. The chemotactic and bacteriocidal activity and the antigen presentation by these cells are not fully competent. Cytokine production by macrophages is decreased, which may be associated with a corresponding decrease in T-cell production.

T cells are found in early gestation in fetal circulation and increase in number from birth to about age 6 months; however, these cells represent an immature transitory population. Neonates are deficient in T cells with the memory cell surface phenotype; however, the number of these T cells increases with maturity as the neonate is exposed to antigenic stimuli. These antigenically naive cells do not proliferate as readily as adult T cells when activated. Also, neonatal T cells do not effectively produce the cytokines that assist with B-cell stimulation and differentiation and with bone marrow stimulation of granulocyte/monocyte proliferation. A delay occurs in the formation of antigen specific memory function following primary infection. The cytotoxic function of neonatal T cells is 50-100% as effective as adult T cells.

The fetus has some preimmune immunoglobulin present; however, preimmune immunoglobulin is relatively limited in fetuses compared to adults. The infant receives immunoglobulin G (IgG) prenatally after 16 weeks of gestation; however, the infant born prematurely has less IgG due to the shorter period of placental transmission of immunoglobulin.

Additionally, if the mother is immunosuppressed, it is possible that less IgG can be transmitted to the infant. The neonate is capable of synthesizing immunoglobulin M (IgM) in utero at 10 weeks of gestation; however, IgM levels are generally low at birth, unless the infant was exposed to an infectious agent during the pregnancy, thereby stimulating increased IgM production. IgG and immunoglobulin E (IgE) may be synthesized in utero; however, only traces are found in cord blood at delivery. The neonate may receive immunoglobulin A (IgA) from breastfeeding but does not secrete IgA until 2-5 weeks after birth. Response to bacterial polysaccharide antigen is diminished and remains so during the first 2 years of life.

Natural killer (NK) cells are found in greater concentration in the peripheral blood of neonates than in that of adults; however, certain antigen expressivity by the cells' membranes is diminished, thereby reducing cytolytic activity. This decreased response has been observed with infection by herpes group viruses in the neonate.

The fetus is capable of complement protein production as early as 6 weeks gestational age; however, wide variability exists among individual neonates in the concentration of the components of the complement system. Some infants who were studied had comparable concentrations to adults. Deficiencies appear to be greater for neonates in the alternative pathway than in the classic pathway. The terminal activity for complement that leads to killing of organisms, especially gram-negative bacteria, is inefficient. This deficiency is more marked in preterm infants. Mature complement activity is not reached until infants are aged 6-10 months. Fibronectin, a serum protein that assists with neutrophil adherence and has opsonic properties, is found in lower concentrations in neonates. Therefore, neonatal sera have reduced opsonic efficiency against GBS, *E coli*, and *S pneumoniae*.

The physical and chemical barriers to infection in the human body are present in the newborn but are functionally deficient. Skin and mucus membranes are broken down easily in the premature infant. Neonates who are ill and/or premature are additionally at risk because of the invasive procedures that breach their physical barriers to infection. Because of the interdependence of the immune response, these individual deficiencies of the various components of immune activity in the neonate conspire to create a hazardous situation for the neonate exposed to infectious threats.

Frequency:

- **In the US:** The incidence of culture-proven sepsis is approximately 2 in 1000 live births. Of the 7-13% of neonates who are evaluated for neonatal sepsis, only 3-8% have culture-proven sepsis. The early signs of sepsis in the newborn are nonspecific; therefore, many newborns undergo diagnostic studies and the initiation of treatment before the diagnosis has been determined. Additionally, because the American Academy of Pediatrics (AAP), American Academy of Obstetrics and Gynecology (AAOG), and Centers for Disease Control and Prevention (CDC) all have recommended sepsis screening and/or treatment for various risk factors related to GBS diseases, many asymptomatic neonates now require evaluation. Because the mortality rate of untreated sepsis can be as high as 50%, most clinicians believe that the hazard of untreated sepsis is too great to wait for confirmation by positive cultures; therefore, most clinicians initiate treatment while awaiting culture results.

Mortality/Morbidity:
The mortality rate in neonatal sepsis may be as high as 50% for infants who are not treated. Infection is a major cause of fatality during the first month of life, contributing to 13-15% of all neonatal deaths. Neonatal meningitis, a serious morbidity of neonatal sepsis, occurs in 2-4 cases per 10,000 live births and significantly contributes to the mortality rate in neonatal sepsis; it is responsible for 4% of all neonatal deaths.

Race: Black infants have an increased incidence of GBS disease and late-onset sepsis. This is observed even after controlling for risk factors of low birth weight and decreased maternal age.

Sex: The incidence of bacterial sepsis and meningitis, especially for gram-negative enteric bacilli, is higher in males than in females.

Age: Studies have shown that premature infants have an increased incidence of sepsis. The incidence of sepsis is significantly higher in infants with very low birth weight (<1000 g), at 26 per 1000 live births, than in infants with a birth weight of 1000-2000 g, at 8-9 per 1000 live births. The risk for death or meningitis from sepsis is higher in infants with low birth weight than in full-term neonates.

CLINICAL	Section 3 of 11

History: The risk factors that are associated most highly with neonatal sepsis include maternal GBS colonization (especially if untreated during labor), premature rupture of membranes (PROM), preterm rupture of membranes, prolonged rupture of membranes, prematurity, and chorioamnionitis.
Predisposing risk factors also are associated with neonatal sepsis. They include low Apgar score (<6 at 1 or 5 min), maternal fever greater than 101°F (38.4°C), maternal urinary tract infection, poor prenatal care, poor maternal nutrition, low socioeconomic status, recurrent abortion, maternal substance abuse, low birth weight, difficult delivery, birth asphyxia, meconium staining, and congenital anomalies. The predisposing risk factors implicated in neonatal sepsis reflect the stress and illness of the fetus at delivery, as well as the hazardous uterine environment surrounding the fetus before delivery.

An awareness of the myriad of risk factors associated with neonatal sepsis prepares the clinician for early identification and effective treatment, thereby reducing mortality and morbidity.

- Maternal GBS status

  - The most common etiology of neonatal bacterial sepsis is GBS. Nine serotypes exist, and each is related to the polysaccharide capsule of the organism. Types I, II, and III are commonly associated with neonatal GBS infection. The type III strain has been shown to be most highly associated with CNS involvement in early-onset infection, whereas type V has been associated with early-onset disease without CNS involvement.
  - The GBS organism colonizes the maternal gastrointestinal tract and birth canal. Approximately 30% of women have asymptomatic GBS colonization during pregnancy. GBS is responsible for approximately 50,000 maternal infections per year in women, but only 2 neonates per 1000 live births are infected. Women with heavy GBS colonization and cultures that are chronically positive for GBS have the highest risk of perinatal transmission. Also, heavy colonization at 23-26 weeks of gestation is associated with prematurity and low birth weight. Colonization at delivery is associated with neonatal infection. Intrapartal chemoprophylaxis of women with positive cultures for GBS has been shown to decrease the transmission of the organism to the neonate during delivery.

- PROM may occur in response to an untreated infection of the urinary tract or birth canal and is also associated with previous preterm delivery, uterine bleeding in pregnancy, and heavy cigarette smoking during pregnancy.

  - Rupture of membranes without other complications for more than 24 hours prior to delivery is associated with a 1% increase in the incidence of neonatal sepsis; however,

when chorioamnionitis accompanies the rupture of membranes, the incidence of neonatal infection is quadrupled.

- o A recent multicenter study demonstrated that clinical chorioamnionitis and maternal colonization with GBS are the most important predictors of subsequent neonatal infection following PROM.
- o When membranes have ruptured prematurely before 37 weeks' gestational age, a longer latent period precedes vaginal delivery, increasing the likelihood that the infant will be infected. The relationship between duration of membrane rupture and neonatal infection is inversely related to gestational age. Therefore, the more premature an infant, the longer the delay between rupture of membranes and delivery, and higher the likelihood of neonatal sepsis.
- o A study by Seaward et al found that more than 6 vaginal digital examinations, which may occur as part of the evaluation for PROM, were associated with neonatal infection even when considered separately from the presence of chorioamnionitis.

- Prematurity: The relationship between preterm PROM and neonatal sepsis has already been described; however, other associations between prematurity and neonatal sepsis increase the risk for premature infants.

  - o Preterm infants are more likely to require invasive procedures, such as umbilical catheterization and intubation.
  - o Prematurity is associated with infection from CMV, HSV, hepatitis B, toxoplasmosis, *Mycobacterium tuberculosis*, *Campylobacter fetus*, and *Listeria* species.
  - o Intrauterine growth retardation and low birth weight are also observed in CMV and toxoplasmosis infections.
  - o Premature infants have less immunologic ability to resist infection.

- Chorioamnionitis: The relationship between chorioamnionitis and other risk variables is strong. Suspect chorioamnionitis in the presence of fetal tachycardia, uterine tenderness, purulent amniotic fluid, elevated maternal WBC count, and unexplained maternal temperature above 100.4°F (38°C).

<mark>Physical:</mark> The clinical signs of neonatal sepsis are nonspecific and are associated with characteristics of the causative organism and the body's response to the invasion. These nonspecific clinical signs of early sepsis syndrome are also associated with other neonatal diseases, such as Respiratory Distress Syndrome (RDS), metabolic disorders, intracranial hemorrhage, and a traumatic delivery. Therefore, diagnose neonatal sepsis by excluding other disease processes, performing an examination, and testing for more specific indications of neonatal sepsis.

- Congenital pneumonia and intrauterine infection: Inflammatory lesions are observed postmortem in the lungs of infants with congenital and intrauterine pneumonia. This may not be caused by the action of the microorganisms themselves but may be caused by aspiration of amniotic fluid containing maternal leukocytes and cellular debris. Tachypnea, irregular respirations, moderate retracting, apnea, cyanosis, and grunting may be observed. Neonates with intrauterine pneumonia may also be critically ill at birth and require high levels of ventilatory support. The chest radiograph may depict bilateral consolidation or pleural effusions.
- Congenital pneumonia and intrapartum infection: Neonates who are infected during the birth process may acquire pneumonia through aspiration of the microorganisms during the delivery process. The colonization may lead to infection with pulmonary changes, infiltration, and destruction of bronchopulmonary tissue. This damage is partly due to the granulocytes' release of prostaglandins and leukotrienes. Fibrinous exudation into the alveoli leads to inhibition of pulmonary surfactant function and respiratory failure with an RDS-like presentation. Vascular congestion, hemorrhage, and necrosis may occur.

  - o *Klebsiella* species and *S aureus* are especially capable of considerably damaging the lungs, producing microabscesses and empyema.

- o Infectious pneumonia is also characterized by pneumatoceles within the pulmonary tissue. Coughing, grunting, costal and sternal retractions, nasal flaring, tachypnea and/or irregular respiration, rales, decreased breath sounds, and cyanosis may be observed.
- o On radiography, segmental or lobar atelectasis or a diffuse reticulogranular pattern may exist, much like what is observed in RDS.
- o Pleural effusions may be observed in advanced disease.

- Congenital pneumonia and postnatal infection: Postnatally acquired pneumonia may occur at any age. Because these infectious agents exist in the environment, the likely cause depends heavily on the infant's recent environment. If the infant has remained hospitalized in an NICU environment, especially with endotracheal intubation and mechanical ventilation, the organisms may include *Staphylococcus* or *Pseudomonas* species. Additionally, these hospital-acquired organisms frequently demonstrate multiple antibiotic resistances. Therefore, the choice of antibiotic agents in such cases requires knowledge of the likely causative organisms and the antibiotic-resistance patterns of the hospital.
- Cardiac signs: In overwhelming sepsis, an initial early phase characterized by pulmonary hypertension, decreased cardiac output, and hypoxemia is postulated to occur. These cardiopulmonary disturbances may be due to the activity of granulocyte biochemical mediators, such as hydroxyl radicals and thromboxane B2, an arachidonic acid metabolite. These biochemical agents have vasoconstrictive actions that result in pulmonary hypertension when released in pulmonary tissue. A toxin derived from the polysaccharide capsule of type III *Streptococcus* has also been shown to cause pulmonary hypertension. The early phase of pulmonary hypertension is followed by further progressive decreases in cardiac output with bradycardia and systemic hypotension. The infant manifests overt shock with pallor, poor capillary perfusion, and edema. These late signs of shock are indicative of severe compromise and are highly associated with mortality.
- Metabolic signs: Hypoglycemia, metabolic acidosis, and jaundice all are metabolic signs that commonly accompany neonatal sepsis syndrome. The infant has an increased glucose requirement because of sepsis. The infant may also have impaired nutrition from a diminished energy intake. Metabolic acidosis is due to a conversion to anaerobic metabolism with the production of lactic acid. When infants are hypothermic or they are not kept in a neutral thermal environment, efforts to regulate body temperature can cause metabolic acidosis. Jaundice occurs in response to decreased hepatic glucuronidation caused by both hepatic dysfunction and increased erythrocyte destruction.
- Neurologic signs: Meningitis is the common manifestation of infection of the central nervous system. It is primarily associated with GBS (36%), *E coli* (31%), and *Listeria* species (5-10%) infections, although other organisms such as *S pneumoniae, S aureus, Staphylococcus epidermis, Haemophilus influenzae*, and species of *Pseudomonas, Klebsiella, Serratia, Enterobacter*, and *Proteus* may cause meningitis. Acute and chronic histologic features are associated with specific organisms.

- o Ventriculitis is the initiating event with inflammation of the ventricular surface. Exudative material usually appears at the choroid plexus and is external to the plexus. Then, ependymitis occurs with disruption of the ventricular lining and projections of glial tufts into the ventricular lumen. Glial bridges may develop by these tufts and cause obstruction, particularly at the aqueduct of Sylvius. The lateral ventricles may become multiloculated, which is similar to forming abscesses. Multiloculated ventricles can isolate organisms in an area, making treatment more difficult. Meningitis is likely to arise at the choroid plexus and extend via the ventricles through aqueducts into the arachnoid to affect the cerebral and cerebellar surfaces. The high glycogen content in the neonatal choroid plexus provides an excellent medium for the bacteria. Ventricular origination of meningitis causes significant treatment problems because the areas are inaccessible. Ventricular obstruction causes an additional problem.
- o Arachnoiditis is the next phase and is the hallmark of meningitis. The arachnoid is infiltrated with inflammatory cells producing an exudate that is thick over the base of the brain and more uniform over the rest of the brain. Early in the infection, the exudate is primarily PMNs, bacteria, and macrophages. Exudate is prominent around the blood vessels and extends into the brain parenchyma. In the second and third

weeks of infection, the proportion of PMNs decreases; the dominant cells are histiocytes, macrophages, and some lymphocytes and plasma cells. Exudate infiltration of cranial roots 3-8 occurs. After this period, the exudate decreases. Thick strands of collagen form, and arachnoid fibrosis occurs, which is responsible for obstruction. Hydrocephalus results. Early-onset GBS meningitis is characterized by much less arachnoiditis than late-onset GBS meningitis.

- o Vasculitis extends the inflammation of the arachnoid and ventricles to the blood vessels surrounding the brain. Occlusion of the arteries rarely occurs; however, venous involvement is more severe. Phlebitis may be accompanied with thrombosis and complete occlusion. Multiple fibrin thrombi are especially associated with hemorrhagic infarction. This vascular involvement is apparent within the first days of meningitis and becomes more prominent during the second and third weeks.

- o Cerebral edema may occur during the acute state of meningitis. The edema may be severe enough to greatly diminish the ventricular lumen. The cause is unknown, but it is likely related to vasculitis and the increased permeability of blood vessels. It may also be related to the cytotoxins of microorganisms. Herniation of edematous supratentorial structures does not occur in neonates because of the cranium's distensibility.

- o Infarction is a prominent and serious feature of neonatal meningitis. It occurs in 30% of infants who die. Lesions occur because of multiple venous occlusions, which are frequently hemorrhagic. The loci of infarcts are most often in the cerebral cortex and underlying white matter but may also be subependymal within the deep white matter. Neuronal loss occurs, especially in the cerebral cortex, and periventricular leukomalacia may subsequently appear in areas of neuronal cell death.

- o Meningitis due to early-onset neonatal sepsis usually occurs within 24-48 hours and is dominated by nonneural signs. Neurologic signs may include stupor and irritability. Overt signs of meningitis occur in only 30% of cases. Even culture-proven meningitis may not demonstrate white cell changes in the CSF. Meningitis due to late-onset disease is more likely to demonstrate neurologic signs (80-90%). Impairment of consciousness (ie, stupor with or without irritability), coma, seizures, bulging anterior fontanel, extensor rigidity, focal cerebral signs, cranial nerve signs, and nuchal rigidity occur.

- o The CSF findings in infectious neonatal meningitis are an elevated WBC count (predominately PMNs), an elevated protein level, a decreased CSF glucose concentration, and positive cultures. The decrease in CSF glucose concentration does not necessarily reflect serum hypoglycemia. Glucose concentration abnormalities are more severe in late-onset disease and with gram-negative organisms. The CSF WBC count is within the reference range in 29% of GBS meningitis infections; in gram-negative meningitis, it is within the reference range in only 4%. Reference range CSF protein and glucose concentrations are found in about 50% of patients with GBS meningitis; however, in gram-negative infections, reference range CSF protein and glucose concentrations are found in only 15-20%.

- o Temperature instability is observed with neonatal sepsis and meningitis, either in response to pyrogens secreted by the bacterial organisms or from sympathetic nervous system instability. The neonate is most likely to be hypothermic. The infant is also floppy, lethargic, and disinterested in feeding. Signs of neurologic hyperactivity are more likely when late-onset meningitis occurs.

- Hematologic signs

  - o The platelet count in the healthy newborn is rarely less than 100,000 per mm^3 in the first 10 days of life. Thrombocytopenia with counts less than 100,000 may occur in neonatal sepsis in response to the cellular products of the microorganisms. These cellular products cause platelet clumping and adherence leading to platelet destruction. Thrombocytopenia is generally observed after sepsis has been diagnosed and usually lasts 1 week, though it can last as long as 3 weeks. Only 10-60% of infants with sepsis have thrombocytopenia. Because of the appearance of newly formed platelets, mean platelet volume (MPV) and platelet distribution width (PDW) are shown to be significantly higher in neonatal sepsis after 3 days. Because of the

myriad of causes of thrombocytopenia and its late appearance in neonatal sepsis, the presence of thrombocytopenia does not aid the diagnosis of neonatal sepsis.

- o WBC counts and ratios are more sensitive for determining sepsis than platelet counts, although normal WBC counts may be observed in as many as 50% of cases of culture-proven sepsis. Infants who are not infected may also demonstrate abnormal WBC counts related to the stress of delivery. A differential may be of more use in diagnosing sepsis. Total neutrophil count (PMNs and immature forms) is slightly more sensitive in determining sepsis than total leukocyte count (percent lymphocyte + monocyte/PMNs + bands). Abnormal neutrophil counts, taken at the time of symptom onset, are only observed in two thirds of infants; therefore, the neutrophil count does not provide adequate confirmation of sepsis. Neutropenia is observed with maternal hypertension, severe perinatal asphyxia, and periventricular or intraventricular hemorrhage.
- o Neutrophil ratios have been more useful in diagnosing or excluding neonatal sepsis; the immature-to-total (I/T) ratio is the most sensitive. All immature neutrophil forms are counted, and the maximum acceptable ratio for excluding sepsis during the first 24 hours is 0.16. In most newborns, the ratio falls to 0.12 within 60 hours of life. The sensitivity of the I/T ratio has ranged from 60-90%, and elevations may be observed with other physiological events; therefore, when diagnosing sepsis, the elevated I/T ratio should be used in combination with other signs.

- Gastrointestinal signs: The gut can be colonized by organisms in utero or at delivery by swallowing infected amniotic fluid. The immunologic defenses of the gut are not mature, especially in the preterm infant. Lymphocytes proliferate in the gut in response to mitogen stimulation; however, this proliferation is not fully effective in responding to a microorganism because antibody formation and cytokine formation is immature until approximately 46 weeks. Necrotizing enterocolitis (NEC) has been associated with the presence of a number of species of bacteria in the immature gut, and bacterial overgrowth of these organisms in the neonatal lumen is a component of the multifactorial pathophysiology of NEC.

Acidosis, Metabolic
Respiratory Distress Syndrome

Lab Studies:

- Blood, CSF, and urine cultures

  - o Aerobic cultures are appropriate for most of the bacterial etiologies associated with neonatal sepsis; however, anaerobic cultures are indicated in neonates with abscess formation, processes with bowel involvement, massive hemolysis, and refractory pneumonia.
  - o A Gram stain provides early identification of the gram-negative or gram-positive status of the organism for preliminary identification.
  - o Bacterial cultures should generally reveal the organism of infection within 36-48 hours; the subsequent initial identification of the organism occurs within 12-24 hours of the growth.
  - o Urine cultures are most appropriate when investigating late-onset sepsis.
  - o Blood and CSF cultures are appropriate for early and late-onset sepsis.
  - o Because of the low incidence of meningitis in the newborn infant with negative

cultures, clinicians may elect to culture the CSF of only those infants with documented or presumed sepsis.

- A CBC and differential may be ordered serially to determine changes associated with the infection, such as thrombocytopenia or neutropenia, or to monitor the development of a left shift or an elevated I/T ratio. Such serial monitoring of the CBC may be useful in aiding the differentiation of sepsis syndrome from nonspecific abnormalities due to the stress of delivery

  - The platelet count in the healthy newborn is rarely less than 100,000 per mm^3 in the first 10 days of life. Thrombocytopenia with counts less than 100,000 may occur in neonatal sepsis, although this sign is usually observed late in the infection. MPV and PDW have been shown to be significantly elevated in infants with sepsis after 2-3 days of life. These measures may assist in determining the etiology of thrombocytopenia.
  - WBC counts and ratios are more sensitive in determining sepsis, although normal WBC counts may be observed in culture-proven sepsis in as many as 50% of cases. Infants who are not infected may also have abnormal WBC counts related to the stress of delivery. A differential may be of more use in diagnosing sepsis. Total neutrophil count (PMNs and immature forms) is slightly more sensitive in determining sepsis than total leukocyte count (percent lymphocyte + monocyte/PMNs + bands). Abnormal neutrophil counts at the time of symptom onset are only observed in two thirds of infants; therefore, neutrophil count does not provide adequate confirmation of sepsis. Neutropenia is also observed with maternal hypertension, severe perinatal asphyxia, and periventricular or intraventricular hemorrhage.
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- The CSF findings in infectious neonatal meningitis are an elevated WBC (predominately PMNs), an elevated protein level, a depressed glucose level, and positive cultures. The decrease in glucose is not reflective of serum hypoglycemia. The CSF abnormalities are more severe in late onset and with gram-negative organisms. The WBC is within the reference range in 29% of GBS meningitis infections; in gram-negative meningitis, it is within the reference range in only 4%. Reference range protein and glucose concentrations are found in about 50% of patients with GBS meningitis; however, in gram-negative infections, reference range protein and glucose concentration are found in only 15-20%.
- C-reactive protein, an acute phase protein associated with tissue injury, is eventually elevated in 50-90% of infants with systemic bacterial infections. This is especially true of infections with abscesses or cellulitis of deep tissue. C-reactive protein usually rises within 24 hours of infection, peaks within 2-3 days, and remains elevated until the inflammation is resolved. The C-reactive protein level is not recommended as a sole indicator of neonatal sepsis, but it may be used as part of a sepsis workup or as a serial study during infection to determine response to antibiotics, duration of therapy, and/or relapse of infection.
- IgM concentration in serum may be helpful in determining the presence of an intrauterine infection, especially if present over a period of time.

Imaging Studies:

- Chest radiographs may depict segmental or lobar atelectasis, but they more commonly reveal a diffuse, fine, reticulogranular pattern, much like what is observed in RDS. Hemothorax and pleural effusions may also be observed.
- A CT scan may be needed late in the course of complex neonatal meningitis to document any occurrence of blocks to CSF flow, the site where the blocks are occurring, and occurrence of major infarctions or abscesses. Signs of chronic stage disease, such as ventricular dilation, multicystic encephalomalacia, and atrophy, are also demonstrated on CT scan.

- Head ultrasonograms in neonates with meningitis show evidence of ventriculitis, abnormal parenchymal echogenicities, extracellular fluid, and chronic changes. Serially, head ultrasonograms can demonstrate the progression of complications.

Procedures: Lumbar puncture is warranted for early- and late-onset sepsis, although clinicians may be unsuccessful in obtaining sufficient or clear fluid for all the studies. Infants may be positioned on their side or sitting with support, but adequate restraint is needed to avoid a traumatic tap. Because the cord is lower in the spinal column in infants, the insertion site should be between L3 and L4. If positive cultures are demonstrated, a follow-up lumbar puncture is often performed within 24-36 hours after antibiotic therapy to document CSF sterility. If organisms are still present, modification of drug type or dosage may be required to adequately treat the meningitis. An additional lumbar puncture within 24-36 hours is necessary if organisms are still present.

Medical Care: Initiate treatment immediately because of the neonate's immunologic weaknesses for fighting infection. Begin antibiotics as soon as diagnostic tests are performed. Additional therapies have been investigated for the treatment of neonatal sepsis; however, no unequivocal proof that these treatments are beneficial exists. These additional therapies include granulocyte transfusion, intravenous immune globulin (IVIG) replacement, exchange transfusion, and the use of recombinant cytokines.

- In the United States and Canada, the most current approach to treat early-onset neonatal sepsis syndrome includes combined IV aminoglycoside and penicillin antibiotic therapy. This provides coverage for gram-positive organisms, especially GBS, and gram-negative bacteria, such as *E coli*. The specific antibiotics to be used are chosen on the basis of maternal history and prevalent trends of organism colonization in individual nurseries.

  o If infection appears to be nosocomial, direct coverage at organisms implicated in hospital-acquired infections, including *S aureus, S epidermis*, and *Pseudomonas* species. Most strains of *S aureus* produce beta-lactamase, which makes them resistant to penicillin G, ampicillin, carbenicillin, and ticarcillin. Vancomycin has been favored for this coverage; however, concern exists that overuse of this drug may lead to vancomycin-resistant organisms, thereby eliminating the best response to these resistant organisms. Cephalosporins are attractive in the treatment of nosocomial infection because of their lack of dose-related toxicity and adequate serum and CSF concentration; however, resistance by gram-negative organisms has occurred with their use. Do not use ceftriaxone in infants with hyperbilirubinemia because it displaces bilirubin from serum albumen. Resistance and sensitivities for the organism are used to indicate the most effective drug.
  o Aminoglycosides and vancomycin are both ototoxic and nephrotoxic; have caution when using them. Check the serum level after 48 hours of treatment to determine if levels are above those required for a therapeutic effect. The dosage amount or interval may need to be changed to ensure adequate but nontoxic coverage. A serum level may be warranted when the infant's clinical condition has not improved to ensure that a therapeutic level has been reached. In addition, perform renal function and hearing screening to determine any short- or long-range toxic effects of these drugs.
  o If cultures are negative but the infant has significant risk for sepsis and/or clinical signs, the clinician must decide whether to provide continued treatment. Three days of negative cultures should provide confidence in the data; however, a small number of infants with proven sepsis at postmortem had negative cultures during their initial sepsis workup. Management is further complicated if the mother received antibiotic therapy before delivery, especially close to delivery. This may result in negative cultures in the infant who is still ill. Review all diagnostic data, including cultures, maternal and intrapartal risk factors, CSF results, the CBC and differential radiographs, and the clinical picture to determine the need for continued therapy. Treatment for 7-10 days may be appropriate, even if the infant has negative cultures at 48 hours.

- o The clinician may require different antibiotic choice, dosage, and/or treatment time if the infant has bacterial meningitis. Perform a follow-up lumbar puncture within 24-36 hours after antibiotic therapy has been initiated to determine if the CSF is sterile. If organisms are still present, modification of drug type or dosage is required to adequately treat the meningitis. Continue antibiotic treatment for 2 weeks after sterilization of the CSF or for a minimum of 2 weeks for gram-positive meningitis and 3 weeks for gram-negative meningitis, whichever period is longest. Chloramphenicol or trimethoprim-sulfamethoxazole has been shown to be effective in the treatment of highly resistant bacterial meningitis.

- Granulocyte transfusion has been shown to be suitable for infants with significant depletion of the storage neutrophil pool; however, the documentation of storage pool depletion requires a bone marrow aspiration, and the granulocyte transfusion must be administered quickly to be beneficial. The number of potential adverse effects, such as graft versus host reaction, transmission of CMV or hepatitis B, and pulmonary leukocyte sequestration, is considerable. Therefore, this therapy remains an experimental treatment.
- IVIG has been considered for neonatal sepsis to provide type-specific antibodies to improve opsonization and phagocytosis of bacterial organisms and to improve complement activation and chemotaxis of neonatal neutrophils; however, difficulties with IVIG therapy for neonatal sepsis exist. The effect has been transient, and adverse effects associated with the infusion of any blood product can occur. Dose-related problems with this therapy decrease its usefulness in neonatal populations.
- Recombinant human cytokine administration to stimulate granulocyte progenitor cells has been studied as an adjunct to antibiotic therapy. These therapies have shown promise in animal models, especially for GBS sepsis, but require pretreatment or immediate treatment to demonstrate efficacy. The use of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) has been studied in clinical trials, but their use in clinical neonatology remains experimental.
- The infant with sepsis may require treatment aimed at the overwhelming systemic effects of the disease. Cardiopulmonary support and intravenous nutrition may be required during the acute phase of the illness until the infant's condition stabilizes. Monitoring of blood pressure, vital signs, hematocrit, and platelets is vital.

Surgical Care: If hydrocephalus associated with neonatal meningitis occurs, and progressive accumulation of CSF is present, placing a ventriculoperitoneal (VP) shunt may be necessary to drain off the excess fluid. The immediate complications of shunt placement are overdrainage, equipment failure, disconnection, migration of catheter, or shunt infection. Abdominal obstruction, omental cysts, and perforation of the bladder, gall bladder, or bowel occur infrequently. The VP shunt may cause long-term neurologic complications, including slit-ventricle syndrome, seizures, neuro-ophthalmological problems, and craniosynostosis; however, the outcome for children with VP shunt placement is generally good with careful follow-up.

Consultations:

- Infectious disease consultation is useful, especially if the infant is not responding to treatment and/or if an unusual clinical sign is present, such as an unknown rash.
- If neonatal meningitis is identified, consultation with a pediatric neurologist may be necessary for assistance with the initial short-term care or for subsequent outpatient follow-up of neurologic sequelae.
- Consultation with a pediatric pharmacologist may be helpful for advice on dosage and/or antibiotic changes that are necessary because of inadequate or toxic levels obtained with therapeutic monitoring.

Diet: The neonate may need to be given nothing by mouth (NPO) during the first days of treatment because of gastrointestinal symptoms or poor feeding. Consider parenteral nutrition to ensure that the patient's intake of calories, protein, minerals, and electrolytes is adequate during this period. Feeding may be restarted via a nasogastric tube for the infant with serious compromise. Encourage that breast milk be given because of the immunologic protection it provides.

Activity: The infant with temperature instability needs thermoregulatory support with a radiant warmer or incubator. Also, encouraging parental contact is important to ease the stress for parents and continue the bonding between the parents and child.

MEDICATION	Section 7 of 11

Some of the antibiotics commonly used to treat neonatal sepsis syndrome are ampicillin, gentamicin, cefotaxime, vancomycin, metronidazole, erythromycin, and piperacillin. The choice of antibiotic agents should be based on the specific organisms associated with sepsis, sensitivities of the bacterial agent, and prevalent nosocomial infection trends in the nursery. Viral infections, such as herpes and fungal infections, can masquerade as bacterial infections.

Drug Category: *Antibiotics* -- Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting.

Drug Name	Ampicillin (Marcillin, Omnipen, Polycillin, Principen, Totacillin) -- A beta-lactam antibiotic that is bacteriocidal for susceptible organisms, such as GBS, *Listeria*, non–penicillinase-producing *Staphylococcus*, some strains of *H influenzae*, and meningococci.
Pediatric Dose	<7 days and <2000 g: 50 mg/kg/dose IV/IM q12h <7 days and >2000 g: 50 mg/kg/dose IV/IM q8h 7-30 days and <1200 g: 50 mg/kg/dose IV/IM q12h 7-30 days and 1200-2000 g: 50 mg/kg/dose IV/IM q8h 7-30 days and >2000 g: 50 mg/kg/dose IV/IM q6h >30 days: 100-200 mg/kg/d IV/IM divided q6h; dosage may be doubled with proven meningitis
Contraindications	Documented hypersensitivity
Interactions	Aminoglycosides reduce effectiveness when coadministered; probenecid and disulfiram elevate levels; allopurinol decreases effects and has additive effects on ampicillin rash
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Adjust dose in renal failure; evaluate rash and differentiate from hypersensitivity reaction
Drug Name	Gentamicin (Garamycin) -- An aminoglycoside that is bacteriocidal for susceptible gram-negative organisms, such as *E coli* and *Pseudomonas, Proteus,* and *Serratia* species. Effective in combination with ampicillin for GBS and *Enterococcus*.
Pediatric Dose	0-4 weeks and <1200 g: 2.5 mg/kg/dose IV/IM q18h <7 days and 1200-2000 g: 2.5 mg/kg/dose IV/IM q12h <7 days and >2000 g: 2.5 mg/kg/dose IV/IM q12h >7 days and 1200-2000 g: 2.5 mg/kg/dose IV/IM q8h >7 days and >2000 g: 2.5 mg/kg/dose IV/IM q8h IV dosage preferred; IM may be used if IV access difficult
Contraindications	Documented hypersensitivity
Interactions	Coadministration with other aminoglycosides, cephalosporins, penicillins, indomethacin, and amphotericin B may increase nephrotoxicity; because aminoglycosides enhance effects of neuromuscular blocking agents prolonged respiratory depression may occur; coadministration with loop diuretics may increase auditory toxicity of aminoglycosides; possible irreversible hearing loss of varying degrees may occur (monitor regularly)
Pregnancy	D - Unsafe in pregnancy

Precautions	Neonates with renal immaturity, renal disease, auditory impairment, vestibular impairment, hypocalcemia, or who are receiving ECMO; monitoring levels is important to avoid possible renal and auditory damage (normal peaks 4-10 mcg/mL, normal troughs <2 mcg/mL)
Drug Name	Cefotaxime (Claforan) – C3G with excellent in vitro activity against GBS and *E coli* and other gram-negative enteric bacilli. Has good serum and CSF concentrations. Concern exists about the emergence of drug-resistant gram-negative bacteria at a more rapid rate than with traditional penicillin and aminoglycoside coverage. Ineffective against *Listeria* and enterococci. Use in combination with ampicillin.
Pediatric Dose	<7 days: 50 mg/kg/dose IV/IM q12h >7 days: 50 mg/kg/dose IV/IM q8h
Contraindications	Documented hypersensitivity
Interactions	Probenecid decreases renal elimination of cefotaxime and prolongs therapeutic half-life; coadministration with furosemide and aminoglycosides may increase nephrotoxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	History of penicillin hypersensitivity, impaired renal function, or history of colitis
Drug Name	Vancomycin (Lyphocin, Vancocin, Vancoled) -- Bacteriocidal agent against most aerobic and anaerobic gram-positive cocci and bacilli. Especially important in the treatment of MRSA. Recommended therapy when coagulase-negative staphylococcal sepsis is suspected. Therapy with rifampin, gentamycin, or cephalothin may be required with endocarditis or CSF shunt infection by coagulase-negative staphylococcus.
Pediatric Dose	<1 month: <1200 g: 15 mg/kg/dose IV qd 1200-2000 g: 10 mg/kg/dose IV q12h >2000 g: 10 mg/kg/dose IV q8h
Contraindications	Documented hypersensitivity; hearing impairment
Interactions	Concurrent ototoxic or nephrotoxic drugs (eg, aminoglycosides, loop diuretics); erythema, histaminelike flushing and anaphylactic reactions may occur when administered with anesthetic agents; effects in neuromuscular blockade may be enhanced when coadministered with nondepolarizing muscle relaxants
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Administer over 60 min to avoid possibility of histamine reaction, which is characterized by a rash; levels greater than therapeutic trough (5-10 mg/dL) may be associated with ototoxicity; caution in renal failure or neutropenia
Drug Name	Metronidazole (Flagyl) -- Antimicrobial that has shown effectiveness against anaerobic infections, especially *Bacteroides fragilis* meningitis.
Pediatric Dose	<4 weeks and <1200 g: 7.5 mg/kg/dose PO/IV q2d <7 days and 1200-2000 g: 7.5 mg PO/IV qd <7 days and >2000 g: 7.5 mg/kg PO/IV q12h >7 days and 1200-2000 g: 7.5 mg/kg PO/IV q12h >7 days and >2000 g: 15 mg/kg/dose q12h
Contraindications	Documented hypersensitivity; first trimester of pregnancy
Interactions	May increase levels of phenytoin; phenobarbital and rifampin may increase metabolism of metronidazole; when administered with food, a decrease and/or delay in reaching peak levels may occur

Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Liver impairment, blood dyscrasias, CNS disease; inject with caution in patients receiving corticosteroids or patients predisposed to edema because the drug molecule contains sodium
Drug Name	Erythromycin (E-Mycin, Erythrocin) -- Macrolide antimicrobial agent that is primarily bacteriostatic and is active against most gram-positive bacteria, such as *Neisseria* species, *Mycoplasma pneumoniae, Ureaplasma urealyticum,* and *Chlamydia trachomatis*. Not well concentrated in the CSF.
Pediatric Dose	<7 days and <2000 g: 5 mg/kg/dose PO/IV/IM q12h <7 days and >2000 g: 5 mg/kg/dose PO/IV/IM q8h >7 days and <1200 g: 5 mg/kg PO/IV/IM q12h >7 days and >1200 g: 10 mg/kg PO/IV/IM q8h
Contraindications	Documented hypersensitivity; hepatic impairment
Interactions	CYP1A2 and CYP3A4 inhibitor; coadministration may increase toxicity of theophylline, digoxin, carbamazepine, and cyclosporine; may potentiate anticoagulant effects of warfarin
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Avoid parenteral administration because of associated tissue damage; caution in liver disease; estolate formulation may cause cholestatic jaundice; GI adverse effects are common (give doses pc); discontinue use if nausea, vomiting, malaise, abdominal colic, or fever occur
Drug Name	Piperacillin (Pipracil) -- An acylampicillin with excellent activity against *Pseudomonas aeruginosa*. Effective against *Klebsiella pneumonia, Proteus mirabilis, B fragilis, S marcescens,* and many strains of *Enterobacter*. Administer in combination with an aminoglycoside.
Pediatric Dose	<7 days and 1200-2000 g: 75 mg/kg IV/IM q12h <7 days and >2000 g: 75 mg/kg IV/IM q8h >7 days and 1200-2000 g: 75 mg/kg IV/IM q8h >7 days and >2000 g: 75 mg/kg/dose IV/IM q6h
Contraindications	Documented hypersensitivity
Interactions	Synergic and antagonistic interactions observed when combined with various cephalosporins; piperacillin at high concentrations may physically inactivate aminoglycosides; coadministration with aminoglycosides has synergistic effects
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Dosage modification required in patients with impaired renal function

Drug Category: *Antivirals* -- A viral infection, such as HSV, may masquerade as bacterial sepsis. At the onset of the infection, treatment must be initiated promptly to effectively inhibit the replicating virus.

Drug Name	Acyclovir (Zovirax) -- Used for treatment of mucosal, cutaneous, and systemic HSV-1 and HSV-2 infections.
Pediatric Dose	1500 mg/m^2/d PO/IV divided q8h or 30 mg/kg/d PO/IV divided q8h for 14-21 d; doses as high as 45-60 mg/kg/d divided q8h have been used in full-term infants Premature infants: 20 mg/kg/d PO/IV divided q12h for 14-21 d
Contraindications	Documented hypersensitivity
Interactions	Concomitant use of probenecid or zidovudine prolongs half-life and increases CNS toxicity of acyclovir

Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Renal disease, dehydration, underlying neurologic disease, patients with hypoxia and hepatic or electrolyte abnormalities
Drug Name	Zidovudine (Retrovir) -- A thymidine analog that inhibits viral replication. Used to treat patients with HIV.
Pediatric Dose	3 months to 12 years: 90-180 mg/m^2/dose PO q6h; not to exceed 200 mg q6h 0.5-1.8 mg/kg/h continuous IV or 100 mg/m^2/dose intermittent IV q6h
Contraindications	Documented hypersensitivity
Interactions	Acyclovir, ganciclovir, or coadministration with drugs that inhibit glucuronidation (eg, acetaminophen, cimetidine, indomethacin) may increase toxicity
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Bone marrow compromise or impaired renal function; rare severe lactic acidosis and hepatomegaly with steatosis, including fatal cases, reported

Drug Category: *Antifungals* -- Fungal infections can masquerade as bacterial infections and/or may appear at the end of prolonged antibacterial therapy. Their mechanism of action may involve an alteration of RNA and DNA metabolism or an intracellular accumulation of peroxide that is toxic to the fungal cell.

Drug Name	Fluconazole (Diflucan) -- Used to treat susceptible fungal infections, including oropharyngeal, esophageal, and vaginal candidiasis. Also used for systemic candidal infections and cryptococcal meningitis. Fungistatic activity. Synthetic oral antifungal (broad-spectrum bistriazole) that selectively inhibits fungal CYP450 and sterol C-14 alpha-demethylation, which prevents conversion of lanosterol to ergosterol, thereby disrupting cellular membranes.
Pediatric Dose	0-14 days: Oropharyngeal candidiasis: 6 mg/kg PO/IV initial dose; after 3 d, 3 mg/kg q3d for a total of 14 d Esophageal candidiasis: 6 mg/kg PO/IV initial dose, followed by 6-12 mg/kg q3d for 21 d Systemic candidiasis: 6-12 mg/kg/dose PO/IV q3d for 28 d Administer the same doses in older infants as in younger infants; however, the dose is daily For acute cryptococcal meningitis, initial dose is increased to 12 mg/kg, and 6-12 mg/kg/dose is administered for 10-12 wk after the CSF cultures become negative
Contraindications	Documented hypersensitivity
Interactions	CYP2C19 and CYP3A4 inhibitor; levels may increase with hydrochlorothiazide; long-term coadministration of rifampin may decrease levels; may decrease phenytoin clearance; may increase concentrations of theophylline, tolbutamide, glyburide, and glipizide; may increase effects of anticoagulants; may increase cyclosporine concentrations
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Perform periodic liver function and renal function tests; dosage modification required in patients with impaired renal function
Drug Name	Amphotericin B (Amphocin, Fungizone) -- Used to treat severe systemic infections and meningitis caused by susceptible fungi, such as *Candida* and *Aspergillus* species, *Histoplasma capsulatum,* and *Cryptococcus*

	neoformans. Polyene antibiotic produced by a strain of *Streptomyces nodosus;* can be fungistatic or fungicidal. Binds to sterols, such as ergosterol, in fungal cell membrane, causing intracellular components to leak and subsequent fungal cell death.
Pediatric Dose	Test dose: 0.1 mg/kg/dose IV; not to exceed 1 mg/dose infused over 20-60 min or 0.25 mg/kg infused over 6 h; if tolerated, administer 0.25 mg/kg/d; gradually increase dose by 0.25-mg/kg/d increments until desired daily dose reached Maintenance dose: 0.25-1 mg/kg/d IV qd infused over 4-6 h; administer total dosage of 30-35 mg/kg over 6 wk
Contraindications	Documented hypersensitivity
Interactions	Coadministration with other nephrotoxic drugs (eg, antineoplastic agents, aminoglycosides, vancomycin, cyclosporine) may enhance renal toxicity; antineoplastic agents may increase risk of bronchospasm and hypotension; corticosteroids, digitalis, and thiazides may potentiate hypokalemia
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Determine BUN and serum creatinine levels qod while therapy is increased and at least weekly thereafter; monitor serum potassium and magnesium closely; check electrolytes, CBC, liver function studies, input and output, BP, and temperature regularly; administer slowly because cardiovascular collapse reported after rapid injection

FOLLOW-UP	Section 8 of 11

Further Outpatient Care: The primary care provider should follow up with the infant within one week of discharge from the hospital. The infant can be evaluated for superinfection associated with antibiotic therapy, especially if the therapy was prolonged. Determine if the feeding regimen and activity have returned to normal. Stress to the family the importance of adhering to the immunization schedule.

Transfer:

- The infant may require transfer to a level III perinatal center, especially if he or she requires cardiopulmonary support and/or parenteral nutrition.
- The multidisciplinary services available are necessary when treating a neonate with acute compromise.

Deterrence/Prevention: The Committee on Infectious Diseases of the AAP recommends that obstetric care include a strategy to manage early-onset GBS disease. Treat women with GBS bacteriuria during pregnancy when it is diagnosed and at delivery. The committee also recommends that women who have previously given birth to an infant with GBS disease be intrapartally treated. Practitioners should use either a strategy based on screening the mother or a strategy based on the presence of intrapartum risk factors to minimize the risk of early-onset GBS disease.

Complications: Infants with meningitis may acquire hydrocephalus and/or periventricular leukomalacia. They may also have complications associated with the use of aminoglycosides, such as hearing loss and/or nephrotoxicity.

Prognosis: With early diagnosis and treatment, infants are not likely to experience long-term health problems associated with neonatal sepsis; however, if early signs and/or risk factors are missed, the mortality rate increases. Residual neurologic damage occurs in 15-30% of neonates with septic meningitis.

Medical/Legal Pitfalls:

- Delay in diagnosis and initiation of treatment may result in death of the infant.

- Failure to provide prophylaxis to women with GBS infection may create liability if the infant subsequently becomes ill.

Special Concerns: The Joint Commission on Infant Hearing of the AAP recommends that infants who received aminoglycosides should have audiology screening before discharge. Screen these infants again at 3 months, but no later than 6 months, to determine whether damage has occurred.

Picture 1. Prevention strategy for early-onset group B streptococcal (GBS) disease using risk factors without prenatal culture screening.

Picture 2. Prevention strategy for early-onset group B streptococci (GBS) disease using prenatal culture screening at 35-37 weeks of gestation. Plus sign indicates positive culture results; minus sign indicates negative culture results.

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Neonatal Sepsis excerpt

Neural Tube Defects in the Neonatal Period

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INTRODUCTION	Section 2 of 11

Congenital deformities involving the coverings of the nervous system are called neural tube defects (NTDs). NTDs vary in severity. The mildest form is spina bifida aperta, in which osseous fusion of one or more vertebral arches is lacking without involvement of the underlying meninges or neural tissue. A slightly more severe form of spina bifida, which is discussed in detail in this article, is spina bifida cystica or myelomeningocele, in which a saclike casing is filled with cerebrospinal fluid (CSF), spinal cord, and nerve roots that have herniated through a defect in the vertebral arches and dura (see Image 1).

Anencephaly and rachischisis are extremely severe forms of NTD in which an extensive opening in the cranial and vertebral bone exists with an absence of variable amounts of the brain, spinal cord, nerve roots, and meninges. Anencephaly has been studied since antiquity, and an almost dizzying array of synonyms and classifications exists. For a more complete description of anencephaly, see the Bibliography for the seminal work written by Lemire, Beckwith, and Warkany in 1978.

Malformations of the brain and spinal cord may result from genetic mutation or may be acquired deformities. Most malformations, especially those such as NTDs, occur early in embryogenesis and are likely the result of aberrant expression of a yet undefined developmental gene or family of genes. The nervous system develops in a precise temporal embryologic sequence; therefore, an interruption of one part of the developmental sequence often affects remaining development.

The NTD discussed in this article is classified as an embryologic induction disorder. It results in failure to properly form both the mesoderm and neuroectoderm. The primary embryologic defect in all NTDs is failure of the neural tube to close, affecting neural and cutaneous ectodermal structures. The inciting event can be traced to days 17-30 of gestation.

The precise etiology and the specific genes that may be involved during this abnormal neural ontogenesis have not yet been elucidated. These deformities are not only disorders of embryologic induction but also disorders of cellular migration and include the secondary mechanical complications that occur with an unprotected nervous system. Specifically, the amniotic fluid can have a caustic and destructive effect on the open neural structures.

As described, the primary defect is a failure of the neural folds to fuse in the midline and form the neural tube, which is neuroectoderm. However, the subsequent defect is the maldevelopment of the mesoderm, which, in turn, forms the skeletal and muscular structures that cover the underlying neural structures. These NTD defects can be open (neural structures that communicate with the atmosphere) or closed (skin covered). They can be ventral or dorsal midline defects.

Pathology
Spina bifida cystica

The 2 major types of defects seen with spina bifida cystica are myelomeningoceles and meningoceles. Cervical and thoracic regions are the least common sites, and lumbar and lumbosacral regions are the most common sites for these lesions.

Myelomeningocele is a condition in which the spinal cord and nerve roots herniate into a sac comprising the meninges. This sac protrudes through the bone and musculocutaneous defect. The spinal cord often ends in this sac in which it is splayed open, exposing the central canal. The splayed open neural structure is called the neural placode. This type of NTD is the subject of most of this article (see Image 1). Certain neurologic anomalies, such as hydrocephalus and Chiari II malformation (discussed later in this article), accompany myelomeningocele. In addition, myelomeningoceles have a higher incidence of associated intestinal, cardiac, and esophageal malformations, as well as renal and urogenital anomalies. Most neonates with myelomeningocele have orthopedic anomalies of their lower extremities and urogenital anomalies due to involvement of the sacral nerve roots.

A meningocele is simply herniation of the meninges through the bony defect (spina bifida). The spinal cord and nerve roots do not herniate into this dorsal dural sac. These lesions are important to differentiate from a myelomeningocele because their treatment and prognosis are so different from myelomeningocele. Neonates with a meningocele usually have normal examination findings and a covered (closed) dural sac. Neonates with meningocele do not have associated neurologic malformations such as hydrocephalus or Chiari II.

A subtype of spina bifida is called lipomeningocele, or lipomyelomeningocele, which is a common form of NTD treated by pediatric neurosurgeons. These lesions have a lipomatous mass that herniates through the bony defect and attaches to the spinal cord, tethering the cord and often the associated nerve roots. The lipomyelomeningocele can envelop both dorsal and ventral nerve roots, only the dorsal nerve roots, or simply the filum terminale and conus medullaris. These lesions do not have associated hydrocephalus but have a more guarded prognosis than simple meningoceles. The surgical correction of these lesions is more complex, and the retethering rate in which an additional surgery is required is as high as 20% in some series.

In a third rare type of spina bifida cystica called myelocystocele, the spinal cord has a large terminal cystic dilatation resulting from hydromyelia. The posterior wall of the spinal cord often is attached to the skin (ectoderm) and is undifferentiated, thus giving rise to a large terminal skin-covered sac. The vast majority of the lesions are dorsal, although a small minority (approximately 0.5%) are ventral in location. The most common ventral variant is an anterior sacral meningocele, which most often is discovered in females as a pelvic mass.

Spina bifida occulta

In this group of NTDs, the meninges do not herniate through the bony defect. This lesion is covered by skin (ie, closed), therefore rendering the underlying neurologic involvement occult or hidden. These patients do not have associated hydrocephalus or Chiari II malformations. Often, a skin lesion such as a hairy patch, dermal sinus tract, dimple, hemangioma, or lipoma points to the underlying spina bifida and neurologic abnormality present in the thoracic, lumbar, or sacral region. Presence of these cutaneous stigmata above the gluteal fold signifies the presence of an occult spinal lesion. Dimples below the gluteal fold signify a benign, nonneurologic finding such as a pilonidal sinus. This is an important point for differentiating the lesions that have neurologic involvement from those that do not.

An experienced pediatrician or surgeon should examine any neonate with cutaneous stigmata on the back around the gluteus. A good rule of thumb is that a lesion (eg, pit, tract) below the gluteal crease is often a pilonidal sinus and needs no further evaluation. Those tracts, pits, or lesions above the gluteal fold should be evaluated with further study.

Lesions that are questionable can be scanned with ultrasound in a neonate or with MRI in an older child. The ultrasound or MRI delineates the presence or absence of a tethered cord or other spinal anomaly. Plain radiology can reveal a panoply of anomalies, such as fused vertebrae, midline defects, bony spurs, or abnormal laminae. An MRI often is useful in evaluating for a split cord malformation (ie, diastematomyelia), in which a bony spur splits the spinal cord, or a duplication of the spinal cord and nerve roots (diplomyelia). More commonly, the neurosurgeon is searching for tethering of the spinal cord by a sinus tract or thickened filum that can cause traction on the spinal cord with subsequent neurologic deficits as the child grows.

A growing body of evidence indicates that the surgical repair of these lesions is more effectively performed in a prophylactic fashion. Once the patient experiences a significant neurologic deficit such as a neurogenic bladder or leg weakness from these occult spinal lesions, the surgical remedy may not return the patient to previous neurologic status.

Signs and symptoms of occult spinal disorders in children include the following:

- Radiologic signs
    - Lamina defects
    - Hemivertebrae
    - Scoliosis
    - Widening of interpedicular distance
    - Butterfly vertebrae
- Cutaneous stigmata
    - Capillary hemangioma
    - Caudal appendage
    - Dermal sinus
    - Hypertrichosis
- Orthopedic findings
    - Extremity asymmetry
    - Foot deformities
- Neurological problems
    - Weakness of leg or legs
    - Leg atrophy or asymmetry
    - Loss of sensation, painless sores
    - Hyperreflexia
    - Unusual back pain
    - Abnormal gait
    - Radiculopathy
- Urologic problems
    - Neurogenic bladder
    - Incontinence

Cranium bifida

Several types of midline skull defects are classified under this term, ranging from simple, with minimal clinical significance, to serious life-threatening conditions. The most benign type of cranium bifidum occultum is the persistent parietal foramina or persistent wide fontanelle. The parietal foramina can be transmitted as an autosomal dominant trait via a gene located on the short arm of chromosome 11. The condition is sometimes called "Caitlin marks," after the family for which it was described. Both parietal foramina and a persistent anterior fontanelle are generally asymptomatic and a pediatric neurosurgeon may be asked to evaluate the child for skull fracture, craniosynostosis, or some other reason related to these findings. The best management is observation over time, as these skull defects often close over time.

Cranium bifidum such as an encephalocele is much more serious. Encephaloceles are theorized to occur when the anterior neuropore fails to close during days 26-28 of gestation. Incidence of this anomaly is 10% of the incidence of spina bifida cystica. In the United States, approximately 80% of lesions are found on the dorsal surface of the skull (see Image 5), with most near the occipital bone. In contradistinction, most encephaloceles in Asia are ventral and involve the frontal bone. In the Philippines and other Pacific countries, incidence of anterior encephaloceles that present as hypertelorism, obstructed nares, anterior skull masses, and cleft palate, among other presentations, is high. In most lesions, the sac that has herniated through a midline skull defect is covered with epithelium.

A small number of encephaloceles are associated with syndromes such as Meckel-Gruber syndrome. This syndrome is characterized by an occipital encephalocele that is associated with holoprosencephaly, orofacial clefts, microphthalmia, polycystic kidneys, and cardiac anomalies. This condition is autosomal recessive and has been mapped to chromosome bands 17q21-q24. In the United States, only about 30% of occipital encephaloceles contain cerebral cortex. The rest contain cerebellar tissue, dysplastic tissue with little normal function, glial tissue, or are simple meningeal sacs filled with CSF (as in cranial meningocele).

An MRI is invaluable in planning a surgical approach. The surgeon needs to know the contents of the sac, which can be quite large. In addition, the surgeon needs to know the relationship of the major cerebral venous sinuses to the sac in order to plan a safe operative approach. Finally, the surgeon needs to know if the patient has hydrocephalus. Approximately 60% of these patients require placement of a ventricular peritoneal (VP) shunt after the removal of their encephalocele. Children whose encephaloceles contain large quantities of cerebral cortex often become microcephalic and display significant developmental and learning disabilities.

Anencephaly

Anencephaly is the most severe form of NTD. Rachischisis and craniorachischisis, often used as synonyms, refer to a severe deformity in which an extensive defect in the craniovertebral bone causes the brain to be exposed to amniotic fluid. Neonates with anencephaly rarely survive more than a few hours or days. Historically, these children have been the subject of myths, folklore, and superstitions, and have been referred to as monsters based on their unusual and frightening appearance (see Images 6-7). More recently, scientists have studied this malformation because it serves as a paradigm of the other dysraphic states.

The fetus has a partially destroyed brain, deformed forehead, and large ears and eyes with often relatively normal lower facial structures. Both genetic and environmental insults appear to be responsible for this outcome. The defect normally occurs after neural fold development at day 16 of gestation but before closure of the anterior neuropore at day 24-26 of gestation.

A variety of teratogens have been implicated, including radiation, folic acid deficiency, drugs, and infections. Regardless, 3 basic defects occur in the developing fetus. The first is the defect in notochord development, which results in failure of the cephalic folds to fuse in the midline and make a normal neural tube. The next defect is failure of the mesoderm to develop; mutual induction of all 3 germ layers in a temporally related sequence fails to occur. Therefore, the calvarium and vertebrae (mesoderm) fail to form correctly, exposing the brain to further insult. Finally, this skull and dural defect permits the brain to be exposed to amniotic fluid, thus destroying the developing forebrain neural cells.

Anencephaly is the most common major central nervous system (CNS) malformation in the Western world, and no neonates survive. It is seen 37 times more frequently in females than in males. The recurrence rate in families can be as high as 35%. The incidence is highest in Ireland, Scotland, Wales, Egypt, and New Zealand and lowest in Japan.

Several interesting characteristics in the epidemiology of neural tube defects are as follows:

- Significant ethnic differences in prevalence exist; people of Celtic origin having the highest rate of spina bifida.
- A female predominance exists, with females accounting for 60-70% of children affected.
- Significant differences in geographic distribution exist, with countries in the British Isles having a higher rate than Asian countries.

A worldwide decline in NTD births has been recognized over the past 3 decades. For example, in the United States, New England has seen the incidence of spina bifida drop from 2.31 per 1000 births during the 1930s to 0.77 per 1000 births during the 1960s.

Reasons for the dramatic drop are not completely clear; however, certain factors probably play a part. The decline in neonates with NTD paralleled the development of commonly used prenatal screening tests such as alpha-fetoprotein (AFP) and ultrasonography (US). Termination of pregnancy increased 50-fold in the British Isles after the introduction of prenatal screening. Termination of pregnancy probably accounted for a significant amount of the decline of NTD in the United States, as well. In Atlanta in the early 1990s, more than 30% of affected pregnancies were terminated based on prenatal test results. When analysis is complete, use of periconception folate in the United States will most likely impact the incidence of NTDs in the late part of the 20th century.

In September of 1992, the US Public Health Service made the following strong recommendation:

All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg folic acid per day for the purpose of reducing the risk of having a pregnancy affected with spina bifida and other neural tube defects. Because the effects of high intakes are not well known, but include complicating the diagnosis of vitamin B-12 deficiency, care should be taken to keep total consumption less than 1 mg per day, except under the supervision of a physician.

That statement and the abundance of scientific data available to the public have reinforced the observation that risk of delivering a child with an NTD decreases significantly with the ingestion of periconception folate.

Prevalence of NTDs such as anencephalus and spina bifida seems to be higher in people of Celtic descent, such as the Welsh, Irish, and Scotch. Their prevalence rate is significantly higher than prevalence rates of persons of Anglo-Saxon or Norman origin. In the United States, the highest rates of NTD are found in Boston in people of Irish descent. In contradistinction, Africans, African Americans, and Asians seem to have very low prevalence rates of NTD. Recurrence risk of giving birth to a second child with an NTD varies with incidence. Investigators found the risk of having an additional affected birth after an anencephalic or spina bifida birth to be approximately 10.4% in Belfast but only about 4.12% in London. The risk in the United States is 1-3%.

The sex difference in prevalence seems to be consistent in most studies. About 55-70% of NTDs occur in females. This female predominance is seen in both stillbirths and live births.

The human embryo passes through 23 stages after conception, each occupying approximately 2-3 days. Two different processes form the central nervous system. The first is primary neurulation, which refers to the formation of the neural structures into a tube, thereby forming the brain and

to the lumbar and sacral elements. The neural plate is formed at stage 8 (days 17-19), the neural fold occurs at stage 9 (days 19-21), and the fusion of the neural folds occurs at stage 10 (days 22-23). Any disruption at stages 8-10 (ie, when the neural plate begins its first fold and fuses to form the neural tube) can cause craniorachischisis, the most severe form of NTD.

Stage 11 (days 23-26) is when the closure of the rostral neuropore occurs. Failure at this point results in anencephaly (see Images 6-7). Myelomeningocele is a result of disruption of stage 12 (days 26-30), closure of the caudal neuropore. Beyond day 26, a disruption is unlikely to be able to cause an NTD such as myelomeningocele (see Image 1).

Studies on mice embryos have provided some unifying theories for explaining the associated anomalies seen with neural tube defects. Associated defects include hydrocephalus and hindbrain malformations such as Chiari II malformation. McLone and Naidich, in 1992, proposed a unifying theory of neural tube defects that explains both the hindbrain anomalies and the spinal cord anomalies. According to these investigators, the initial event is a failure of the neural folds to completely close, leaving a dorsal defect or myeloschisis. This permits the CSF to leak from the ventricles through the central canal and into the amniotic fluid and creates a collapse of the primitive ventricular system.

Failure of the primitive ventricular system to increase in size and volume leads to both downward and upward herniation of the small cerebellum. In addition, the posterior fossa does not develop to its full size, and the neuroblasts do not migrate outward at a normal rate from the ventricles into the cortex. Therefore, the entire panoply of defects occurs from an initial inciting event.

The precise genes (overexpressed or underexpressed) in this event have not been identified. The sonic hedgehog (*Shh*) gene has been identified in defects that cause hydrocephalus secondary to holoprosencephaly. This gene is believed to induce growth of the neural plate and helps close the neural tube by exerting a strong influence on the ventral and medial structure of the prosencephalon. The precise relationship of the *Shh* gene with neural tube defects is yet to be defined. Below is a table with the suspected embryologic event and result.

Table 1. Human Central Nervous System Malformations

Days of Gestation	Event	Resultant Malformation
0-18	Formation of three germ layer and neural plate	Death or unclear effect
18	Formation of neural plate and groove form	Anterior midline defects
22-23	Appearance of optic vessels	Hydrocephalus (18-60 d)
24-26	Close anterior neuropore	Anencephaly
26-28	Close posterior neuropore	Cranium bifidum, spina bifida cystica, spina bifida occulta
32	Vascular circulation	Microcephaly (30-130 d), migration anomalies
33-35	Splitting of prosencephalon to make paired telencephalon	Holoprosencephaly
70-100	Formation of corpus callosum	Agenesis of the corpus callosum

Over the last century, teratogens implicated in the etiology of NTD in experimental animals and in humans include potato blight, hyperthermia, low economic status, antihistamine and sulfonamide use, nutritional deficiencies, vitamin deficiencies, and anticonvulsant use. Of all the suspected teratogens, carbamazepine, valproic acid, and folate deficiency have been most strongly tied to the development of NTD. In humans, carbamazepine and valproic acid have been definitively identified as teratogens. Valproic acid is a known folate antagonist and may work through that action. A woman taking valproic acid during pregnancy has an estimated risk of 1-2% of having a child with an NTD. Therefore, women taking antiepileptic drugs during pregnancy are advised to undergo routine prenatal screening with AFP.

Smithells first advanced the concept that nutrition may be related to the development of NTD in the 1970s. He noted that a low erythrocyte folate and leukocyte ascorbic acid during the first trimester resulted in more pregnancies affected by NTDs than in controls. His early work led to 2 important randomized controlled studies on the use of periconception folate by British and Hungarian research groups.

The Medical Research Council in Britain performed a prospective, randomized, double-blind, multicenter trial to see if women who previously gave birth to children with NTDs could lower the recurrence rate with multivitamins or folate (4 mg/d). Thus, 1817 women who had had a previous child with an NTD and 1195 women who had not were randomized into 4 groups. One group received multivitamins, another group received folate, the third group received both, and the fourth group received neither. The study was terminated early when a significant protective effect was observed in the groups that received folic acid but not in the groups that did not. Multivitamins alone had no significant protective effect. Folic acid ingestion in the preconception period prevented an estimated 72% of recurrent NTDs. The article with this conclusion was published in *Lancet* in 1991.

Hungarian investigators performed a randomized, double-blind, multicenter trial of folic acid to see if it had a protective effect for a first occurrence of NTD. One group of 2104 women received 0.8 mg of folic acid with their multivitamins, while the second group of 2052 women received no folic acid with their multivitamins. The folic acid group had no cases of NTD, while the non–folic-acid group had 6 cases. This finding, published in the *New England Journal of Medicine* in 1992, indicated that ingestion of preconception folic acid significantly decreased the first occurrence of NTD. For this reason, the US Public Health Service issued their strongly worded recommendation to women of childbearing age to take folic acid supplements.

However, several important issues have been raised. Since only 50% or fewer of the pregnancies in the United States are planned, compliance with the request to ingest preconception folic acid is not always easy to achieve. Folic acid is not protective unless ingested in the periconception period. The NTD occurs before day 26 postfertilization, often before many women have discovered their pregnancy. The precise minimal dose of folate required to be protective against an NTD has not been determined, thus making routine food fortification a difficult issue. Furthermore, folic acid can mask a vitamin B-12 deficiency that can cause neurologic damage. For these reasons, ingesting daily folic acid in the form of a multivitamin tablet has become the preferred recommendation. Finally, the precise mechanism in which folic acid is protective is unclear.

Over the past decade, fetal surgery for NTDs (specifically, myelomeningocele) has developed. Interest in this approach to the treatment of NTDs stems from a growing body of literature that supports the 2-hit hypothesis. Initially, most investigators believed that all the neurologic deficits seen in NTDs resulted from the neurulation defect that occurs during days 26-28 of gestation. However,

with skin in utero theoretically decreases the damage to the exposed neural structures. In addition, it has been suggested that the loss of CSF through the central canal can be halted by in utero closure of the neural placode, thereby reversing some of the potentially devastating neurologic sequelae of NTDs.

The 2 neurologic sequelae of major concern are shunt-dependent hydrocephalus and hindbrain injury from progressive hindbrain herniation through the foramen magnum (Chiari II malformation). In 1999, Vanderbilt University researchers, led by pediatric neurosurgeon Noel Tulipan, MD, and obstetrician Joseph P. Bruner, MD, reported in *JAMA* their experience with in utero surgery for NTD over the previous decade. This was a single-institution nonrandomized, observational study conducted between 1990 and 1999. A cohort of 29 patients with isolated myelomeningocele underwent intrauterine repair of the NTD between 24 and 30 weeks of gestation. These patients were compared to 23 lesion-matched controls who underwent postnatal surgery. The main outcome measure was requirement for placement of a ventriculoperitoneal shunt for the treatment of hydrocephalus.

Results of the study have been promising. NTD patients who underwent in utero surgery experienced a lower incidence of hydrocephalus than the control group (59% versus 91%). Also, a reduced incidence of hindbrain herniation was evident in the in utero group (38% versus 95%). One death occurred in the in utero group, as did an increased risk of oligohydramnios (48% versus 4%), and an earlier age of delivery by about 4 weeks. Regardless, the results have encouraged a group of investigators from both Vanderbilt and Children's Hospital of Pennsylvania (CHOP) to propose that a few select centers investigate whether this approach will yield durable results. (CHOP published their results in *The Lancet* in 1998). Since that proposal, the NIH has funded grants to study the efficacy of in utero surgery in this patient population. Currently, the following 3 centers are conducting this research: CHOP/University of Pennsylvania, Vanderbilt, and the University of California at San Francisco.

Specific questions to be answered are as follows:

- Will the decreased rate of shunt dependency hold up through time?
- Will the decreased incidence of hindbrain herniation translate into a decreased incidence of hindbrain-related neurologic complications?
- Will the decreased incidence in hydrocephalus and hindbrain herniation translate into improved neurologic status for both the hindbrain structures and the lower extremities?
- Will the significant risks to the fetus and mother be outweighed by the long-term potential benefits to the NTD-affected child?

These questions have not yet been answered, and only further long-term study that compares the experimental results to those of a historical cohort can accurately answer these questions. Until then, this approach still is considered experimental. So far, the Vanderbilt center has performed over 100 in utero surgeries for NTD. To read more on the subject, 2 very interesting web sites are as follows: fetalsurgeons.com and fetal-surgery.com.

DIAGNOSTIC DETECTION OF NTDS AND ASSOCIATED NEUROLOGIC LESIONS	Section 7 of 11

Presence of open NTDs can be detected with the measurement of AFP in the amniotic fluid or maternal bloodstream. AFP is the major serum protein in early embryonic life and is 90% of the total serum globulin in a fetus. It is believed to be involved in preventing fetal immune rejection and is first made in the yolk sac and then later in the gastrointestinal system and liver of the fetus. It goes from the fetal blood stream to the fetal urinary tract, where it is excreted into the maternal amniotic fluid. The AFP also can leak into the amniotic fluid from open NTDs such as anencephaly and myelomeningocele in which the fetal blood stream is in contact with the amniotic fluid.

The first step in prenatal screening is drawing the maternal AFP between 15 and 20 weeks of gestation. A patient-specific risk then is calculated based on gestational age and AFP level. Normal

AFP concentration in the maternal serum is usually lower than 500 ng/mL. Determining precise gestational age is essential because fetal AFP levels are age specific and can peak in a normal fetus at 12-15 weeks of gestation. For example, at 20 weeks' gestation, a maternal serum AFP concentration higher than 1,000 ng/mL would be indicative of an open NTD. The measurement of maternal serum AFP levels is more than 75% accurate in detecting an open NTD at more than 15 weeks of gestation. In patients in whom a question persists, amniotic AFP can be obtained. It is a significantly more accurate test, especially at 15-20 weeks' gestation, and detects approximately 98% of all open NTDs, although this method is not the preferred screening test. Amniotic fluid acetylcholinesterase levels add an increased degree of resolution.

Detection of an NTD with fetal ultrasound in the hands of a skilled ultrasonographer usually is 98% specific. False-positive findings can result from multiple pregnancies or inaccurate fetal dating. However, closed NTDs also can sometimes remain undetected, especially in cases of skin-covered lipomyelomeningoceles and meningoceles, in which the AFP also may be normal. These closed NTDs comprise about 10% or more of total NTDs discovered. A skilled ultrasonographer can detect these lesions with almost 95% sensitivity.

A partial list of the fetal anomalies that are associated with an elevated AFP is as follows:

- Anencephaly
- Spina bifida cystica
- Encephalocele (leaking)
- Conjoined twins
- Omphalocele
- Turner syndrome
- Gastroschisis
- Extrophy of the cloaca
- Oligohydramniosis
- Sacrococcygeal teratoma
- Polycystic kidneys
- Fetal death
- Urinary tract obstruction

If the parents decide not to terminate a pregnancy in which the fetus is affected with an NTD, extensive counseling takes place. Parents are educated on optimal prenatal care and expectations once a child is born. If diagnosed early enough, a discussion of fetal surgery is warranted. Currently, this option is available at only 2 major centers: Vanderbilt Medical Center and University of Pennsylvania. Although this approach has not been proven scientifically advantageous, preliminary evidence suggests that this experimental approach has promise in decreasing resultant neurologic problems in the neonate. Long-term outcome data are currently lacking.

If conventional delivery is chosen, the study by Shurtleff and his colleagues is important to note. Infants with NTD who were exposed to labor and vaginal delivery were more than 2 times more likely to have severe paralysis or motor deterioration than those delivered by cesarean section without labor. Although this remains a controversial point, most centers such as that of the author recommend a cesarean section prior to labor in mothers carrying a fetus with a myelomeningocele.

EVALUATION AND TREATMENT: MEDICAL AND SURGICAL	Section 8 of 11

Neurologic lesions

The myelomeningocele is a saccular protrusion containing a neural placode bathed in CSF (see Image 1). The surface of the sac is covered by arachnoid but no dura or skin. The sac appears velvety red or yellow with thin fragile vessels imbedded in the arachnoid. The nerve roots pass

cases, the spinal cord is attached to the superior aspect of the sac. The myelomeningocele has many other associated CNS anomalies that require attention.

Table 2. Anomalies of the CNS Associated with Myelomeningocele

Anomalies Associated with Myelomeningocele	Approximate Percent of Patients
Chiari II malformation	90%+
Hydrocephalus	90%+
Syringomyelia	88%
Brainstem malformations (cranial nerve)	75%
Cerebral ventricle abnormalities	90%+
Cerebellar heterotopias	40%
Cerebral heterotopias	40%
Agenesis of the corpus callosum	12%
Polymicrogyria	15-30%

Chiari II malformation

Symptomatic Chiari II malformation can occur anytime after birth. The symptomatic Chiari II presentation can be as subtle as new hoarseness and pneumonia or as obvious as a progressive quadriparesis. A brain and cervical cord MRI in patients with myelomeningocele invariably demonstrates a Chiari II malformation with a herniated vermis and syringomyelia. Very few patients require decompression after their first year of life for a symptomatic Chiari II malformation. The surgeon must first and foremost check to see if the shunt apparatus is functioning. Most of the time, a partial or complete obstruction of a VP shunt (based on a shunt tap or surgical exploration) is the etiology of the new brainstem findings. A shunt malfunction causes the hindbrain to herniate and compress the cord, thus causing many of the new findings. Timely repair of the shunt leads to a good outcome with reversal of most deficits.

Hindbrain anomalies

Pathophysiology of Chiari malformations (CMs) has fascinated neurosurgeons and provided a constant stream of literature on the presentation and presumed etiology for the past century. Although originally thought to be a rare neuroembryological disorder associated with NTD, CMs have been recognized with increased frequency in the past 5 decades. The number of patients seen for this disorder has increased since the widespread application of MRI. Another increase in patient referrals has occurred more recently as with improved understanding of the rather wide spectrum of clinical presentation.

In 1883, John Cleland published "Contribution to the study of spina bifida, encephalocele and anencephalus" in the *Journal of Anatomy and Physiology*. Cleland made several novel observations regarding hindbrain malformations on infant autopsy specimens. He described an elongated brainstem and cerebellar vermis, which protruded into the cervical canal in a full-term infant with spina bifida and craniolacunae. Eight years later, Hans Chiari, professor of morbid anatomy at Charles University in Prague, published similar observations on congenital anomalies in the cerebellum and brain stem and commented on the a priori contributions of Cleland. Chiari further

separated his patients into 3 different classifications of hindbrain abnormality, and to ensure no confusion, the descriptions were accompanied by beautiful and detailed illustrations first in 1891, and then later in 1896.

Many textbooks and papers still refer to these hindbrain malformations as Arnold-Chiari malformations. However, the name Arnold-Chiari malformation is not historically accurate. The relatively minor contribution of Arnold to the understanding of this malformation was a report in 1894, which consisted of a description of 1 infant with a teratoma and cerebellar herniation. It was really students of Arnold, namely Schwalbe and Gredieg, in 1907, who erroneously suggested the term Arnold-Chiari Malformation. Unfortunately, this 1907 article failed to correctly attribute the rather significant contributions of Cleland. The subsequent 93 years have not corrected this misnomer. Attempts to name this malformation, Cleland-Arnold-Chiari or Cleland-Chiari malformation have not succeeded. Therefore, for the remainder of this article, the author adheres to a more historically accurate term and refers to these hindbrain anomalies simply as Chiari malformations or CMs.

The different CMs of the hindbrain were later classified as Chiari types I-III, terms that have been employed in a relatively consistent manner over the last century. These lesions are at the extreme end of the spectrum, and patients with these anomalies are difficult to treat from a surgical perspective. Type I is described as downward herniation of the cerebellar tonsils through the foramen magnum.

Type II malformation is herniation of the cerebellar vermis and brainstem below the foramen magnum. Type II malformation also has kinking of the cervicomedullary junction, an upward trajectory of the cervical nerve roots, and associated syringomyelia. The medulla often protrudes below the foramen magnum and into the spinal canal, compressing the cervical cord. The medulla then buckles dorsally and forms a medullary kink" Also, the fourth ventricle often is below the foramen magnum, and the midbrain tectum forms a sharp corner on midsagittal MRI and looks like a beak. Type II malformations are the subject of this section. Type III malformation is essentially a posterior fossa encephalocele or a cranium bifidum with herniation of the cerebellum through the posterior fossa bone and is a more severe neural tube defect.

The only deviation from the consistent terminology is the eponym Chiari type IV malformation. The Chiari type IV malformation consists of cerebellar hypoplasia, not herniation, and is no longer considered a Chiari malformation.

Description and diagnostic studies

A CM II is downward displacement of the cerebellar vermis, fourth ventricle, and brainstem below the foramen magnum into the cervical canal (see Image 4).

In recent years, the terms hindbrain herniation, displacement, descent, and ectopia have been used synonymously in a wide range of posterior fossa conditions. From a historical point of view (prior to MRI), the diagnosis of CM II most often was made using autopsy, air or contrast myelogram, or CT/myelography. Thus, the diagnosis was made infrequently, although all patients with myelomeningocele were thought to have a CM II.

Currently, radiological diagnosis is made using MRI. The crucial measurement in relation to descent of the hindbrain and vermis below the foramen magnum usually is assessed on sagittal section of MRI. The hindbrain or vermis displacement is measured from a straight line drawn between the basion to the opisthion of the foramen magnum. A perpendicular line dropped from the basion/opisthion line to the vermis tip is considered the extent of the herniated brain.

Syringomyelia is a cavitation of the spinal cord whose walls are comprised of glial tissue, whereas hydromyelia is a cavitation or dilatation of the central canal lined by ependyma. The author uses the term syringomyelia in this chapter instead of the more descriptive term syringohydromyelia to avoid generating scientific and semantic confusion. The association of CM II with syringomyelia varies from 80-90%, depending on the patient population studied.

Syringomyelia, the common finding associated with CM, is derived from the Greek words, *syrinx* (meaning tube or pipe) and *muelos* (meaning marrow). Estienne, from France, first described the spinal cord cavitation called syringomyelia in human cadavers in 1546. In 1824, Charles Ollivier d'Angers provided the very descriptive name syringomyelia to the cylindrical dilatation of the spinal cord, which in his illustrative case report, communicated with the fourth ventricle. In 1892, Abbe and Coley from New York performed a myelotomy to drain the syrinx cavity. This was the first recorded surgical procedure to treat syringomyelia.

Hindbrain malformations are the leading cause of syringomyelia. This cavitation of the spinal cord usually is gradually progressive and can cause neurologic deterioration over time. The fluid in the syrinx is identical to the CSF found elsewhere in the subarachnoid space; therefore, theories based on aberrant CSF physiology are invoked to explain the relationship of syringomyelia in patients with CM II. Nevertheless, the pathophysiologic mechanisms that cause these 2 disorders are not well understood. Many excellent theories have been suggested, however, none have been conclusively proven or universally accepted. Examination of the spinal cord in many neonates with myelomeningocele reveals atrophic or poorly developed anterior horn cells, incomplete posterior horns, and small nerve roots.

Initial examination

The initial neurologic examination of a neonate born with a neural tube defect should focus on the neurologic sequelae of the NTD. Specifically, evaluate (1) site and level of the lesion, (2) motor and sensory level, (3) presence of associated hydrocephalus, (4) presence of associated symptomatic hindbrain herniation (eg, CM II), and (5) presence of associated orthopedic deformity.

The lesion is first examined after the birth of a neonate. Myelomeningocele is a consequence of failed closure of the dorsal neural tube. Thus, the lesion appears as a red, raw neural plate structure devoid of dura and skin covering. The sac comprising arachnoid laced with thin, fragile vessels can be filled with CSF escaping from the central canal. A meningocele, in contradistinction, does not have neural tissue in the sac and usually has a nearly complete skin covering.

Open neural tube defects should be immediately covered with a saline-moistened sponge to avoid rupture of the sac and drying of the exposed neural placode. The neonate is maintained and examined in the prone or lateral recumbent position. An IV is placed, and feedings are held until a full assessment can be completed. The neonate is treated with systemic antibiotics consisting of ampicillin at meningitic doses and gentamicin. Common neonatal organisms, such as group B streptococci, and nosocomial organisms must be prevented from entering the CSF, especially through a leaking myelomeningocele.

The neonatologist, pediatric geneticist, pediatric neurosurgeon, and pediatric orthopedist should immediately evaluate the child. Possible cardiac abnormalities are evaluated with ultrasound. An initial ultrasound of the head to evaluate for hydrocephalus also may be performed. Urologic examination by ultrasound followed by a complete pediatric urologic evaluation may be performed initially or at a later date. Orthopedic evaluation is performed shortly before discharge, as up to 10% of neonates with an NTD may have hip dislocations. In addition, presence of a varus or valgus extremity disorder is documented. A higher motor level lesion, such as L3-L4, can predispose some children to hip dislocations due to the unopposed hip flexors.

The pediatric neurosurgeon carefully evaluates the patient to assess the site and type of lesion, including assessment of lower extremity function. Evaluate the symmetry of the motor and sensory levels affected by the NTD. Flaccid paralysis below the L4 level may reveal a strong psoas, but not hip adduction, knee hyperextension, or foot inversion deformities. Flaccid paralysis of the foot with a weak gastrocnemius-soleus complex may result in foot dorsiflexion deformities.

Attention to the anus helps to assess sacral nerve root function. Flaccid musculature in the S2-4 region often presents with a flat buttocks, absence of a well-developed gluteal cleft, and a patulous anus with no anal wink. The thoracic or lumbar region may have a large hump due to kyphosis or scoliosis of the spine; this can be so severe that it impedes the ability to place skin flaps over the NTD

Head ultrasound can be performed during the neonatal period to evaluate the extent of ventricular enlargement. Initially, the ventricles may be normal or only slightly enlarged. However, after the NTD is closed surgically, the ventricles often enlarge. Incidence of hydrocephalus associated with myelomeningocele ranges from 80-95%. In 2 studies performed in the 1980s and 1990s, approximately 85-90% of all patients with NTD required a VP shunt for progressive hydrocephalus. The highest incidence in shunt dependence occurs in thoracic lesions; the lowest incidence occurs in sacral lesions. The risk of shunt revision in this population may be no different from that of other children with shunts. Approximately 40-50% of all children with NTDs require shunt revision in the first year and approximately 10% every year after that.

An MRI may reveal defects in cellular migration in the cerebral cortices. These include gray matter heterotopia, schizencephaly, gyral abnormalities, agenesis and thinning of the corpus callosum, abnormal thalami, and abnormal white matter findings.

Meaningful surgical treatment of myelomeningocele was not undertaken until the invention of the shunt valve by Holter in the 1950s. Prior to that, closure of a myelomeningocele was possible, but the ensuing uncontrolled hydrocephalus decreased the chance of survival. In the 1980s, the US Department of Health and Human Services issued the Baby Doe directive, stating that medical and surgical treatment could not be withheld simply because a neonate is handicapped. Although the directive was struck down, the decision to operate on NTD in neonates was already an accepted practice in the United States. Furthermore, outcome studies by McClone, Shurtleff, and others presented a more positive outcome than had previously been thought for these children.

Timing of myelomeningocele repair

In the 1960s, the birth of a patient with myelomeningocele was a neurosurgical emergency, and immediate closure of the defect was required. Studies have subsequently shown that closure within 48 hours was both safe and effective. A study by Charney et al comparing delayed closure (3-7 d) to immediate closure (<48 h) showed little difference in survival, ventriculitis, or worsening paralysis. The implications of this study were immense: surgeons could plan a deliberate but thorough workup on a neonate with an NTD. Parents would have time to ask questions and be acclimated to the intensive surgical therapy that was about to commence. In the author's Children's Hospital setting, a great deal of time is spent performing a detailed workup and counseling parents. Closure is performed on the next available elective operative time, usually within 72 hours after birth.

Operative approach

Any major procedure on a neonate with myelomeningocele must be performed in such a fashion as to avoid hypovolemia, hypothermia, and airway compromise. Operative techniques vary by institution but, in general, the goal is similar: to circumnavigate the neural placode without injuring any of the neural elements. Once that is completed, the neural placode is placed into the spinal canal.

The next step entails the identification and dissection of the dura. The neural placode is covered by the dura by a watertight closure. If the dura is absent, as sometimes occurs, the muscle fascia is reflected off the muscle and used to create a watertight tube to enclose the neural placode. Skin closure is achieved by mobilizing the skin from the underlying paraspinal fascia in an avascular plane. The skin is then closed in layers, and an attempt is made to ensure little tension is placed on the wound. The skin may look somewhat pale immediately after closure, especially if the slightest bit of tension is present on the wound.

Care is taken to avoid necrosis or ischemia of the skin flap. The skin closure is protected with a sterile dressing.

Shunt placement during myelomeningocele closure

Approximately 20% of all patients with myelomeningoceles have significant hydrocephalus at birth;

placement of a shunt during the same operation for closure of a myelomeningocele is entirely reasonable. At the author's institution, patients who manifest ventriculomegaly after birth undergo shunt placement after myelomeningocele closure but while under the same anesthetic. Shunt placement not only decreases future anesthetic risk, but also it decreases the chance of CSF leaking through the myelomeningocele closure.

Treatment of Chiari II malformations

In CM II, decompression of the posterior fossa and/or cervical cord, with its variable anatomy, is surgically challenging and requires an experienced surgeon. The torcular can come in low near the foramen magnum, the cerebellum often is adherent to the medulla, and there are many venous sinuses. Catastrophic blood loss is the major risk when a sinus is inadvertently opened. Prior to decompressing a CM II, ensure the shunt is functioning. CT scan findings can be misleading, as ventricles can remain small despite an obstruction in the shunt. Shunt tap or exploration is the most reliable test prior to embarking on a Chiari decompression.

The main signs and symptoms of a CM II that requires decompression are those of brainstem compression. For example, neonates can have stridor, central apnea, dysphagia, quadriparesis, or failure to thrive. Patients may have subtle signs, such as worsening strabismus, nystagmus, myelopathy, or aspiration of unclear etiology. Symptomatic CM II is the leading cause of death in our patients with myelomeningocele. (Approximately 30% of children die that develop brainstem symptoms when <5 y.) Symptomatic deterioration from a Chiari II can constitute a neurosurgical emergency and, despite urgent decompression, children can die from hindbrain compression. Patients who fare the worst are those who have ventilatory difficulties shortly after birth. Autopsies on these clinically challenging patients often show brainstem anomalies, such as disorganized brainstem nuclei, as well as cortical and subcortical abnormalities.

Signs and symptoms of problematic CM II in neonates include the following:

- Stridor with vocal cord paralysis
- Central apnea
- Aspiration
- Dysphagia
- Hypotonia
- Progressive brainstem function
- Myelopathy
- Hypotonia, quadriparesis
- Nystagmus, strabismus, progressive
- Swallowing difficulties, poor suck

Lipomyelomeningocele

Although this skin-covered NTD deserves an entire article of its own, a few salient points should be included here. The neonate often presents with a skin-covered mass above the buttocks (see Image 8). The natural history of these lesions consists of eventual neurologic deterioration. Appropriate prophylactic surgical treatment of these lesions can halt the progression of the neurologic deficits and improve neurologic function, and the risk of surgery in skilled hands is quite low.

The surgical goal in treating these lesions is to detach the lipoma of the buttocks from the lipoma that emerges through the dura, fascia, and bony defect. The technique requires the surgeon to identify normal anatomy and travel down to the location where the lipoma pierces the dura and enters the spinal cord. Often with use of microsurgical technique and/or a carbon dioxide laser, the lipoma is disconnected from the spinal cord (see Image 9). All of the lipoma need not be removed. Take care to leave some lipoma on the cord in order to avoid injuring the underlying neural substrate. The filum terminale also is divided to further untether the cord. A patulous graft is then placed over the dural opening to establish a pool of CSF around the cord to help prevent retethering.

Major issues in evaluating the outcome of children with myelomeningocele are hydrocephalus, intellect, ambulation, continence, orthopedic problems, and employment and independent living status Treatment of NTDs in neonates has evolved over the past half century. Historically, there was a period when neonates with NTDs were either left untreated or selectively treated. The natural history of neonates with NTDs left untreated is poor. Most died of meningitis, hydrocephalus, and sepsis. Laurence described a cohort of 290 children with spina bifida (mostly myelomeningoceles) left untreated in Wales during the 1950s and 1960s. Only 11% of those children lived past the first decade of life. Lorber and Salfield reported their results with selected treatment of neonates with myelomeningocele. More than 80% of the selected neonates lived, whereas 97% of the neonates denied treatment died in the first year of life. The tremendous ethical implications of selected neonatal treatment led to its abandonment.

In the United States during the 1960s, most children with myelomeningocele were treated, which resulted in a higher survival rate (>80% for the first decade) than that in Great Britain. Recognized causes of death include shunt malfunctions, seizures, infections, and uncontrolled brainstem symptoms from CM II and/or hydrocephalus. During the past 3 decades, aggressive treatment of neonates with myelomeningocele has been pursued in almost all pediatric centers in the United States.

Intellect

Cognitive ability is, in part, influenced by hydrocephalus, CNS infections, and degree of impairment. In most series, 60-70% of the children with myelomeningocele had intelligence quotients (IQs) greater than 80; the others had IQs in the delayed or severely delayed range. In the McLone series, children who had CNS infections such as ventriculitis, or shunt infections fared worse than those who did not. Children with myelomeningocele without hydrocephalus had an average IQ of 102; those with hydrocephalus had an average IQ of 95. However, the average IQ dropped to 73 when a CNS infection complicated the picture. Children with moderate physical impairments, in most series, have a better intellectual outcome than those with significant sensory levels and paraplegia. The reasons most likely are multifactorial.

Continence

Only 10-15% of all children with myelomeningoceles are continent of urine. This issue often causes the children to be separated from their peers, which, in turn, leads to other neuropsychologic deficits. Despite the development of catheters and Crede manipulation (pushing on the pelvis over the bladder to engender urination), children with NTDs still experience a high rate of infections, vesicoureteral reflux, kidney failure, hydronephrosis, and obstruction. Clean intermittent catheterization (CIC) has led to a marked improvement of the lifestyles and lifespan of these children. CIC can make more than 75% of these children socially continent and significantly decreases the rate of urosepsis. As a result of CIC, urinary diversions are less commonly performed. Use of anticholinergic drugs combined with CIC has resulted in a better self-image and greater educational and vocational opportunities for children with NTDs.

Bowel continence is achieved with a combination of medication, diet control, manual disimpaction, and enemas. Most patients with NTDs can be continent of stool with these measures.

Ambulation

The ability to ambulate is influenced by the level of the neural lesion, hydrocephalus, pelvic anatomy, limb deformities, tethered cord, scoliosis, kyphosis, and syringomyelia, and varying degrees of ambulation exist. Strong hip flexors, adductors, and quadriceps are required to be ambulatory. Some children can ambulate in the community, some only in the home, others can only stand but not walk, and the rest are wheelchair bound. However, many children with NTDs, such as lumbar myelomeningocele, lose their ability to ambulate as they get older. In general, patients with a sacral lesion can ambulate, those with a thoracic lesion cannot.

Independent living, vocation, education

Steinbok noted that about 60% of children with NTDs attended normal classes, while 40% were in special classes or operated below their grade level. Approximately 10-40% of children with myelomeningocele are probably employable at some level, depending on the patient's intellectual abilities, ambulation status, and environmental influences.

Latex allergies

Over the past 2 decades, allergy to latex has been recognized in an increasing number of children with myelomeningocele. Up to 50% of children with myelomeningocele may be latex sensitive. This appears to be a result of a massive immunoglobulin E (IgE) response to the antigen in latex that is derived from the *Heva brasiliensis* plant. Most patients with myelomeningocele should be treated with latex precautions when undergoing surgery. Surgeons and health care providers should work with latex-free gloves and plastics so that they can avoid latex-induced anaphylaxis, which can be life threatening. Medications such as corticosteroids, Benadryl, bronchodilators, and epinephrine should be available as a precaution during surgery on these children.

Late complications

Neurosurgeons need to be wary of late-life neurologic deterioration in children and adults. The most common deterioration seen is from a tethered spinal cord. A routine MRI reveals a spinal cord that ends in the lumbar or sacral regions in almost all patients with myelomeningocele (see Image 3). This is normal in many patients without any new neurologic complaints. Despite careful surgical closure of the original neural placode, approximately 20% or more of all patients with myelomeningocele require an untethering of their spinal cord later in their life. They may present with gait difficulty, back pain, leg weakness, sensory loss, a new foot deformity, or simply a change in their urodynamic data or urinary continence. These patients require a surgical exploration to free the neural placode and nerve roots from the dorsal surface of their dura. Patients with tethered cords on MRI but no new complaints do not require reexploration.

Diastematomyelia can be diagnosed using MRI or CT/myelogram. An enlarging syringomyelia can be the result of a symptomatic CM II or retethering of the spinal cord. Many functional deteriorations result from progressive orthopedic deformities such as scoliosis, pelvic obliquity, and limb deformities. An orthopedic surgeon well versed in the care of patients with NTDs is required to execute a reasonable plan to repair or stabilize treatable disorders.

In general, a multidisciplinary team consisting of neonatologist, pediatrician, pediatric neurosurgeon, pediatric urologist, pediatric orthopedic surgeon, physical therapist, nurse, nutritionist, psychologist, and teacher are required to direct the care of children with NTDs.

Picture 1. Neural tube defects in the neonatal period. Neonate with a lumbar myelomeningocele with an L5 neurologic level. Note the diaphanous sac filled with cerebrospinal fluid and containing fragile vessels in its membrane. Also, note the neural placode plastered to the dorsal surface of the sac. This patient underwent closure of his back and an untethering of his neural placode. The neural placode was circumnavigated and placed in the neural canal. A dural sleeve was fashioned in such a way to reconstruct the neural tube geometry.

Picture 2. Neural tube defects in the neonatal period. This anteroposterior skull radiograph demonstrates the craniolacunia or Lückenschädel seen in patients with myelomeningocele and hydrocephalus. Mesodermal dysplastic changes cause defects in the bone. The thin ovoid areas of calvaria often are surrounded by dense bone deposits. They are most likely the result of defective membranous bone formation typical of neural tube defects and not increased intracranial pressure as once thought. These characteristic honeycomb changes are seen in about 80% of the skulls in children with myelomeningocele and hydrocephalus.
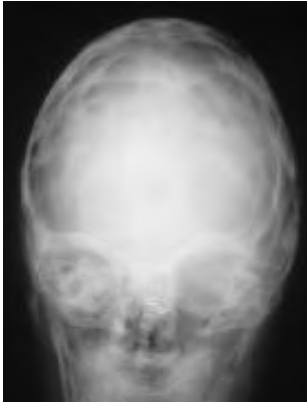
Picture 3. Neural tube defects in the neonatal period. Sagittal T1-weighted MRI image of a child after closure of his myelomeningocele. Child is aged 7 years. Note the spinal cord ends in the sacral region far below the normal level of T12-L1. It is tethered at the point in which the neural placode was attached to the skin defect during gestation. The MRI showed dorsal tethering, and the child complained of back pain and had a new foot deformity on examination.

Picture 4. Neural tube defects in the neonatal period. Sagittal T1 MRI image of a child with a myelomeningocele and associated Chiari II malformation. Note the cerebellar vermis and part of the brainstem has herniated below the foramen magnum and into the cervical canal (arrow). This patient had multiple brainstem symptoms and findings to include stridor and cranial nerve paresis (cranial nerves III, VI, IX, X) despite having a well-functioning ventricular-peritoneal shunt. He required a posterior fossa decompression of his hindbrain in order to relieve the symptoms of hindbrain herniation and brainstem compression. Often times, especially in older children, a shunt revision may alleviate some of the symptoms of hindbrain compression.

Picture 5. Neural tube defects in the neonatal period. Neonate with a large occipital encephalocele lying in the prone position prior to surgical intervention. Note the large skin-covered sac that represents a closed neural tube defect. Often called cranium bifidum, it is a more serious condition that represents a failure of the anterior neuropore to close. In this patient, a defect in the skull base (basicranium) was associated with this large sac filled with cerebrospinal fluid and a small, disorganized remnant of brain. The patient fared satisfactorily after the surgery in which the encephalocele was excised. However, the patient needed placement of a ventricular-peritoneal shunt to treat the resultant hydrocephalus, which is not uncommon. At age 5 years, the child was doing well and had only moderate developmental delay.

Picture 6. Neural tube defects in the neonatal period. Autopsy specimen on a child with anencephaly. This is one of the most common CNS malformations in the West. The neonate, like almost all with such a severe forms of neural tube defects, did not survive more than a few hours or days. This malformation represents a failure of the anterior neuropore to close. This photograph also reveals an absence of the calvarium and posterior bone elements of the cervical canal, as well as the deficiency in the prosencephalon. Photo courtesy of Professor Ron Lemire.

Picture 7. Neural tube defects in the neonatal period. Ventral view of a child with anencephaly that, like the previous picture, shows the loss of cranium and enclosed nervous tissue.

Picture 8. Neural tube defects in the neonatal period. These 2 photographs depict the lumbar regions on 2 different children with closed neural tube defects. Both children have lipomyelomeningocele. The child in the left has a dorsal lipoma that is pedunculated. The child on the right has a more common-appearing lipomatous mass that is heaped up beneath the skin. Both lipomas lead from the subcutaneous tissue, through the dura and into the intradural space, where they are attached to the spinal cord. Photos courtesy of Professor J.D. Loeser.

Picture 9. Neural tube defects in the neonatal period. Photograph of a child undergoing a neurosurgical procedure in which the spinal cord is being detached (untethered) from the intradural and extradural lipomatous mass that fixes it to the subcutaneous tissue. The white arrow shows the laser char on the lipoma that has been shaved off the spinal cord and was connected to the extradural mass. The black arrow shows the extradural lipoma, which crept through the dura and attached to the spinal cord, thereby firmly fixing the spinal cord at too low and too dorsal a location in the sagittal plane.

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Neural Tube Defects in the Neonatal Period excerpt

Omphalitis

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INTRODUCTION	Section 2 of 10

Background: Omphalitis is an infection of the umbilical stump. Omphalitis typically presents as a superficial cellulitis that may progress to necrotizing fasciitis, myonecrosis, or systemic disease. The introduction of aseptic umbilical cord care has greatly reduced the occurrence of omphalitis in newborn infants. Omphalitis has become rare in industrialized countries; however, it remains a common cause of neonatal mortality in less developed areas. Omphalitis is predominantly a disease of the neonate. Although several cases have been reported in adult patients, adult omphalitis is extremely uncommon and is not discussed in this article.

Approximately 85% of cases are polymicrobial in origin. Aerobic bacteria are present in approximately 85% of infections, predominated by *Staphylococcus aureus*, group A *Streptococcus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. In the past, studies emphasized the importance of gram-positive organisms (eg, *S aureus* and group A *Streptococcus*) in the etiology of omphalitis; however, more recent studies have highlighted gram-negative organisms as the cause. These studies suggest that the change in etiology may be caused by the introduction of prophylactic umbilical cord care using antistaphylococcal agents, such as hexachlorophene and triple dye, and the subsequent increase in gram-negative colonization of the umbilical stump. In addition, anaerobic bacteria colonize the maternal genital tract.

When techniques adequate for the recovery of anaerobic bacteria were used in studying newborns with omphalitis, anaerobes were recovered from one third of patients. The predominant anaerobic isolates were *Bacteroides fragilis* and *Clostridium perfringens*. Several mothers whose newborns had omphalitis caused by *B fragilis* also had amnionitis caused by this organism. Isolated cases due to other anaerobic organisms, including *Clostridium sordellii*, also are reported. Neonatal tetanus caused by *Clostridium tetani* usually results from contamination of the umbilical cord during improperly managed deliveries outside of a medical facility or the cultural practice of placing cow dung on the umbilical stump after delivery. Neonatal tetanus is rare in the United States but is common in developing countries.

- The umbilical stump represents a unique but universally acquired wound, in which devitalized tissue provides a medium that supports bacterial growth. Normally, the cord area is colonized with potential bacterial pathogens during or soon after birth. These bacteria have the potential to invade the umbilical stump, leading to omphalitis. If this occurs, the infection may progress beyond the subcutaneous tissues to involve fascial planes (necrotizing fasciitis), abdominal wall musculature (myonecrosis), and the umbilical and portal veins (phlebitis). The factors that cause colonization to progress to infection are not well understood.

Frequency: Internationally:

- Overall incidence varies from 0.2-0.7% in industrialized countries. Incidence is higher in hospitalized preterm infants than in full-term infants. Episodes of omphalitis are reported and usually are sporadic, but rarely, epidemics occur, eg, due to group A *Streptococcus*.

Mortality/Morbidity:

- Outcome usually is favorable in infants with omphalitis associated with cellulitis of the anterior abdominal wall. In a study by Sawin and colleagues, no deaths occurred among 32 infants with omphalitis in the absence of necrotizing fasciitis and myonecrosis. The mortality rate among all infants with omphalitis, including those who develop complications, is estimated at 7-15%. The mortality rate is significantly higher (38-87%) after the development of necrotizing fasciitis or myonecrosis. Suggested risk factors for poor prognosis include male sex, prematurity or being small for gestational age, and septic delivery (including unplanned home delivery); however, data are limited and conclusions cannot be drawn regarding the role of these factors in the mortality rate.
- Sequelae of omphalitis may be associated with significant morbidity and mortality, including necrotizing fasciitis, myonecrosis, endocarditis, portal vein thrombosis, sepsis, septic embolization, and death (see Complications).

Sex: No sex predilection has been reported, although male may have a worse prognosis than female

Age:

- In full-term infants, the mean age at onset is 5-9 days.
- In preterm infants, the mean age at onset is 3-5 days.

CLINICAL	**Section 3 of 10**

History:

- A detailed review of the pregnancy, labor, delivery, and the neonatal course is important (see below). A history of poor feeding or feeding intolerance may be an early indication of infection. A history of change in mental status, such as irritability, lethargy, and somnolence, or a history of a decreased level of activity may be an important indicator of systemic dissemination of the infection.
- Anaerobic bacteria are part of the normal flora of the female genital tract and are commonly involved in ascending infections of the uterus and in septic complications of pregnancy; therefore, the higher incidence of omphalitis caused by anaerobes (especially *B fragilis*) in infants with adverse perinatal histories, such as premature or prolonged rupture of membranes and amnionitis, may relate to exposure to maternal infection.
- History of urine or stool discharge from the umbilicus suggests an underlying anatomic abnormality.

- Local disease: Physical signs vary with the extent of disease. Signs of localized infection include the following:

  - Purulent or malodorous discharge from the umbilical stump
  - Periumbilical erythema
  - Edema
  - Tenderness

- Extensive local disease: The following signs indicate more extensive local disease, such as fasciitis or myonecrosis. These signs also may suggest infection by both aerobic and anaerobic organisms and include the following:

  - Periumbilical ecchymoses
  - Crepitus
  - Bullae
  - Progression of cellulitis despite antimicrobial therapy

- Systemic disease: Signs of sepsis or other systemic disease are nonspecific and include disturbances of thermoregulation or evidence of dysfunction of multiple organ systems. Examples include the following:

  - Disturbances of thermoregulation - Fever (temperature >38°C), hypothermia (temperature <36°C), or temperature instability
  - Cardiovascular disturbances - Tachycardia (pulse >180 beats per minute [bpm]), hypotension (systolic blood pressure <60 mm Hg in full-term infants), or delayed capillary refill (<2-3 s)
  - Respiratory disturbances - Apnea, tachypnea (respirations >60/min), grunting, flaring of the alae nasi, intercostal or subcostal retractions, or hypoxemia
  - Gastrointestinal tract disturbances - Rigid or distended abdomen or absent bowel sounds
  - Cutaneous abnormalities - Jaundice, petechiae, or cyanosis
  - Neurologic abnormalities - Irritability, lethargy, weak sucking, hypotonia, or hypertonia

Causes:

- Omphalitis is a polymicrobial infection typically caused by a mixture of aerobic and anaerobic organisms. Associated risk factors include the following:

  - Low birthweight (<2500 g)
  - Prior umbilical catheterization
  - Septic delivery (as suggested by premature rupture of membranes, nonsterile delivery, or maternal infection)
  - Prolonged rupture of membranes

- Omphalitis occasionally manifests from an underlying immunologic disorder. Several infants with chronic omphalitis were subsequently diagnosed with leukocyte adhesion deficiency, a rare immunologic disorder with an autosomal recessive pattern of inheritance. These infants typically present with the following:

  - Leukocytosis
  - Delayed separation of the umbilical cord
  - Recurrent infections

- Omphalitis also may be the initial manifestation of neutropenia in the neonate. Infants with neonatal alloimmune neutropenia have presented with omphalitis. Neonatal alloimmune neutropenia is a disease analogous to Rh-hemolytic disease and results from maternal sensitization to fetal neutrophils bearing antigens that differ from the mother's. Maternal immunoglobulin G antibodies cross the placenta and result in an immune-mediated neutropenia that can be severe and last for several weeks to 6 months. Affected infants may present with other cutaneous infections, pneumonia, sepsis, and meningitis. Since omphalitis complicated by sepsis also can be associated with neutropenia, the underlying immune-mediated neutrophil destruction may not be immediately appreciated in affected newborns.
- Rarely, an anatomic abnormality may be present, such as a patent urachus or patent omphalomesenteric duct.
- Other abnormalities associated with serious systemic infection include the following:

  - Hypoglycemia
  - Hypocalcemia (often related to saponification with fatty acids released by bacterial lipases in subcutaneous tissue)
  - Metabolic acidosis

Other Problems to be Considered:

The clinical picture of omphalitis is sufficiently characteristic that diagnosis can be made with fair certainty on clinical grounds. Determining whether associated complications are present, such as systemic infection or necrotizing fasciitis, myonecrosis, endocarditis, or portal vein thrombosis, is important. In neonates with omphalitis and either delayed separation of the umbilical cord or neutropenia, the presence of a predisposing anatomic abnormality (eg, patent urachus) or an immunologic problem (eg, leukocyte adhesion deficiency or neonatal alloimmune neutropenia) must be considered.

Persistence of a portion of the embryonic tract between the bladder and the umbilicus results in a variety of urachal anomalies. A patent urachus, a free communication between the bladder and umbilicus, may result in persistent drainage from the umbilicus, which can be mistaken as a sign of infection. Incomplete obliteration of the urachal remnant may lead to the formation of an isolated extraperitoneal cyst, which can present with a secondary bacterial infection mimicking omphalitis. However, these cysts rarely present with secondary infections in the neonatal period.

Lab Studies:

- Obtain specimens from umbilical infection routinely, and submit specimens for Gram stain and culture for aerobic and anaerobic organisms. If myonecrosis is suspected, obtain specimens from the involved muscle rather than the wound surface.
- Obtain a blood culture for aerobic and anaerobic organisms.
- Obtain a complete blood count with manual differential.

  - Neutrophilia or neutropenia may be present in acute infection. An immature-to-total neutrophil ratio greater than 0.2 may be a useful indicator of systemic bacterial infection in the first few days of life.
  - Thrombocytopenia may be present.

- Other nonspecific laboratory tests, either alone or in combination with a defined scoring system, have been evaluated for their usefulness in rapid detection of bacterial infection in neonates, although none has demonstrated sensitivity or specificity sufficiently high to dictate clinical care. The tests include the following:

  - C-reactive protein levels
  - Erythrocyte sedimentation rate
  - Limulus lysate test, which detects endotoxin

- The following laboratory studies are suggested in neonates in whom sepsis and disseminated intravascular coagulation (DIC) are suspected:

  - Prothrombin time
  - Activated partial thromboplastin time
  - Fibrinogen
  - Fibrinogen split products or D-dimer

Imaging Studies:

- Abdominal radiographs may reveal intra-abdominal wall gas.
- Computed tomographic (CT) scan of the abdomen may determine the presence and extent of muscle involvement.

Procedures:

- Lumbar puncture may be warranted in infants in whom sepsis is suspected.

Histologic Findings:

- Analysis of biopsy specimens may reveal necrotizing fasciitis, which is an acute inflammatory infiltrate found in subcutaneous fat and connective tissue, or myonecrosis, which is an acute inflammatory process surrounding muscle bundles, many of which are no longer viable.

Medical Care: Treatment of omphalitis (periumbilical edema, erythema, and tenderness) in the newborn includes antimicrobial therapy and supportive care.

- Antimicrobial therapy

  - Include parenteral antimicrobial coverage for gram-positive and gram-negative organisms. A combination of an antistaphylococcal penicillin and an aminoglycoside antibiotic is recommended.
  - Some believe that anaerobic coverage is important in all patients. Omphalitis complicated by necrotizing fasciitis or myonecrosis requires a more aggressive approach, with antimicrobial therapy directed at anaerobic organisms as well as gram-positive and gram-negative organisms.
    - Metronidazole may provide anaerobic coverage.
    - Clindamycin may be substituted for the antistaphylococcal penicillin.
    - As with antimicrobial therapy for other infections, consider local antibiotic susceptibility patterns.
    - *Pseudomonas* species have been implicated in particularly rapid or invasive disease.

  - Expect erythema of the umbilical stump to improve within 12-24 hours after the initiation of antimicrobial therapy.

- Supportive care: In addition to antimicrobial therapy, supportive care is essential to survival. These measures include the following:
    - Provide ventilatory assistance and supplementary oxygen for hypoxemia or apnea unresponsive to stimulation.
    - Administer fluid, vasoactive agents, or both for hypotension.
    - Administration of platelets, fresh frozen plasma, or cryoprecipitate for DIC and clinical bleeding is suggested.
    - Treat infants at centers capable of supporting cardiopulmonary function.

- Other treatment considerations

    - Monitor patients for progression of disease. Early surgical intervention may be lifesaving.
    - The role of hyperbaric oxygen in treatment of patients with anaerobic necrotizing fasciitis and myonecrosis is controversial because no prospective controlled data are available and pediatric data are scarce. In the treatment chambers, tissue levels of oxygen are maximized when the patient breathes 100% oxygen at 2-3 atm. The delivery of high concentrations of oxygen to marginally perfused tissues may have a detrimental effect on the growth of anaerobic organisms and improve phagocyte function. However, surgical therapy has the highest priority, and initiation of hyperbaric oxygen therapy should not delay transport to a facility with staff capable of performing surgical debridement.

Surgical Care:

- Management of necrotizing fasciitis and myonecrosis involves early and complete surgical debridement of the affected tissue and muscle. Although the extent of debridement depends on the viability of tissue and muscle, which is determined at the time of surgery, excision of preperitoneal tissue (including the umbilicus, umbilical vessels, and urachal remnant) is critically important in the eradication of the infection. These tissues can harbor invasive bacteria and provide a route for progressive spread of infection after less extensive debridement. Delay in diagnosis or surgery allows progression and spread of necrosis, leading to extensive tissue loss and worsening systemic toxicity. Several surgical procedures may be required before all nonviable tissue is removed.

Consultations:

- Infectious disease specialist - For appropriate antimicrobial selection, particularly if necrotizing fasciitis or myonecrosis occurs
- Surgeon - If necrotizing fasciitis or myonecrosis is suspected (consult early in the disease course)

Diet:

- Once omphalitis is suspected, do not feed the infant enterally. Enteral feedings may be resumed once the acute infection resolves.
- Parenteral nutrition is required in infants with omphalitis.

MEDICATION	**Section 7 of 10**

A combination of a parenterally administered antistaphylococcal penicillin and an aminoglycoside antibiotic is recommended for uncomplicated omphalitis. Some believe that anaerobic coverage also should be considered in all infants with omphalitis. Omphalitis complicated by necrotizing fasciitis or myonecrosis requires a more aggressive approach, and antimicrobial therapy directed at anaerobic organisms, as well as gram-positive and gram-negative organisms, is suggested. Metronidazole may be added to the combination of antistaphylococcal penicillin and aminoglycoside to provide anaerobic

biopsy specimen culturing.

Blood products (eg, packed red blood cells, platelets, fresh frozen plasma) and other medications (eg, inotropic agents, sodium bicarbonate) may be required for supportive care.

Drug Category: *Antibiotics* -- Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting.

Drug Name	Gentamicin (Garamycin) -- Aminoglycoside antibiotic for gram-negative coverage. Used in combination both with an agent against gram-positive organisms and with an agent that covers anaerobes.
Adult Dose	80 mg IV q8h; adjust according to serum levels and renal clearance
Pediatric Dose	Postconception and postnatal age: <29 w (postconception) or 0-28 days (postnatal): 2.5 mg/kg/dose IV q24h 30-36 w (postconception) or 0-14 days (postnatal): 3 mg/kg/dose IV q24h >37 w (postconception) or 0-7 days (postnatal): 2.5 mg/kg/dose IV q12h Postnatal age: 7-14 days: 2.5 mg/kg/dose IV q8h 15-28 days: 2.5 mg/kg/dose IV q12h >28 days: 3 mg/kg/dose IV q24h
Contraindications	Documented hypersensitivity
Interactions	Amphotericin B, cyclosporine, cephalosporins, or furosemide may increase the risk of renal toxicity; coadministration with other aminoglycosides, cephalosporins, penicillins, and amphotericin B may increase nephrotoxicity; because aminoglycosides enhance effects of neuromuscular blocking agents, prolonged respiratory depression may occur; coadministration with loop diuretics may increase auditory toxicity of aminoglycosides; possible irreversible hearing loss of varying degrees may occur (monitor regularly)
Pregnancy	D - Unsafe in pregnancy
Precautions	Nephrotoxicity and ototoxicity may be associated with prolonged elevated trough concentrations; monitor levels to minimize risk of toxicity and to optimize therapy (ie, peak 6-10 mg/L, trough <2 mg/L); caution in renal failure (not on dialysis), myasthenia gravis, hypocalcemia, and conditions that depress neuromuscular transmission; adjust dose in renal impairment

Drug Name	Oxacillin (Bactocill) -- Antistaphylococcal penicillin. Bactericidal antibiotic that inhibits cell wall synthesis. Used in the treatment of infections caused by penicillinase-producing staphylococci. May be used to initiate therapy when staphylococcal infection is suspected.
Adult Dose	250 mg to 2 g IV q6h; not to exceed 2 g q6h
Pediatric Dose	Postnatal age <7 days: <2 kg: 50 mg/kg/d IV divided q12h >2 kg: 75 mg/kg/d IV divided q8h Postnatal age >7 days: <1.2 kg: 50 mg/kg/d IV divided q12h 1.2-2 kg: 75 mg/kg/d IV divided q8h >2 kg: 100 mg/kg/d IV divided q6h
Contraindications	Documented hypersensitivity; patients with combined renal and hepatic impairment
Interactions	Probenecid decreases elimination
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	May cause rash and bone marrow suppression; caution in renal insufficiency (decrease dose)

Drug Name	Clindamycin (Cleocin) -- Used to treat infections caused by anaerobic bacteria. Lincosamide for treatment of serious skin and soft tissue staphylococcal infections. Also effective against aerobic and anaerobic streptococci (except enterococci). Inhibits bacterial growth, possibly by blocking dissociation of peptidyl tRNA from ribosomes causing RNA-dependent protein synthesis to arrest.
Adult Dose	1200-1800 mg IV divided bid/qid; not to exceed 4.8 g/d
Pediatric Dose	Postnatal age <7 days: <2 kg: 5 mg/kg IV q12h >2 kg: 5 mg/kg IV q8h Postnatal age >7 days: <1.2 kg: 5 mg/kg IV q12h 1.2-2 kg: 5 mg/kg IV q8h >2 kg: 5 mg/kg IV q6h
Contraindications	Documented hypersensitivity; meningitis
Interactions	Increases duration of neuromuscular blockade induced by tubocurarine and pancuronium; erythromycin may antagonize effects; antidiarrheals may delay absorption
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	May cause diarrhea, rash, granulocytopenia, thrombocytopenia, and Stevens-Johnson syndrome; adjust dose in severe hepatic dysfunction; no adjustment necessary in renal insufficiency; associated with severe and possibly fatal colitis by allowing overgrowth of *Clostridium difficile*
Drug Name	Metronidazole IV (Flagyl) -- Anaerobic antibiotic that also has amebicide and antiprotozoal actions.
Adult Dose	250-500 mg PO/IV q6-8h or 30 mg/kg/d divided q6h; not to exceed 4 g/d
Pediatric Dose	Postnatal age <7 days: <1.2 kg: 7.5 mg/kg IV q48h 1.2-2 kg: 7.5 mg/kg/d IV >2 kg: 15 mg/kg/d IV divided q12h Postnatal age >7 days: <1.2 kg: 7.5 mg/kg IV q48h 1.2-2 kg: 15 mg/kg/d IV divided q12h >2 kg: 30 mg/kg/d IV divided q12h
Contraindications	Documented hypersensitivity; liver disease
Interactions	May increase levels or toxicity of phenytoin, lithium, and warfarin; phenobarbital and rifampin may increase metronidazole metabolism; disulfiram reaction may occur with orally ingested ethanol (caution with elixir preparations)
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Requires dose adjustment in patients with renal and liver disease; may cause CNS toxicity (eg, seizures, neuropathy, headache, vomiting)

Further Inpatient Care:

- Examine the patient frequently, and immediately debride any tissue showing signs of advancing infection or necrosis. Postoperatively, inspect the gross appearance of the tissue on the perimeter of the debrided area several times a day or more frequently if the infant has any unresolved signs of systemic infection.
- Monitor aminoglycoside levels, and adjust dose accordingly.
- Monitor and manage metabolic abnormalities, which are common in any ill neonate.

Further Outpatient Care:

- Routine postsurgical follow-up care is indicated.
- Infants developing portal vein thrombosis require follow-up care for complications associated with portal hypertension.

In/Out Patient Meds: IV antimicrobial therapy with an antistaphylococcal penicillin, aminoglycoside, and clindamycin, or metronidazole if indicated, are administered during hospitalization.

Transfer: Critically ill infants, including those who may require surgical intervention, may require transfer to an ICU equipped to treat infants. Transport the patient with advanced life support technology in place and qualified personnel in attendance. Options for further treatment or intervention must be immediately available. (See Transport of the Critically Ill Newborn.)

Deterrence/Prevention:

- Antimicrobial agents are applied to the umbilicus to decrease bacterial colonization and to prevent omphalitis and associated complications. Several effective umbilical cord care regimens are available, including the following:
  o Triple dye applied once daily until cord separation
  o Triple dye applied once, then alcohol applied daily until cord separation
  o Triple dye applied once, then no further antimicrobial treatment
  o Povidone-iodine applied daily until cord separation
  o Silver sulfadiazine applied daily until cord separation
  o Bacitracin ointment applied daily until cord separation
  o Gladstone and colleagues evaluated these regimens and found no significant difference in either the incidence or type of bacteria colonizing the umbilical stump among 271 healthy full-term infants. However, the duration of umbilical cord attachment was significantly less in infants treated with either povidone-iodine daily (9.8 d), bacitracin daily (11.8 d), triple dye applied once followed by alcohol daily (12.5 d), silver sulfadiazine daily (13.8 d), or triple dye once (12.9), compared to infants in whom triple dye was applied daily (17.4 d). No infant developed omphalitis in this study of full-term newborns with uncomplicated births not requiring instruments.

Complications:

- The sequelae of omphalitis may be associated with significant morbidity and mortality. These include necrotizing fasciitis, myonecrosis, endocarditis, portal vein thrombosis, sepsis, septic embolization, and death.

  o Necrotizing fasciitis is a florid bacterial infection of the skin, subcutaneous fat, and superficial and deep fascia that complicates 8-16% of cases of neonatal omphalitis. It is characterized by rapidly spreading infection and severe systemic toxicity.
    ▪ Necrotizing soft tissue infections are caused by production of factors (by single or

multiple organisms) that lead directly to tissue cell death, enzymatic destruction of supporting connective tissue, and destruction of host humoral and cellular immune responses to infecting organisms.

- Certain organisms are well known to invade tissue and proliferate in necrotic areas. Group A *Streptococcus*, *S aureus*, and *Clostridium* species may elaborate extracellular enzymes and toxins that can damage tissue, may facilitate movement of organisms through soft tissue planes, and may limit host defenses and penetration of systemic antimicrobial agents.

o Myonecrosis refers to infectious involvement of muscle.
- In infants with omphalitis, development of myonecrosis usually depends on conditions that facilitate the growth of anaerobic organisms. These conditions include the presence of necrotic tissue, poor blood supply, foreign material, and established infection by aerobic bacteria such as staphylococci or streptococci. *C perfringens*, in particular, does not replicate under conditions of an oxidation-reduction potential (Eh) greater than -80 mV; the Eh of healthy muscle is 120-160 mV. In infections with mixtures of facultative aerobes and anaerobes, the aerobic organisms use oxygen available in tissue, thereby further reducing the Eh in tissues inoculated by *Clostridium* species or other anaerobic bacteria, often to less than -150 mV, allowing anaerobic bacterial growth.
- The toxins produced in the anaerobic environment of necrotic tissue allow rapid spread of organisms through tissue planes. Local spread of toxins extends the area of tissue necrosis, allowing continued growth of organisms and increasing elaboration of toxins. Because of progressive deep tissue destruction and subsequent systemic spread of toxins, anaerobic infections, in particular, may be fatal if not treated promptly. In addition, rapid development of edema, which constricts the muscle within its fascia, may lead to ischemic myonecrosis.

o Septic embolization: If septic embolization arises from infected umbilical vessels, it may lead to metastatic foci in various organs, including the liver, lungs, pancreas, kidneys, and skin.
o Sepsis: This is the most common complication of omphalitis. In a study by Mason and colleagues, bacteremia was a complication in 13% of infants with omphalitis. In these infants, DIC and multiple organ failure may occur.
o Other complications related to omphalitis are much less common.

Prognosis: The prognosis for infants with omphalitis is variable.

Patient Education: Referral for psychosocial counseling may assist the family in coping with a critically ill infant.

Medical/Legal Pitfalls:

- Failure to recognize necrotizing fasciitis or myonecrosis may result in delay of appropriate surgical intervention.

Special Concerns:

- The relatively high incidence of necrotizing fasciitis following omphalitis in the newborn, with its attendant morbidity and mortality, requires close observation and early surgical intervention if any question exists regarding the diagnosis.

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Omphalitis excerpt

Omphalocele and Gastroschisis

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INTRODUCTION	Section 2 of 10

Background: Gastroschisis and omphalocele are among the most frequently encountered congenital anomalies in pediatric surgery. Combined incidence of these anomalies is 1 in 2000 births, which means, for example, that a pediatric surgeon will see 2 such babies for every 1 born with esophageal atresia or tracheoesophageal fistula. Although specialists such as neonatologists and pediatric surgeons are responsible for the care of these babies, this topic is included in a text of general pediatrics to bring about a more thorough understanding of these anomalies and enable physicians to care for these children more empathetically.

Many babies have correctable lesions and simply require routine pediatric care. For others, the abdominal wall defect is part of a larger constellation of unresolved problems, and further care by specialists is necessary. All of these children, however, require general management by pediatricians who have knowledge of their particular anomalies and their past surgical histories. For example, physicians should know if an associated malrotation was corrected (to prevent midgut volvulus) and whether an abnormally located appendix was removed (to prevent occurrence of atypical appendicitis).

Pathophysiology:

Embryology

Fetal growth and definition of form are orchestrated by processes that are specific regarding time and location. Growth spurts often are followed by delays. Cellular differentiation, proliferation, migration, and deposition are involved in the formation of new tissue. Initially, the embryo is flat within the umbilical ring, which is defined histologically by the junction of cylindrical epithelium of the epiblast (ectoderm) and the cuboidal epithelium of the amnion. Two layers comprise the embryo: the epiblast (ectoderm), which becomes either neuroectoderm or surface epithelium, and the hypoblast, which becomes the inner epithelium of gut-derived organs. Formation of a third germ layer (mesoblast) occurs along with the change in the embryo's shape. Elongation of the embryonic disc and longitudinal and lateral enfolding create a cylinder with a recognizable body plan.

Several processes combine to form the mesoblast cell layer, as follows:

- Apoptotic cell death with disruption of the epithelial basement membrane
- Phagocytosis of the dead cells with enlargement of the intercellular space
- Migration of ectoderm cells from the epithelial layer to the mesodermal layer

These processes take place in the following 3 areas:

- The primitive streak, which is a groove-like structure located in the dorsocaudal portion of the embryo
- The neural crest, which is located in the cranial half of the embryo at the transition of neuroectoderm and surface epithelium
- The umbilical ring

Proliferation of the neuroectoderm and underlying mesoderm, coupled with growth arrest at the umbilical ring, pushes the embryonic disc above the umbilical ring and beyond the underlying yolk sac like a growing mushroom. Simultaneously, the embryo folds ventrally, forming the thoracic and abdominal cavities distinct from the extraembryonic coelom. The amniotic cavity enlarges and bulges over the embryo, and the amnion attaches to the yolk sac and the connecting stalk, forming the umbilical cord. Caudal enfolding of the embryo incorporates the proximal yolk sac into the hindgut and allantois (a diverticulum of the yolk sac) into the urogenital sinus. The cloacal membrane covers the openings of the hindgut and urogenital sinus; the perineum lies between these openings. Elongation of the primitive gut and the urogenital sinus, and fusion of the surrounding mesoderm, coincides with the appearance of the urorectal septum.

In summary, the human embryo initially is disc-shaped and composed of 2 cell layers. It acquires a third cell layer as it grows above the umbilical ring and becomes cylindrical by elongation and inward folding. The body folds (cephalic, caudal, lateral) meet in the center of the embryo where the amnion invests the yolk sac. Defective development at this critical location results in a spectrum of abdominal wall defects. By the sixth week, rapid growth of the midgut causes a physiologic hernia of the intestine through the umbilical ring. The intestine returns to the abdominal cavity during the tenth week, and rotation and fixation of the midgut occur. This process does not occur in babies with gastroschisis or omphalocele, resulting in an increased risk of midgut volvulus.

Pathogenesis of omphalocele and gastroschisis

Abdominal wall defects occur as a result of failure of the mesoderm to replace the body stalk, which persists in a region normally occupied by somatopleure. Embryonic dysplasia causes insufficient outgrowth at the umbilical ring. Decreased apoptotic cell death and underdevelopment of the mesodermal cell compartment cause enlargement of the umbilical ring's diameter. The amnion does not apply itself to the yolk sac or connecting stalk but remains at the margin of the body wall defect, causing faulty development of the umbilical cord and a persistent communication between the intraembryonic body cavity and the extraembryonic coelom.

In babies with omphalocele (see Image 1, Image 4), failure of central fusion at the umbilical ring by growth of the mesoderm causes defective abdominal wall closure and persistent herniation of the midgut. The abdominal viscera are contained within a translucent sac, which is composed of amnion, Wharton jelly, and peritoneum. The umbilical vessels radiate onto the wall of the sac. In 50% of cases, the liver, spleen, and ovaries or testes accompany the extruded midgut.

Possible explanations of the embryology of abdominal wall defect in gastroschisis (see Image 2) include the following:

- Defective mesenchymal development at the body stalk-abdominal wall junction results in a dysplastic abdominal wall that may rupture with increased abdominal pressure.
- Abnormal involution of the right umbilical vein or a vascular accident involving the omphalo-mesenteric artery causes localized abdominal wall weakness that subsequently ruptures.

- Rupture of a small omphalocele with absorption of the sac and growth of a skin bridge between the abdominal wall defect and the umbilical cord has been chronicled on prenatal ultrasound.

Pathogenesis of Other abdominal wall defects

In umbilical cord hernias, the umbilical ring is oversized but the amnion is applied normally around the yolk sac and connecting stalk.

Urachal remnants and omphalomesenteric duct malformations result from absent or deficient apoptotic cell death of the epithelium of the urachus and yolk stalk, which, in normal embryogenesis, cause these structures to disappear.

Abnormal development of the lower body wall results from defective enfolding of the caudal pole of the embryo and deficient incorporation of the yolk sac and allantois; this is associated with malformation of external genitalia. Bladder exstrophy (hypogastric omphalocele) has an incidence of 3.3 in 100,000 births. The bladder develops during the fifth to ninth gestational weeks, and urine mixes with amniotic fluid by the tenth week. Normally, the bladder can be visualized by ultrasound by the end of the first trimester. The bladder mucosa is soft and pliable at birth, but within 48 hours' exposure, it becomes firm and polypoid and prone to malignant degeneration. Surgical closure is staged and varied, but the goal of reconstruction is voluntary urination with continence and correction of the associated vesicoureteral reflux. Characteristic findings include the following:

- Anterior vagina and rectum, which may be prolapsed
- Epispadias, bifid clitoris or penis and scrotum
- Dorsal chordee
- Poor urinary sphincter control
- Waddling gait due to outward and downward rotation of the anterior pelvic ring and pubic symphysis diastasis

Prune belly syndrome (abdominal wall dysplasia, see Images 17-18) occurs as a result of increased apoptotic cell death in the body wall placode, which leads to insufficient mesodermal cell deposition. Retention of an abnormally large amount of yolk sac causes attenuation of the abdominal musculature. Muscle fibers are absent and replaced by a thick collagenous aponeurosis. Intercellular conduction of electrical impulses is disturbed, which leads to faulty muscular contractions and ineffective peristalsis.

Characteristics of prune belly syndrome include a thin, flaccid abdominal wall and hypertrophy of the bladder wall with dilation of the bladder, ureters, and renal collecting system, which may be associated with obstruction of the prostate urethra at its junction with the bladder neck. Incidence is 1 in 30,000-50,000 births. Approximately 95% of patients are male. Patients are infertile, since absence of prostate and seminal fluid precludes normal sperm development. Surgical repair includes reconstruction of the urinary collecting systems and the abdominal wall, along with bilateral orchiopexies.

Faulty development of the urorectal septum leads to anal agenesis and nondivision of the cloaca. Cloacal exstrophy (lower midline syndrome, see Images 19-25) has an incidence of 1 in 200,000-400,000 births. Chromosomal abnormalities are associated with low-set ears, fetal uropathy leading to oligohydramnios, pulmonary hypoplasia, and compression abnormalities, such as indented thorax, deformed digits, talipes, bowed limbs, and dislocated hips. Characteristic features include the following:

- Bladder exstrophy with a central strip of everted intestine
- Duplicated colon and appendix, or colonic atresia and imperforate anus (agenesis of the hindgut)
- Sacral and neurologic anomalies, such as myelomeningocele, hydromyelia, and diastematomyelia

- **In the US:** Combined incidence of omphalocele and gastroschisis is 1 in 2000 births. Epidemiologic data compiled over the last 40 years show that the incidence of omphalocele has remained constant and is associated with increased maternal age. An inherited predilection is indicated by its occurrence in twins, in consecutive children, and in different generations of the same family.
  Incidence of gastroschisis is increasing, and it is associated with young maternal age and low gravity. Prematurity and low birth weights, secondary to in utero growth retardation, are more common in babies with gastroschisis.

Mortality/Morbidity:

- Over the past 30 years, the survival rate of babies with gastroschisis and omphalocele has steadily improved, from approximately 60% in the 1960s to more than 90% currently. The observed decline in morbidity and mortality has resulted from improvements in the care of low birth weight and premature babies, particularly those who, because of open abdominal wounds and extruded intestine (gastroschisis), are especially prone to hypothermia, dehydration, sepsis, and hypoglycemia. Anesthetic management and surgical techniques have improved and the development and availability of excellent parenteral nutrition for these and other surgical patients has had a significant impact.
- Long-term morbidity from gastroschisis is related to intestinal dysfunction and wound problems.
- Short gut syndrome may be caused by a number of factors. An antenatal mesenteric vascular accident or constriction of the extruded intestine's mesentery by a small abdominal wall defect may cause an obstructed, shortened intestine with diminished absorptive capacity. Gut necrosis may complicate excessively tight closure of the abdominal wall defect by impeding splanchnic blood flow with resultant intestinal ischemia and necrotizing enterocolitis (NEC), or it may occur consequent to closed loop obstruction caused by adhesions or midgut volvulus. Loss of intestinal length exacerbates the dysfunction consequent to antenatal exposure of the intestine to amniotic fluid.
- Management of babies with short gut syndrome also has improved significantly as a result of providing nutrition by parenteral and enteral routes, obtaining venous access and treating catheter sepsis, and optimizing gut adaptation with innovative surgical procedures and aggressive treatment of bacterial overgrowth within stagnant intestinal loops. Even so, babies with short gut as a consequence of gastroschisis comprise a large percentage of children undergoing intestinal transplantation.
- Poor healing of the abdominal wound usually results in a ventral hernia, which may require secondary surgical repair.
- Paradoxically, babies with small (unimpressive) omphaloceles are most likely to have associated abnormalities, including intestinal problems (Meckel diverticulum, atresia), genetic syndromes (Beckwith-Wiedemann), and congenital heart disease.
- Babies with giant omphaloceles usually have small, bell-shaped, thoracic cavities and minimal pulmonary reserve; reduction and repair of the omphalocele frequently precipitates respiratory failure, which may be chronic and require a tracheotomy and long-term ventilator support. The authors recently cared for a baby with giant omphalocele and diaphragmatic hernia. Both conditions are associated with pulmonary hypoplasia, and when they are combined, the severity of the pulmonary deficit precludes survival, even with Extracorporeal Membrane Oxygenation (ECMO) support, as provided for our patient.
- Even with successful repair, which usually requires a synthetic patch, and good clinical outcome, the location of the child's liver is central, directly beneath the patch, rendering it more vulnerable to trauma.

Race: No geographic or racial predilection exists for omphalocele or gastroschisis.

Sex: The male-to-female ratio is 1.5:1.

- Omphalocele

  o In babies with omphaloceles, the size of the abdominal wall defect ranges from 4-12 cm, and the location of the defect may be central, epigastric, or hypogastric.
  o Although the ease of surgical reduction and repair correlate with the size of the abdominal wall defect, a small omphalocele is no guarantee of an uncomplicated clinical course. Associated genetic syndromes involving multiple organ systems, or abnormalities of the intestine, such as an atresia or a patent omphalomesenteric duct, are potential problems.
  o With a large omphalocele, dystocia may occur and result in injury to the baby's liver; hence, a cesarean section may be indicated.
  o The omphalocele sac is usually intact, although it may be ruptured in 10-20% of cases. Rupture may occur in utero or during or after delivery.
  o Babies with the Beckwith-Wiedemann syndrome (ie, exomphalos, macroglossia, gigantism, see Image 7) have large, rounded facial features, hypoglycemia from hyperplasia of the pancreatic islet cells, and visceromegaly. They may have genitourinary abnormalities, and they are at risk for development of Wilms tumors, liver tumors (hepatoblastoma), and adrenocortical neoplasms.
  o Pentalogy of Cantrell (see Image 8) describes an epigastric omphalocele associated with a cleft sternum and anterior diaphragmatic hernia (Morgagni), cardiac defects (eg, ectopia cordis, ventricular septal defect [VSD]) and an absent pericardium.
  o Giant omphaloceles have large central or epigastric defects. The liver is centrally located and entirely contained within the omphalocele sac. The abdominal cavity is small and undeveloped, and operative closure is very difficult. The thoracic cavity is also small. Associated pulmonary hypoplasia or restrictive lung disease may be present.

- Gastroschisis

  o The defect is fairly uniform in size and location; a 5-cm vertical opening to the left of the umbilical cord.
  o However, the extent of intestinal inflammation and resultant edema and turgor greatly affect reduction and closure of the abdomen. Inflammation so distorts the bowel's appearance that it may be difficult to determine if associated intestinal atresia (see Images 5-6) is present.
  o Once reduction and closure is obtained, inflammation resolves, and the intestine softens and regains a normal appearance. Correction of associated intestinal atresia is best left until this time, usually 3 weeks after the first operative procedure.
  o Intestinal dysfunction takes longer to normalize, from 6 weeks to several months.
  o If gastroschisis is identified, perform serial examinations to assess intestinal integrity and amniocentesis to monitor lung maturity.

- Factors associated with high-risk pregnancies, such as maternal illness and infection, drug use, smoking, and genetic abnormalities, also are associated with the birth of babies with omphalocele and gastroschisis. These factors contribute to placental insufficiency and the birth of small for gestational age (SGA) or premature babies, among whom gastroschisis and omphalocele most commonly occur.
- Folic acid deficiency, hypoxia, and salicylates have caused laboratory rats to develop abdominal wall defects, but the clinical significance of these experiments is conjectural. Certainly, elevation of maternal serum alpha-fetoprotein (MSAFP) warrants investigation by high-resolution sonography to determine if any structural abnormalities are present in the fetus. If such abnormalities are present and associated with an omphalocele, perform amniocentesis to check for a genetic abnormality.

- Polyhydramnios suggests fetal intestinal atresia, and this possibility should be investigated by ultrasound. Ideally, such information will prompt referral to a tertiary care facility, where the infant can receive expeditious specialty care.

Other Problems to be Considered:

In babies with omphalocele, a 35-80% incidence of other clinical problems is seen. These include congenital heart disease, cleft palate, and musculoskeletal and dental occlusion abnormalities. Patent omphalomesenteric duct and small bowel atresias may occur in babies with umbilical cord hernias where the size of the defect is smaller than 4 cm.

Incidence of associated chromosomal abnormalities is 10-40%. These include trisomies 12, 13, 15, 18, and 21.

Babies with gastroschisis, in which the incidence of chromosomal anomalies is less than 5 percent, may have gastroesophageal reflux disease or Hirschsprung disease in addition to abnormal intestinal absorption and motility.

Lab Studies:

- Maternal serum alpha-fetoprotein

  - Prenatal diagnosis of abdominal wall defects can be made by detection of an elevation in MSAPF.
  - MSAPF levels are greater in gastroschisis than in omphalocele.
  - MSAPF also is increased in spina bifida, which additionally demonstrates an increased ratio of acetylcholinesterase and pseudocholinesterase.

Imaging Studies:

- Fetal sonography may detect a genetic abnormality, with identification of a structural marker of the karyotypic abnormality.
- Fetal echocardiography also may identify a cardiac abnormality.
- Confirm positive findings suggestive of a genetic abnormality by amniocentesis.
- If serial ultrasounds show dilatation and thickening of the intestine in a baby with gastroschisis, and if lung maturity can be verified by amniocentesis, delivery is induced.

Medical Care:

- Intestinal inflammation

  - Intestinal inflammation may occur with either gastroschisis or ruptured omphalocele.
  - The eviscerated intestine may be either normal or abnormal in structure and function. The degree of abnormality depends upon the extent of the inflammatory and ischemic injury, manifested by shortened length and surface exudate (peel), which is related to the composition and duration of the intestine's exposure to the amniotic fluid and fetal urine.

- o Inflamed intestine is thick and edematous, the loops of bowel are matted together, and the mesentery is congested and foreshortened.
- o Histologically, atrophy of the myenteric ganglion cells is seen.
- o The intestine is dysmotile, with prolonged transit time and decreased absorption of carbohydrate, fat, and protein. These deleterious effects remit as the inflammation resolves, usually in 4-6 weeks. During this time, total parenteral nutrition (TPN) is required.

- Intact omphalocele

  - o Usually, neonates with intact omphalocele are in no distress, unless associated pulmonary hypoplasia is present.
  - o Examine the baby carefully to detect any associated problems, such as Beckwith-Wiedemann syndrome, chromosomal abnormalities, congenital heart disease, or other associated malformations. Give nothing by mouth (NPO) pending operative repair.
  - o Administer maintenance IV fluids, and cover the omphalocele sac with sterile saline-soaked gauze and with plastic wrap, using sterile technique. As an alternative, the baby's lower torso may be placed in a bowel bag. The omphalocele should be supported to avoid excessive traction to the mesentery.
  - o Give prophylactic antibiotics preoperatively, because of the possibility of an associated intestinal anomaly.
  - o Closure of a small or moderate size omphalocele usually is accomplished without difficulty.
  - o A ruptured omphalocele is treated like gastroschisis.
  - o Closure of a giant omphalocele that contains the liver can be very challenging.

- Gastroschisis

  - o Respiratory distress in neonates with gastroschisis may respond to gastric decompression, although endotracheal intubation may still be needed.
  - o Fluid, electrolyte, and heat losses must be minimized and corrected. Administer an intravenous fluid bolus (20 mL/kg LR), followed by 5% dextrose ¼ NS at 2-3 times the baby's maintenance fluid rate.
  - o The baby should be placed under a radiant heater, and the exposed intestines should be covered with plastic wrap and supported to avoid excessive traction on the mesentery. As an alternative, the baby's lower torso may be placed in a bowel bag.
  - o Insert a urinary catheter to monitor urine output and facilitate reduction of the herniated viscera by avoiding bladder distention.
  - o Administer antibiotics to prevent infection, since neonates have low levels of circulating immunoglobulin G (IgG).
  - o Place a central venous line to provide parenteral nutrition, thereby minimizing protein loss during the period of gastrointestinal dysfunction.

Surgical Care:

- Omphalocele

  - o Ambroise Pare, the 17th-century French surgeon, accurately described omphalocele and the dire consequences of opening the sac to attempt surgical closure. Certainly, his admonition encouraged conservative treatment, ie, squeezing the sac to effect reduction of the herniated viscera or painting the sac with escharotic agents to promote epithelization.
  - o The problem with this approach is that it is slow. During this time the sac may rupture, resulting in a wound infection. Even if complications do not occur, the healing of such a large wound exacts a significant metabolic and nutritional toll.
  - o Healing may be hastened by surgically mobilizing skin flaps sufficient to cover the omphalocele sac, thereby obtaining closure of the abdominal wall defect in a way comparable to closing a burn wound with skin grafts (Gross technique). This, however, results in the creation of a ventral hernia.
  - o In 1967, Schuster developed a technique that may be used in the initial treatment of a

baby with a giant omphalocele or in correcting the ventral hernia created by skin flap closure. An incision is made along the skin-sac junction of the abdominal wall defect, which is enlarged in the midline. The anterior rectus fascia is exposed from the xiphoid to the pubis, and Teflon sheets are sutured to its medial edge. The Teflon sheets are then closed over the omphalocele sac and gradually tightened, approximating the rectus muscles over the abdominal viscera.

- Gastroschisis

  o In 1969, Allen and Wrenn adapted Schuster's technique for treatment of gastroschisis
  o Silastic sheets are sutured to the full thickness of the enlarged abdominal wall defect and closed over the eviscerated intestine, whose reduction is facilitated by stretching the abdominal musculature, emptying the stomach and bladder, and manually evacuating the colon.
  o A major factor in the reduction of the extruded viscera is resolution of intestinal inflammation, which results in a change from a rigid, congealed mass of bowel to soft, pliable loops of intestine, which squeeze into the abdominal cavity.
  o Too tight a closure of the abdominal wall must be avoided, for this limits excursion of the diaphragm and necessitates increased inspiratory pressure to compensate for the increase in airway resistance. In general, peak inspiratory pressures (PIPs) higher than 25 mmHg should be avoided. High-frequency oscillatory ventilation may be an alternative to conventional ventilation if intraabdominal pressures are markedly increased.
  o In addition, tight closure of the abdominal cavity impedes venous return to the heart, compromising cardiac output and decreasing renal blood flow and glomerular filtration rate. Renal vein thrombosis and renal failure may ensue.
  o Diminished mesenteric blood flow may facilitate the development of necrotizing enterocolitis.
  o In order to avoid these problems, techniques have been developed to monitor central venous pressure (CVP), intraabdominal pressure, intravesicular pressure, and intragastric pressure (which should not exceed 20 cm of water).

Consultations:

- Neonatologists and pediatric surgeons usually care for babies with these anomalies.
- Consult with cardiology, pulmonology, gastroenterology, and genetics, as indicated.

Diet:

- Babies with omphalocele usually do not require special formulas; their intestines are typically normal, with the exception of occasional atresias, which, in the author's experience, are located in the distal ileum and are not associated with short gut.
- Babies with gastroschisis, on the other hand, typically require special elemental, crystalline amino acid, or protein hydrolysate formulas with nonlactose carbohydrate and medium-chain triglycerides because of the associated gut inflammation and resultant tendency towards substrate malabsorption and allergy.
- Babies with short gut syndrome absorb medium-chain triglycerides more readily than long-chain triglycerides; however, the latter are more valuable with regard to gut adaptation.

Activity:

- A child with a repaired giant omphalocele has an epigastric liver. In this location, the liver is more vulnerable to trauma. Avoidance of contact sports is prudent.

Further Inpatient Care:

- Omphalocele

  o Babies with omphalocele usually have rapid return of intestinal function after surgical repair, even if intestinal atresia occurs concomitantly, because no associated gut inflammation is present.
  o Babies with giant omphaloceles usually have a protracted hospital course; and overall morbidity and mortality is higher for these patients. Multiple procedures are necessary to obtain closure of the abdominal wall defect.
  o Respiratory compromise may complicate the repair and require prolonged support and possibly a tracheotomy. Ventilator management, tracheotomy care, and, ultimately, decannulation require close cooperation by the neonatologist, pulmonologist, and pediatric surgeon.

- Gastroschisis

  o Even if primary closure of the abdominal wall defect is obtained, a period of several weeks of intestinal dysfunction (ileus) usually follows, as a result of associated gut inflammation. In this situation, parenteral nutrition is essential, followed by the gradual introduction of enteral feedings. Continuous drip feedings usually are tolerated optimally.
  o If reduction of the herniated intestine requires the use of a silo (see Image 9), it usually is removed within 5-7 days. The period of ileus follows, during which the baby requires parenteral nutrition until the gradual return of intestinal function. If this expected recovery does not occur within 3-4 weeks, intestinal obstruction is presumed, and a contrast study is obtained to document intestinal transit.
  o If intestinal obstruction is present, a laparotomy must be performed.

Further Outpatient Care:

- After hospital discharge, babies require close follow-up care to assess growth and weight gain
- Patients usually have gastroesophageal reflux and may require medical therapy, but fundoplication should not be necessary.
- Hirschsprung disease (aganglionic megacolon) also may occur. Physicians should be alert to a history of constipation.

Transfer: The best way to treat the exposed intestines of a baby with gastroschisis who is being transported to a tertiary center includes the application of a moist lap pad. The moist lap pad is placed over the intestines and held directly over the abdominal wall defect with dry Kerlix wrap applied around the baby's torso including the extruded intestine. This prevents traction upon the mesentery. A warm, wet, lap pad placed in a bowel bag with the eviscerated intestine soon becomes a cold, wet, lap pad.

Complications:

- The following case report illustrates some of the complications that a baby with giant omphalocele might experience (See Images 10-15).

  o A 6-week-old male infant from Accra, Ghana, presented with a giant omphalocele. His liver and intestines were contained within the omphalocele sac, and his abdominal cavity was undeveloped and diminutive. The sac was partly covered by skin and partly by granulation tissue.
  o An open wound is a metabolic drain. Despite devoted nursing care, the nutritional status of this patient was not good. The granulating portion of the wound was excised, and the abdominal cavity was closed with a patch; however, skin approximation was not possible

without extensively undermining the flaps. This was inadvisable because of the risk of wound infection and the desire to avoid too tight a closure of the abdominal cavity, which could compromise the infant's ability to ventilate by limiting diaphragmatic excursion and compromise cardiovascular function by diminishing blood return. The patient was treated with antibiotics and parenteral nutrition. Postoperatively, the wound appeared clean, and the patch incorporated well into the baby's tissue. The patient was weaned from the ventilator, despite copious respiratory secretions.

- o Two weeks later, the patch was tightened, approximating the skin flaps. However, this precipitated respiratory failure and ventilator dependency. The patient would not be able to return to his family in Africa if he was ventilator-dependent. While the patient's respiratory status was monitored, his patch became infected, and he became critically ill. The only way to resolve the infection was to remove the patch. The author attempted to stretch the abdominal wall and obtain wound closure without a patch; however, this was not possible because hepatomegaly and soft tissue edema combined to produce a small rigid abdominal cavity. The only recourse was to mobilize flaps and move skin from his flank onto the exposed abdominal viscera, and skin graft the donor wounds.
- o The patient's condition improved dramatically once closure of the abdominal cavity was achieved. Again, the author tried to wean him from the ventilator, but his copious secretions and episodes of high fever and drenching sweats prevented this. Finally, it was determined that the patient was experiencing narcotic withdrawal. He had been postoperative for so long, and narcotics had been used liberally to provide postoperative pain relief.
- o The need for long-term ventilator assistance was realized, and a tracheotomy was performed. Although wound closure was achieved, a huge ventral (abdominal wall) hernia had been created. The skin flaps were separated from the abdominal viscera, and a new patch was inserted. This added rigidity to his abdominal wall, and, by stabilizing the patient's trunk musculature, movements of his torso, including breathing, were facilitated. The patch gradually separated from the rectus fascia, and this dehiscence required repair. The patient was weaned from the ventilator to pressure support. Discharge from the hospital seemed imminent.
- o One night, a low-grade fever developed, and the patient became irritable. A culture was taken, but the patient was not treated with antibiotics. Death occurred within 6 hours. The blood culture grew group B streptococci, but the autopsy was otherwise unremarkable. The initial wound culture grew *Pseudomonas* species, which was later cultured from the patient's tracheal secretions. The wound infection, which required removal of the patch, was caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Prognosis:

- Omphalocele

  - o Prognosis is dependent upon the severity of the associated problems. Babies with omphalocele are considerably complex, with involvement of many other organ systems.
  - o Even giant omphaloceles can be closed, although multiple procedures may be necessary.
  - o The limiting factor for many of these babies, however, is their diminutive thoracic cavities and associated pulmonary hypoplasia and resultant chronic respiratory failure. Even so, lung growth and development continue well into childhood, encouraging optimism regarding the ultimate prognosis.

- Gastroschisis

  - o Prognosis is dependent mainly upon severity of associated problems, including prematurity, intestinal atresia, short gut, and intestinal inflammatory dysfunction.
  - o Many pediatric surgeons believe that prognosis has improved because of maternal ultrasound diagnosis and monitoring, which leads to expeditious delivery of babies at tertiary centers.
  - o Years ago, obtaining primary closure of a baby with gastroschisis was unusual. Usually, it was necessary to use a silo. Now, primary closure is commonly attained.

- Instruct parents regarding the significance of bilious (green) vomiting, since these babies may develop adhesive small bowel obstruction or midgut volvulus.
- Inform parents that their child's appendix is probably in an unusual location and that a CT scan may be the most reliable way to diagnose acute appendicitis.

MISCELLANEOUS	Section 8 of 10

Special Concerns:

- Prenatal care and planning

  - With increased availability of sonography, prenatal diagnosis is more frequent.
  - Diagnosis of omphalocele mandates further workup to determine if an associated genetic abnormality is present, in which case appropriate counseling is necessary.
  - When gastroschisis is diagnosed, perform serial examinations to detect signs of intestinal injury (decreased peristalsis or distension).
  - Provide the baby's parents with information concerning the anomaly before delivery. Also, optimal management requires that the obstetrician understands the particular needs of these babies and ensures that they are delivered in a facility where neonatal, pediatric anesthesia, and pediatric surgery services are available.

PICTURES	Section 9 of 10

Picture 1. Omphalocele and gastroschisis. Baby with an omphalocele.

Picture 2. Omphalocele and gastroschisis. Baby with an umbilical cord hernia.

Picture 3. Omphalocele and gastroschisis. Baby with gastroschisis.

Picture 4. Omphalocele and gastroschisis. Baby with a ruptured omphalocele.

Picture 5. Omphalocele and gastroschisis. Baby with gastroschisis and associated intestinal atresia.

Picture 6. Omphalocele and gastroschisis. Shown here is a baby with gastroschisis and colon atresia. The bulbous proximal end of the atretic colon is excised and a colostomy created at the abdominal wall defect. An anastomosis of the proximal, dilated colon to the distal "microcolon" (in view of its small caliber) would not function properly. The colostomy can be closed 4-6 weeks later. (Gastrostomy tubes are no longer routinely used.)

Picture 7. Omphalocele and gastroschisis. Note the enlarged tongue in this baby with Beckwith-Wiedemann syndrome.

Picture 8. Omphalocele and gastroschisis. Baby with pentalogy of Cantrell.

Picture 9. Omphalocele and gastroschisis. Silo closure of a baby with gastroschisis.

Picture 10. Omphalocele and gastroschisis. Completed reduction of the bowel contained within the silo; the silo is about to be removed and the abdominal wall closed.

Picture 11. Omphalocele and gastroschisis. Baby with a giant omphalocele.

Picture 12. Omphalocele and gastroschisis. Same patient as in Image 11. Closure of the giant omphalocele using a synthetic patch.
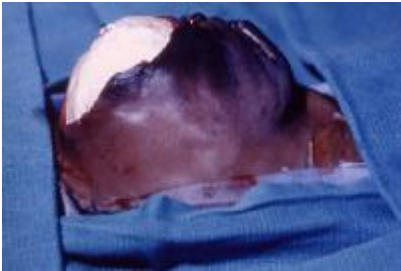
Picture 13. Omphalocele and gastroschisis. Same patient as in Images 11-12. Tightening the abdominal wall closure

Picture 14. Omphalocele and gastroschisis. Same patient as in Images 11-13. Flank flaps were used to close the giant omphalocele in the baby whose patch became infected.

Picture 15. Omphalocele and gastroschisis. Same patient as in Images 11-14. The flank wounds were skin grafted and closure of the giant omphalocele obtained.

Picture 16. Omphalocele and gastroschisis. A 6-week-old male infant from Accra, Ghana, who experienced fatal complications after presenting with a giant omphalocele. See "Complications" section.

Picture 17. Omphalocele and gastroschisis. Baby with prune belly syndrome.

Picture 18. Omphalocele and gastroschisis. Note the laxity of the abdominal wall in this baby with prune belly syndrome.

Picture 19. Omphalocele and gastroschisis. Baby with cloacal exstrophy.

Picture 20. Omphalocele and gastroschisis.Note the bifid genitalia in this baby with cloacal exstrophy

Picture 21. Omphalocele + gastroschisis. In the repair of cloacal exstrophy, the ileum in the middle of the bifid bladder is excised and used to create an ostomy, the bladder halves are approximated.

Picture 22. Omphalocele and gastroschisis. Closure of the bladder exstrophy.

Picture 23. Omphalocele and gastroschisis. Baby with bladder exstrophy and epispadias; note the appearance of the bladder mucosa, indicating chronic inflammation.

Picture 24. Omphalocele and gastroschisis. Another view demonstrating the epispadias shown in23.

Picture 25. Omphalocele and gastroschisis. Baby with isolated epispadias.

Picture 26. Omphalocele and gastroschisis. An operative photo from the repair of a draining umbilicus.

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Perinatal Drug Abuse and Neonatal Drug Withdrawal

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INTRODUCTION	Section 2 of 10

Background: The use and abuse of addictive drugs has occurred throughout many centuries. Only recently have certain drugs under question become defined as illicit. Therefore, many pregnant women have used such medications without prior consideration to the adverse effects of these substances upon their unborn children. The effects of chemicals, such as opiates, cocaine, nicotine, alcohol, and new recreational drugs, on fetal development have been seriously studied only in the last 30 years.

The difficulty in evaluating research in this area is enormous. Clear methods for differentiating drug use from drug abuse are not established. The question of whether the mere presence of the chemical in maternal serum alludes to fetal damage needs to be answered. Evaluating if the mother in question has told the whole truth about her drug use is difficult. Given the stigma of substance abuse during pregnancy, lack of disclosure by the mother to her health provider is common because such damaging information ultimately could lead to the separation of mother and child.

Many confounding factors, such as the probability of polysubstance use and how this affects single-drug studies, may exist. Additionally, the fact that a mother has used an illicit drug (or even a legal substance such as alcohol or tobacco) intertwines with many other factors that can affect a child. Socioeconomic status, support systems, role of the father, lack of prenatal care, and the caregiving ability of the mother all play tremendous roles in child development.

Pathophysiology:

Maternal alterations

Almost all drugs of abuse follow a similar mechanism of action in the adult brain; this mechanism alters the pathways for reward. Through complex neurochemical interactions, various chemicals act to increase dopaminergic pathways from the midbrain ventral tegmental area (VTA) to the nucleus accumbens (NAc) in the striatum. Additionally, the NAc provides a negative feedback loop to the VTA using the inhibitory monoamine gamma-aminobutyric acid (GABA). Blocking such a pathway also attenuates the reward mechanism in the adult brain.

Fetal alterations

Although the full spectrum of physical damage that drugs of abuse can cause is not documentable, one thing is certain: the effect of maternal drug use on fetal brain development is the most critical and most studied effect. The 2 broad classes of fetal brain insult are as follows:

1. In the first 20 weeks of gestation, damage can occur during cytogenesis and cell migration.
2. In the second half of gestation, damage can occur during brain growth and differentiation.

Continuous abuse, especially during the first half of gestation, is likely to disrupt the complicated neural wiring and associative connections that allow the developing brain to learn and mature. Most drugs of abuse freely cross the placental barrier; however, damage to the fetus also can occur via indirect methods. In particular, the vasoconstrictive properties of cocaine have been discussed as a potential cause for the delivery of growth-retarded infants.

<mark>Frequency:</mark>

- **In the US:** The definitions of maternal drug abuse and newborn withdrawal syndrome have been difficult to standardize (see Background). Therefore, documented disease prevalence varies tremendously. The prevalence of prenatally exposed newborns to one or more illicit drugs averages approximately 5.5%, with a range of 1.3-50%. Variations depend on the geographical detail (eg, local vs state) as well as the method of testing (eg, maternal history, urine testing, meconium testing, a combination of these tests).
  In 1998, Lester reported that the Maternal Lifestyles Study (MLS), a multicenter clinical study, evaluated the effects of fetal exposure to opiates, cocaine, or both in the US. The overall exposure rate was 10%. Of these pregnancies, the rate of perinatal morbidity was higher than the nonexposed group, but it was less than 5% overall. Prematurity, lower growth parameters, compromised cognitive ability, and neurological symptoms were barely significant compared to nonexposed newborns.

- **Internationally:** Perinatal drug abuse and neonatal drug withdrawal is probably a recognized problem in neonatal and postnatal care in every country in the world.

<mark>Mortality/Morbidity:</mark>

- Neonatal withdrawal syndrome occurs in 60% of all fetuses exposed to drugs. Withdrawal syndromes for heroin, codeine, methadone, and meperidine have been described extensively. As more psychotropic medications are prescribed, more withdrawal syndromes are described. Heroin, cocaine, and amphetamine withdrawal usually occurs within the first 48 hours of life; however, a syndrome associated with intrauterine cocaine use has not been well defined. Methadone withdrawal can occur up to 2 weeks after birth, but most likely occurs within the first 96 hours after birth. The syndrome is typically an autonomic multisystemic reaction, the symptoms of which are mostly neurological and may be prolonged.

- Alcohol is the only drug of abuse that is well associated with other teratogenic effects. The classic triad of fetal alcohol syndrome (FAS) consists of growth retardation, physical anomalies (with a characteristic facies), and CNS dysfunction. The risk of delivering child with FAS increases with gravidity in an alcoholic mother. The fetal alcohol effect (FAE) has also been described, representing a milder dose-dependent version of the entire syndrome. More severe aspects are associated with first trimester use of alcohol, especially in those women with a poor diet. At this time, a safe level of alcohol use during pregnancy is not known; therefore, the amount of alcohol that can be consumed without resulting in either condition (ie, FAS, FAE) is not known.

Race:

- The difficulty in assessing drug use confounds research into racial differences.

- Overall, cocaine use is higher among African American women (5% of all African American women) than Caucasian women (2% of all Caucasian women).

- The use of amphetamines, opioids and cannabinoids appears to be equal between African Americans and Caucasian women.

Sex: By definition, perinatal drug abuse is a disease exclusively of pregnant women; however, several interesting epidemiological patterns emerge among mothers who abuse substances. These patterns include the following:

- Genetics: Approximately 60% of mothers who abuse drugs describe a family history of substance abuse, particularly alcoholism. The closer the relative who abuses drugs, the higher the potential for the patient to be an abuser as well. Twin and adoption studies show a weaker genetic role in women than in men. Environmental factors may play a more dominant role for mothers who abuse substances. Patients who describe families of alcohol abuse also describe greater parental-marital conflicts and parent-child conflicts during their childhoods.

- Sexual abuse and domestic violence: In a sample of 1099 women, Wilsnack et al reported that those with a history of being sexually abused in childhood were 2.5 times more likely to abuse substances and 3 times more likely to abuse alcohol than those who were not sexually abused. In another study, Hein et al reported that 60% of women who abuse substances claimed to have an adult partner who committed domestic violence. Likewise, many women report that their own drug use is initiated by their male partners.

- Psychiatric comorbidity: A report from the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area Survey showed that people who abuse substances were 4.5 times more likely to have a comorbid mental disorder than those individuals who do not abuse substances. Of those with a lifetime alcohol or drug disorder, more than 50% were likely to have a comorbid psychiatric disorder. Females with comorbidities to their substance abuse were more likely than men to have affective and anxiety disorders. Also, comorbidity varies with the drug of abuse. People with opioid addictions tend to have a higher associated comorbidity of affective, anxiety, and personality disorders. Cocaine addiction tends to be associated with attention deficit/hyperactivity disorder (ADHD).

Age:

- Few data exists on the age stratification of substance abusing mothers. Research has focused on the adolescent mother. In particular, a link between adolescent pregnancy and substance use may be present.

- If teenage pregnancy is believed to be a high-risk condition, then it might follow that those individuals are prone to other high-risk behaviors. Evidence does support a clustering of teen pregnancy with substance abuse, most notably abuse of cigarettes, alcohol, and marijuana.

- However, the statement that most pregnant and parenting teenagers abuse substances is a gross oversimplification. The literature supports that most pregnant teenagers do not use substances. Among those teens that do use substances, the amount used is far lower than the amount used by adult users who are pregnant.

History:

- Maternal history: Pregnancy actually offers an excellent opportunity for a mother to seek help and to change her life to protect another. However, given the large numbers of mothers who abuse drugs and whose use goes undetected by their obstetricians and pediatricians, the history-taking practice in prenatal clinics must improve.
- Previous attempts at universal toxicology screens for women who are pregnant typically have uncovered one half of all women who abuse drugs. Urine toxicology in combination with a well-performed history is likely to have synergistic results in discovering mothers who abuse substances.
- All too often, the wish to perform an efficient prenatal screening consists solely of asking whether the woman who is pregnant uses drugs. Such questioning carries such stigma and lack of empathy that it is likely to prevent a mother-to-be from admitting her habit of substance abuse. Questioning should be nonjudgmental (ie, ask in a neutral tone of voice), specific (ie, ask about each potential drug of abuse starting with the least innocuous to the most), and asked in succession with the other standard screening inquiries (eg, general medical condition, diet).
- Although several perinatal complications have been thought to be highly associated with in utero drug use, none are pathognomonic or specific enough to cause suspicion.

Physical: Severity of newborn withdrawal from substances depends on the drugs and the frequency of use by the mother during pregnancy.

- Nonopiate drug withdrawal: Withdrawal syndromes that are related to individual nonopiate drugs have been difficult to study. The high prevalence of polydrug use prevents clinicians from witnessing the effects of isolated medications. At this time, there is little support to describe a cocaine-abstinence syndrome.
- Alcohol withdrawal: Signs of alcohol withdrawal may include hyperactivity, crying, irritability, poor sucking, tremors, seizures, poor sleeping patterns, hyperphagia, and diaphoresis. Signs usually appear at birth and may continue until 18 months of age.
- Barbiturate withdrawal: Signs may include irritability, severe tremors, hyperacusis, excessive crying, vasomotor instability, diarrhea, restlessness, increased tone, hyperphagia, vomiting, and disturbed sleep.
- Marijuana withdrawal: For marijuana, a mild opiatelike withdrawal syndrome has been observed. Signs may include fine tremors, hyperacusis, and a prominent Moro reflex; however, these symptoms rarely require treatment.
- Nicotine withdrawal: Mild signs are observed, including fine tremors and variations in tone; however, no comprehensive syndrome that typically requires treatment exists.
- Acute narcotic withdrawal: This withdrawal usually begins 24-48 hours after birth, depending on time of last dose. However, signs may not appear in the infant until 3-4 days after birth.
- Methadone withdrawal: Symptoms may not start until the infant is aged 3 weeks. Also, newborn methadone withdrawal is more severe with higher in utero methadone doses.
- Opiate withdrawal: Signs include hyperirritability, gastrointestinal dysfunction, respiratory distress, and vague autonomic symptoms (eg, yawning, sneezing, mottling, fever). Tremors and jittery movements, high-pitched cries, increased muscle tone, and irritability are common. Normal reflexes may be exaggerated. Loose stools are common, leading to possible electrolyte imbalances and diaper dermatitis. Long-term symptoms have been difficult to study, but evidence supports that these children show hyperphagia, increased oral drive, sweating, hyperacusis, irregular sleep patterns, poor tolerance to environmental changes, and continued loose stools.

Causes: Through multiple mechanisms, all drugs of abuse can cause molecular and cellular changes that ultimately lead to changes in neural migration, cell structure, neurotransmitter dynamics, and overall brain formation. These alterations are likely associated with a whole range of

behavioral and cognitive changes. Maternal polydrug use is likely to be far more damaging than use of any single drug.

- Ethanol

  - Alcohol produces teratogenic effects associated with FAS and its variations. The suggested pathway for teratogenicity involves a direct effect on the anterior neural tube and surrounding structures. This leads to decreased brain development as well as typical FAS facies.
  - In animal models, evidence shows disruption in the hippocampus, cortical cytostructure, and neuronal migration. Changes in subsequent behavior in animal models reveal deficits in object permanence, increased distractibility, and delays in gross motor development.

- Nicotine

  - Studies on in utero effects of nicotine typically have focused on low birth weight and smaller head circumference. Evidence that nicotine causes more than 50% of all low birth weight babies exists.
  - Further studies on nicotine's effects on behavior and neurochemistry are eagerly anticipated.

- Cocaine

  - Cocaine can freely cross the placental barrier. A widely held belief was that cocaine caused fetal hypoxia from placental vasoconstriction.
  - Animal studies have shown disruptions in the neural and glial organization and migration.
  - Dopamine, serotonin, or both may mediate withdrawal from cocaine.
  - From a behavioral standpoint, cocaine has been shown to attenuate an animal's classic conditioning ability to noxious stimuli. Adult animal models of cocaine exposure tend to show a higher predisposition to self-administration for reward.

- Opiates

  - In utero opioid exposure consistently has shown a decrease in nucleic acid synthesis and protein production in the brain, suggesting that overall brain growth is compromised. Effects on neurotransmitter concentrations and production have not been confirmed.
  - Behaviorally, prenatally exposed animals tend to show decreased exploration and increased response latency to noxious stimuli.

DIFFERENTIALS	Section 4 of 10

Colic
Hypocalcemia
Hypoglycemia
Hypomagnesemia
Meningitis, Bacterial
Neonatal Sepsis

Lab Studies:

- Obtain a serum glucose level.
- Obtain a serum calcium level.
- Perform a complete blood count (CBC) with differential and platelets.
- Consider blood culture and other cultures to rule out newborn sepsis.
- Confirm maternal hepatitis status and treat accordingly.
- Consider HIV testing.
- A urine toxicological screen may be helpful in determining drug use. It is important to understand that a urine screen only signifies recent use or heavy use of drugs. In general the length of time that a drug is present in urine after use is as follows:

    o Marijuana: 7 days to 1 month in an adult, perhaps even longer in an infant
    o Cocaine: 24-28 hours in an adult, 72-96 hours in an infant
    o Heroin: 24 hours in an adult, 24-48 hours in an infant
    o Methadone: Up to 10 days in an infant

Other Tests:

- Neonatal abstinence scoring

    o In 1986, Finnegan et al created the Neonatal Abstinence Scoring (NAS) system, which provides an objective measure of a newborn's symptom severity (see Image 1). NAS currently is used as a diagnostic tool as well as a monitor for a withdrawing newborn's response to pharmacotherapy.
    o Each of the 21 different symptoms is scored depending upon severity. All scores are then added. Scoring is performed in 4-hour intervals. If the newborn receives a score of 8 or greater, then scoring should occur every 2 hours. If NAS scores in the first 96 hours of life are consistently 8 or less, then scoring can be discontinued and pharmacotherapy typically is not needed.
    o If the maternal urine screen or history is positive for drug use, first assess the infant at 2 hours after birth. Scores should reflect the symptoms observed during the entire interval, not just at a single point. Scores involving sleep and behavior should reflect any changes during the test period. For instance, if the child was awakened for the examination, do not score against the child for diminished sleep.
    o A higher total score implies a more severe withdrawal syndrome. Likewise, as the child responds to treatment, use NAS scores to titrate the amount of pharmacotherapy needed.
    o Although NAS is designed primarily for withdrawal from opiates or CNS depressant drugs, it has been used for other drugs (eg, cocaine, amphetamines). Its efficacy in these situations is likely from a preponderance of polypharmacy use.

Medical Care:

- Treatment and medication primarily focus on opiate and cocaine withdrawal. Although understanding polydrug interactions is difficult, no specific treatment plan for amphetamine, marijuana, tobacco, or alcohol withdrawal exists (unless teratogenic effects are observed).
- Until the child has been weaned off medication, or until the symptoms have abated (as confirmed by NAS), the patient should constantly be monitored by newborn nursery staff. Vital signs should be checked, NAS should be obtained, seizure precautions should be taken, and frequent weight checks should be performed.

- All medically treated newborns should constantly be monitored for cardiovascular, respiratory, and oxygen saturation changes (see Medications).
- In newborns with severe symptoms, IV fluids with electrolytes may be needed. Oral feedings may need to be withheld.

- Hospital social services: A positive drug screen in a newborn of a mother without a prescription for the suspected drug warrants an investigation by the state child protection agency. The hospital social services staff can coordinate and supervise the interactions of staff, parents, and state services.
- Occupational and physical therapy: Use of a team of therapists decreases the overall treatment time. Issues surrounding environmental stressors and patient contact can be addressed.

Diet:

- Breastfeeding: Many infants in this situation have difficulties in establishing breastfeeding or bottle-feeding.

  - Encourage breastfeeding if the mother is well maintained on methadone.
  - Withhold breastfeeding if other substances are suspected or if the mother is HIV positive.

- Increased caloric intake

  - The newborn withdrawing from drugs has higher caloric demands. In addition to the catabolism resulting from withdrawal symptoms, these patients lose calories from vomiting, drooling, and diarrhea.
  - Consider provision of hypercaloric (100.42 J/oz) formula in frequent small feedings. The daily caloric goal should be 627.6-1046 J/kg/d.

Activity:

- The child's comfort is paramount. Being a newborn is extremely stressful in the first few weeks of life, given that every external stimulus is entirely new to the infant. Add the stress of the internal stimuli from drug withdrawal, and the usefulness of environmental control can be understood. With this in mind, consider that 40% of all withdrawing newborns can be treated symptomatically (without medication). Specific methods include the following:

  - Loose swaddling, as well as holding and slow rocking the infant, may be helpful.
  - Perform environmental controls emphasizing quiet zones, low lighting, and gentle handling. At Massachusetts General Hospital, a battery-operated vibrating box that clips to the bassinet is used often. The device creates a tactile "white noise" that allows the newborn withdrawing from drugs to focus away from multiple-environmental stimuli. Anecdotal evidence exists to support improved outcomes with its use.
  - Use a pacifier for excessive sucking.
  - Frequent diaper changes are necessary. Diaper dermatitis is common in infants who are withdrawing from narcotics and have loose stools.
  - Position the newborn to reduce aspiration. The guidelines of the American Academy of Pediatrics specifically discourage prone position sleeping for newborns. Some recent evidence suggests that lying babies in the left lateral position is more useful to decrease gastroesophageal reflux than lying babies in the right lateral or supine position.

Opiate substitutes and phenobarbital are the mainstays of treatment. Despite some encouraging data regarding other medications for adult withdrawal (most notably clonidine), many are not provided in a liquid oral dose suitable for newborns.

Drug Category: *Opioids* -- Treatment of choice for neonates known to be at risk of withdrawal from opiates. Medication, such as paregoric, can be administered orally and is titrated easily. Likewise, paregoric still offers the best results in treating the withdrawal of maternal polydrug use.

Drug Name	Opium, deodorized tincture 1:25 dilution -- Use a 1:25 dilution. When ordering such a medication, be sure to emphasize that a dilute solution of the deodorized tincture is needed in a 1:25 ratio. Without this emphasis, the pharmacy may deliver undiluted deodorized tincture of opium (used for adults) or the camphorated tincture of opium (Paregoric), which contains 45% alcohol, camphor, anise oil, and benzoic acid.
Pediatric Dose	Starting dose: 0.05-0.1 mL/kg PO q4-6h Maintenance dose: 0.05 mL/kg q4-6h; increase by 0.05 mL/kg at the end of every 4-h period until desired response is achieved; then, maintain dose for 3-5 d; then begin taper of 10% (of peak dose) every 2-3 d; rare to exceed 0.7 mL/dose; not to exceed 1-2 mL/kg/24h
Contraindications	Severe respiratory, renal, or hepatic disease
Interactions	Beware of respiratory effects when using other CNS depressants (eg, phenobarbital)
Pregnancy	D - Unsafe in pregnancy
Precautions	Until weaning has begun, constantly monitor patient's vital signs and oxygen saturation; adverse effects include sedation and constipation; overdosing may cause narcosis, manifested by decreased reflexes and poor Moro reflex, sucking, grasping, and response to pain; more profound narcosis includes hypotonia, obtundation, coma, irregular shallow respirations, apnea, bradycardia, and hypothermia; if signs of opioid toxicity are observed, do not give naloxone; withdrawal seizures can occur
Drug Name	Morphine elixir, 1 mg/mL -- May be used as an alternative to diluted deodorized tincture of opium.
Pediatric Dose	Starting dose: 0.02 mg/kg PO q4-6h Maintenance dose: 0.02 mg/kg PO q4-6h; increase by 0.02 mg/kg at the end of every 4-h period until the desired response is achieved; then maintain dose for 3-5 d; then, begin taper of 10% (of peak dose) q2-3d
Contraindications	Severe respiratory, renal, or hepatic disease; hypotension; potentially compromised airway where establishing rapid airway control would be difficult
Interactions	Beware of respiratory effects when using other CNS depressants (eg, phenobarbital)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Until weaning has begun, constantly monitor patient's vital signs and oxygen saturation Adverse effects include sedation and constipation; overdosing may cause narcosis, manifested by decreased reflexes and poor Moro reflex, sucking, grasping, and response to pain; more profound narcosis includes hypotonia, obtundation, coma, irregular shallow respirations, apnea, bradycardia, and hypothermia If signs of opioid toxicity are observed, do not give naloxone; withdrawal seizures can occur

Drug Category: *Barbiturates* -- Although barbiturates also are available for neonatal withdrawal syndrome, their optimal use is limited to several clinical situations, including the following:

1. The newborn with a nonopiate withdrawal
2. The newborn with a known polydrug withdrawal
3. The newborn with abstinence-related seizures
4. The newborn who has already received the maximum safe level of paregoric

Drug Name	Phenobarbital (Luminal) -- Interferes with transmission of impulses from thalamus to cortex of brain. Used as a sedative.
Pediatric Dose	Loading dose: 20 mg/kg PO If continued NAS scores are >8 for 3 consecutive periods or if scores are >12 for 2 consecutive periods, then administer another 10 mg/kg q12h until a serum level of 40 mcg/mL is achieved Maintenance dose: 2-5 mg/kg/d PO divided q8-12h, provided serum phenobarbital level is therapeutic; with good control, continue maintenance phenobarbital dose for another 72h Weaning: The goal is to lower the serum level by 15% q24h; lower maintenance dose to 2 mg/kg/d; if serum level falls by >20% q24h, increase to 3 mg/kg/d; if serum level falls by only 10% q24h, decrease dose to 1 mg/kg/d; discontinue phenobarbital once serum level is <10 mcg/mL and the patient is clinically in good control
Contraindications	Severe respiratory disease; marked impairment of liver function; nephritic patients
Interactions	Beware of respiratory effects when combining other CNS depressants (eg, morphine, tincture of opium); may decrease effects of chloramphenicol, digitoxin, corticosteroids, carbamazepine, theophylline, verapamil, metronidazole, and anticoagulants (patients stabilized on anticoagulants may require dosage adjustments if added to or withdrawn from their regimen); coadministration with alcohol (contained in tincture of opium) may produce additive CNS effects and death; chloramphenicol, valproic acid, and MAOIs may increase phenobarbital toxicity; rifampin may decrease phenobarbital effects
Pregnancy	D - Unsafe in pregnancy
Precautions	Constantly monitor vitals and oxygen saturation; draw serum phenobarbital levels daily; once discontinued from medication, observe for any abstinence for another 1-3 d Adverse effects include sedation, poor sucking, and heightened pain sensitivity; some patients may experience a paradoxical increase in irritability with phenobarbital

FOLLOW-UP

Further Outpatient Care:

- Early intervention and developmental pediatrics: Any newborn who has been exposed to drugs is considered at risk for developmental and cognitive compromises. These children should have regular follow-up care with a team of child development specialists to quickly identify potential deficits.
- State child protective services: In the event of court-imposed custody, children should be monitored through the foster family and adoption process.
- General pediatrics: As with any newborn, perform regular follow-up care for immunizations, anticipatory guidance, and physical examinations.

In/Out Patient Meds: Administer paregoric and phenobarbital for withdrawal of opiates and barbiturates, respectively (see Medications).

<mark>**Complications:**</mark>

- Perinatal complications

  o Incidence of medical and obstetric complications increases with in utero drug exposure. In particular, the incidence of premature delivery, abruptio placentae, breech presentation, and intrauterine growth retardation are increased significantly in mothers who are dependent on drugs. The doses of analgesia are typically higher to match the tolerance to drugs already being used.
  o In particular, cocaine use, with its vasoconstrictive properties, has been associated with an increase in vaginal bleeding, abruptio placentae, placenta previa, premature rupture of membranes, abortion, pneumothorax, pneumonia, malnutrition, and seizures.
  o Amphetamine use presents similarly to cocaine use and is related to an increased rate of abruptio placentae, maternal hypertension, and renal disease. Hypertension can often be confused with preeclampsia, leading to an increased cesarean delivery rate.
  o Opioid use has been shown to increase the rate of premature labor, premature rupture of membranes, breech presentation, antepartum hemorrhage, toxemia, anemia, uterine irritability, and infection (eg, HIV, hepatitis, syphilis).
  o Alcohol use has been associated with an increased rate of abruptio placentae. Complications for mothers who drink alcohol heavily can include increased spontaneous abortions and premature placental separation.
  o Cannabinoid use has been associated with an increased serum carboxyhemoglobin level. A slightly elevated incidence of precipitate labor, meconium staining, and dysfunctional labor occurs in mothers who use cannabinoids.

- Prematurity is accompanied by a host of medical complications including asphyxia, neonatorum, intracranial hemorrhage, respiratory distress syndrome, hypoglycemia, hypocalcemia, septicemia, and hyperbilirubinemia.
- Although gross generalizations, the following growth characteristics may occur as a result of exposure to drugs:

  o Tobacco is described as perhaps the most common cause of low birth weight deliveries. Symmetric decreases are observed in all growth parameters, but these children exhibit appropriate catch-up growth.
  o Alcohol may cause symmetric decreases in all growth parameters. Support for a synergistic effect in growth retardation with concomitant cocaine abuse exists.
  o Amphetamines and cocaine may cause symmetric decrease in all growth parameters. However, the growth-restricting effect of cocaine is more likely a result of maternal malnutrition. Likewise, growth retardation resulting from cocaine use tends to resolve with catch-up growth within 2 years after birth.
  o Opiate use may result in normal growth parameters. In particular, newborns exposed to methadone tend to have higher-than-expected growth parameters.

<mark>**Prognosis:**</mark>

- Growth deficiency

  o Children with prenatal nicotine exposure exhibit appropriate catch-up growth but are known to have smaller lungs and, possibly, decreased ventilatory drive in response to carbon dioxide.
  o Children with prenatal amphetamine and cocaine exposure exhibit catch-up growth within 2 years of life.
  o Children with prenatal opiate exposure typically do not exhibit changes in growth parameters.

- Cognitive and developmental defects

  o Infants exposed to nicotine tend to score higher on auditory habituation but lower on the orientation cluster of the Brazelton Newborn Behavioral Assessment Scale (NBAS).
  o Infants exposed to alcohol may develop mental retardation, which is one of the hallmarks of FAS. An apparent dose-dependent relationship is present, and FAS now accounts for approximately 33% of all mental retardation. Milder cognitive effects include prolonged language delays and sleep dysfunction. Newborns exposed to alcohol also tend to be hypotonic.
  o Infants exposed to cocaine may exhibit fetal brain malformation resulting from changes in the homeostatic neurochemistry. Serious debate concerning the actual deleterious effects of in utero cocaine exposure exists. Consequences previously described include altered behavior on NBAS scores (eg, poor state regulation, decreases in alertness and orientation, abnormal reflexes, tone and motor maturity), increased tone (described as hypertonic tetraparesis), electroencephalogram (EEG) changes, and prolonged behavioral and language delays. However, data are inconsistent to prove that cocaine is solely responsible for these problems. The more plausible explanation is that these children exhibit such abnormalities as a result of a cumulative risk involving environmental and maternal psychosocial factors.
  o Infants exposed to opioids may have increased overall activity upon NBAS testing. They tend to have difficulty with being consoled.

Patient Education:

- Government programs are available to help the prevention of perinatal drug use. Many have published documents that address support for pregnant women who abuse substances, addiction prevention, and treatment programs and guidelines for clinicians managing patients who abuse substances. These publications are available to primary care physicians and obstetricians and can be ordered free of charge from the National Clearinghouse for Alcohol and Drug Abuse Information (NCADI) by telephone (800-729-6686 or 301-468-2600 or TDD for hearing impaired at 800-487-4889) and on the Internet.

- The following Internet sites provide guidelines for providers:

  o American Academy of Pediatrics (AAP)
  o Benton Foundation for topics pertaining to child care, health, and education
  o National Institute on Drug Abuse (NIDA)
  o Substance Abuse and Mental Health Services Administration (SAMHSA) to find the Center for Substance Abuse Prevention

PICTURES	Section 9 of 10

Picture 1. Perinatal drug abuse and neonatal drug withdrawal. Neonatal abstinence scoring form.

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Perinatal Drug Abuse and Neonatal Drug Withdrawal excerpt

Perioperative Pain Management in Newborns

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INTRODUCTION	Section 2 of 10

The practice of medicine has become progressively more sophisticated. Physicians can now achieve the goal of facilitating the healing process while simultaneously minimizing or even eliminating the pain once thought necessary to achieve this goal. Adults were the first to benefit from these advances. Only within the last 2 decades has the sophisticated medical establishment realized that pediatric patients, including neonates, also feel pain and require medical intervention to alleviate unnecessary suffering.

Medical intervention to alleviate unnecessary suffering is significantly affected by the beliefs of the caregiver. Before the late 1980s and early 1990s, the belief remained commonplace that neonates experienced no pain or less pain than adults, children, or infants who underwent similar surgical procedures. A health care provider who believes that neonates feel less pain tends to observe fewer clinical signs of pain in neonates. Furthermore, this group of practitioners tends to believe that narcotic administration is associated with increased risk in neonates.

These practitioners may administer narcotic analgesics; however, less aggressive intervention and, frequently, subtherapeutic regimens are employed in preverbal patients as compared to adults.

The fear of respiratory depression most significantly limits the administration of narcotics postoperatively, especially in nonintubated neonates or neonates undergoing minor surgical procedures. While these concerns may have some pharmacologic basis, they should not prevent the appropriate administration of narcotic analgesics to neonates who have experienced significant surgery.

Furthermore, other therapeutic regimens formerly reserved for adults, adolescents, and older children may also be used safely to manage postoperative pain for the neonate. This article expressly and specifically considers the application of medical advances in pain management to the care of our youngest perioperative patients, neonatal surgical patients.

Suffering can be minimized during the preoperative visit when physicians avoid unnecessary laboratory studies, especially those that require phlebotomy. Furthermore, inappropriately long NPO (ie, nothing by mouth) periods can be eliminated, thereby avoiding unwarranted patient agitation. Postoperative pain management should be discussed when the surgical neonate and family are seen preoperatively. Issues that may eventually affect decisions about postoperative pain management, and should therefore be addressed, include coexisting disease states, surgical site, postoperative disposition, and family consent for pain management techniques that are being considered.

Neonates who are unstable, septic, or likely to remain intubated postoperatively are frequently managed with narcotic administration intraoperatively and are continued on narcotics as needed postoperatively. Narcotic administration is pursued more cautiously in neonates who will be in a non-ICU setting postoperatively. Neonates undergoing outpatient surgery or surgery associated with minor postoperative pain are frequently managed postoperatively with acetaminophen with regional or local anesthetic infiltration. Neonates who undergo lower extremity, abdominal, or thoracic surgery are excellent candidates for regional anesthesia, whether undergoing inpatient or outpatient surgery. As in adults, coexisting pulmonary disease in neonates may be an excellent reason to consider regional anesthesia for postoperative pain management. Finally, anxiety among family members concerning a pain control strategy should be thoroughly addressed and considered in postoperative pain management decision-making.

After extensive work in the 1980s and 1990s, the fact that neonates experience pain and mount a stress response has been established and appreciated. Metabolic and hormonal indicators of the degree of stress a surgical patient experiences have been monitored during and after surgery. These indicators are, in fact, elevated in neonates perioperatively. Even premature neonates undergoing surgery are capable of mounting a significant stress response, as measured by hormonal and metabolic indicators. Stress indicators include plasma adrenaline, noradrenaline, glucagon, insulin, and cortisol as well as blood glucose, lactate, pyruvate, and alanine.

The mounting of a surgical stress response results in catabolic responses, including glycogenolysis, gluconeogenesis, and lipolysis during the perioperative period. These catabolic responses, when unmodulated by medical intervention, may have a detrimental effect on the clinical course of a neonatal surgical patient. Adverse circulatory and respiratory events are also more likely during the postoperative course of neonates who have had inadequate interventions to minimize stress response. Tachycardia, systemic hypertension, pulmonary hypertension, respiratory embarrassment, and intraventricular hemorrhage may be associated with inadequate pain control in neonates. Furthermore, inadequate treatment of pain in neonates may have implications that extend beyond the neonatal period, including hypersensitivity to noxious stimuli later in life.

To a large extent, management of the surgical stress response in neonates can be accomplished with the same pharmacologic interventions that characterize anesthetic care of other surgical patients. Volatile anesthetic agents remain the most common means of providing anesthesia and analgesia intraoperatively. This is probably because they meet, at least to some degree, each of the criteria required for a complete anesthetic, including some degree of hypnosis, amnesia, analgesia, and muscle relaxation. Anand demonstrated that blood levels of hormonal and metabolic indicators of the stress response were lower in neonates who received volatile anesthetics during surgery. Furthermore, clinical stability of neonates during and after surgery was improved by adequate administration of volatile anesthetic agents intraoperatively.

The relative potency of each volatile anesthetic agent is measured in terms of the minimum alveolar concentration (MAC) of an inhaled anesthetic agent at which 50% of patients do not have skeletal muscle movement in response to surgical incision or another noxious stimulus. The patient's age appears to influence the MAC of a given volatile anesthetic, and MAC is higher in infants than in any other age group. MAC may be 15-25% lower in neonates than in infants and is even lower in premature neonates. Volatile anesthetic agents are potent myocardial depressants and vasodilators.

Consequently, systolic blood pressure and mean arterial blood pressure may decrease when these agents are administered. In some neonates, other analgesic agents may be used to decrease volatile anesthetic agent requirements intraoperatively, thereby avoiding some of the hemodynamic changes that may occur with volatile anesthetic administration.

In fact, surgical anesthesia can be accomplished without the use of any volatile anesthetic agents.

Narcotics are not complete anesthetic agents; they do not provide muscle relaxation or amnesia, which are essential functions of complete anesthetics. However, they are potent analgesic medications. Administration of these agents intraoperatively may be associated with less of a decrease in blood pressure in neonates than might occur with volatile anesthetic administration. Furthermore, narcotics are useful adjuncts to anesthetics based on volatile agents because they can reduce the volatile agent requirement, thereby reducing any hemodynamic lability. Narcotic-based anesthetics are commonly used during cardiovascular procedures in neonates.

Physicians should note that the pharmacokinetics of narcotics administered to neonates differs from that of older infants, children, and adolescents. Neonates have a lower clearance, greater volume of distribution, longer elimination half-life, and higher plasma concentration after narcotic boluses than older patients. Consequently, the postoperative disposition of neonates may be affected when narcotics are used intraoperatively. Narcotics commonly used for intraoperative analgesia in neonates include morphine, fentanyl, sufentanil, and remifentanil.

Ketamine, a phencyclidine derivative, produces amnesia and intense analgesia. This drug affects opioid receptors and *N*-methyl-D-aspartate (NDMA) receptors, as well as voltage-sensitive calcium ion channels as it induces its analgesic effects. Ketamine actually stimulates the cardiovascular system and thus is frequently associated with increases in both systolic and mean arterial blood pressure, as well as heart rate, when administered intraoperatively. While ketamine may not be associated with increased blood pressure in preterm neonates, it is certainly associated with smaller decreases in mean arterial pressure and systolic blood pressure than the other analgesic medications commonly used intraoperatively. Beneficial effects of ketamine include production of bronchodilation and less depression of ventilation. Adverse effects that may occur in neonates include increased salivary and tracheobronchial secretion production, cerebral vasodilation, and apnea in neonates with increased intracranial pressure.

One factor that has contributed to inadequate pain management in neonates has been the pervasive belief that neonates do not feel pain. This misconception has been perpetuated, at least in part, by the conspicuous absence of adequate tools to assess pain levels in this patient population. To a large extent, pain assessment in older patients relies upon the patient's ability to report pain level in some form to the caregiver. When patients cannot express pain verbally, pain assessment depends more on evaluations by the caregiver. Even when pain is evident, quantifying the pain level is not easy. An effective pain assessment tool must be able to objectively quantify the pain level of the patient so that the healthcare provider can accurately measure the effectiveness of interventions designed to alleviate unnecessary suffering. Although no perfect tool exists yet for assessing pain in neonates, infants, and preverbal children, several very useful tools are available.

The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) was one of the first observational pain scales. This tool includes the categories of (1) cry, (2) facial expression, (3) verbal response, (4) torso position, (5) leg activity, and (6) arm movement in relationship to the surgical wound. In general,

each category is scored 0, 1, 2, or 3, with higher scores indicating higher pain levels, but the scale varies with each category evaluated. Originally, CHEOPS was used to evaluate postoperative pain in children aged 1-7 years. Evaluators determined that it was both valid and reliable for assessing pain in this patient group. Admittedly, a pain assessment tool that is appropriate for other preverbal children may not be appropriate for neonates. However, the development of CHEOPS has provided a tool against which the validity of other pediatric pain assessment tools can be measured.

The Objective Pain Scale (OPS), developed by Broadman and Hannallah, has demonstrated both validity and reliability in pain assessment. OPS assesses (1) blood pressure, (2) crying, (3) movement, (4) agitation, (5) posture, and (6) verbalization. Each parameter is scored 0, 1, or 2, with higher scores indicating greater distress. This instrument is important because it includes a cardiovascular parameter in the assessment of postoperative pain. Many advocate use of cardiovascular parameters as the most objective means of measuring the pain response in preverbal children. However, the utility of cardiovascular parameters is limited because other causes of distress may also cause dramatic changes in these parameters. Cardiovascular parameters, while not sufficient as the sole means of assessing pain in this patient population, may be helpful. Unfortunately, OPS, like CHEOPS, has been used largely for infants and children, not neonates.

The COMFORT scale has been favorably received as a tool to assess postoperative pain in the neonatal population. This tool was originally developed to assess distress in ventilated patients in the pediatric ICU. However, the COMFORT scale demonstrated reliability and validity for assessing pain in postoperative patients in one large study that evaluated pain in 158 neonates along with older infants and children.

This scale is composed of 6 behavioral items, (1) alertness, (2) calmness, (3) muscle tone, (4) movement, (5) facial tension, and (6) respiratory response, and 2 physiologic items, (1) heart rate and (2) mean arterial blood pressure. Each item may be scored 1, 2, 3, 4, or 5, with a higher score indicating a greater level of distress. The greater number of variables assessed and the increased number of scores possible for each variable may enable this tool to identify more subtle changes in patient discomfort. On the other hand, greater complexity may be a disadvantage in terms of the clinical utility of this scale. A fourth scale, CRIES, may also be useful to assess the pain of neonates postoperatively. This scale analyzes 5 variables, (1) crying, (2) requirement of increased oxygen administration, (3) increased vital signs, (4) expression, and (5) sleeplessness. Each variable is scored 0, 1, or 2. This instrument has demonstrated validity, reliability, user friendliness, and acceptance as a postoperative pain assessment tool among neonatal intensive care nurses.

Each of the pain assessment instruments discussed has strengths and limitations. For optimal use of any pain assessment tool, the physicians and neonatal nursing staff of a given hospital should select a tool, familiarize staff with its use, and systematically integrate its use into the institution's policies. This maintains the validity and reliability of the tool in measuring pain in neonates and allows appropriate intervention to be undertaken, thereby minimizing unnecessary suffering in the postoperative neonatal patient.

After appropriate pain assessment practices are established, the most formidable hindrance to alleviating postoperative pain in neonates is unfamiliarity with the safety and practicality of the pain management options. Implementing an effective pain management strategy in the neonatal surgical patient is a complex process. The strategy for pain management should begin during the preoperative assessment and continue with the intraoperative anesthetic management as formerly discussed. Furthermore, the physician responsible for pain management must be aware that pain management has an impact upon the other components of postoperative care. When treating pain in neonates, one must consider the pharmacodynamic and pharmacokinetic issues unique to the neonatal period, the severity of the surgical insult and any coexisting diseases in the patient, the surgical site, the postoperative management plans of the surgeons and neonatal or pediatric physicians, and the disposition of the neonate postoperatively.

Opioid administration remains the most common means of achieving pain control in surgical patients. Neonates who are expected to have moderate-to-severe postoperative pain are no exception. Opioids may be administered safely to neonates when a well-constructed pain management plan is implemented. While certainly not prohibitive, the risk of apnea cannot be ignored. As during the intraoperative period, more than one opioid may be considered in managing postoperative pain in the surgical neonate. Fentanyl and morphine are the most common selections for postoperative opioid administration.

Fentanyl

This drug is most appropriately administered by IV infusion to neonates who are ventilated preoperatively and are expected to remain ventilated for a period postoperatively. When administered by IV bolus (2 mcg/kg/h), fentanyl is associated with more severe episodes of apnea than continuous IV infusion (1-2 mcg/kg/h). However, respiratory depression may be less problematic when fentanyl is used in older infants. As with many other medications administered to neonates, fentanyl pharmacokinetics are highly variable. Of particular interest, neonates who postoperatively have increased abdominal pressure may have a prolonged fentanyl half-life because of impaired hepatic blood flow.

Morphine

Morphine remains the opioid analgesic most commonly used for moderate-to-severe pain in neonates postoperatively. Surgical procedures that may be included in this category include craniotomy, thoracotomy, sternotomy, and laparotomy. Incremental IV boluses of 20 mcg/kg, not to exceed 100 mcg/kg, are typically administered for acute pain management in the postanesthesia recovery unit. When a continuous IV infusion is used for postoperative pain management in neonates, the initial rate varies depending upon the age of the neonate.

Initial IV infusion rates of 10 mcg/kg/h for neonates younger than 1 week are acceptable. Neonates older than 1 week tolerate 15 mcg/kg/h, while older infants may tolerate 20-40 mcg/kg/h. Supplemental IV boluses of up to 50 mcg/kg may be administered for breakthrough pain episodes in neonates receiving morphine by continuous infusion. No difference exists in the respiratory response to morphine in term neonates compared to older infants and children when identical plasma levels of morphine are achieved and maintained. Greater caution may be advisable when initiating morphine infusions in preterm neonates, who may require significantly lower infusion rates to achieve the same plasma levels of morphine as term neonates. Above a steady-state plasma concentration of 20 ng/mL, respiratory depression becomes more likely in all neonates.

Practitioners who administer morphine infusions for postoperative pain control should be aware of the pharmacokinetic disadvantages, which place neonates at risk for respiratory depression (because of increased plasma concentrations). Neonates have immature hepatic enzyme systems. This may result in a doubling of the elimination half-life of morphine in neonates (ie, 10-20 h) compared with older infants (ie, 5-10 h). Lower plasma protein levels in neonates may result in higher levels of free drug and slower plasma clearance of morphine. Morphine clearance in neonates may be as little 50% of that of older infants and 25% of adult values. Furthermore, the rate of glucuronidation (the primary metabolic pathway of morphine) is slower in neonates compared to older infants and adults.

Coexisting surgical and medical conditions may impact the pharmacokinetics of morphine in neonates. As mentioned before, abdominal surgery that results in increased abdominal pressure postoperatively may impair drug metabolism or drug elimination, thus increasing the half-life of these medications. Additionally, the pharmacokinetics of medications may be different in neonates with cardiac comorbidity compared to those without congenital heart disease. Whether this is secondary to impaired cardiac performance or the impact of abnormal circulatory dynamics on hepatic or renal function is unclear. Use of preservative-free morphine should also be considered because neonates are more susceptible to respiratory depression caused by some preservatives.

Seldom used for postoperative management of pain in neonates, meperidine can be administered in doses of 1 mg/kg. However, its pharmacokinetic profile shows dramatic variability in individual neonates. Furthermore, meperidine has epileptogenic metabolites, which tend to accumulate in patients with impaired renal function, as is inherent in the neonatal period. In the author's opinion, the disadvantages of meperidine outweigh the advantages of its use in the neonatal patient.

POSTOPERATIVE PAIN CONTROL: NONNARCOTIC AND NONPHARMACOLOGIC MODALITIES — Section 8 of 10

Nonnarcotic analgesics

Nonnarcotic pain management modalities are important in pain management of the postoperative neonate. Acetaminophen is useful either as a sole analgesic for mild discomfort or as an adjuvant medication for moderate-to-severe pain when narcotic or regional analgesia is employed. Either oral or rectal administration may be employed. Rectal administration is associated with lower plasma levels and a longer elimination half-life. While 15 mg/kg may be administered orally, this dose is associated with subtherapeutic plasma levels when administered rectally to neonates. An initial dose of 20-35 mg/kg is recommended for the initial preincision dose or the immediate postoperative dose administered per rectum.

Ketorolac is not approved by the Food and Drug Administration (FDA) for use in neonates, and reports of its use in this patient population are absent from the literature. Moreover, ketorolac may be no more effective than high-dose rectal acetaminophen in some older patients.

Nonpharmacologic interventions

A discussion of nonnarcotic pain modalities would be incomplete without a discussion of nonpharmacologic interventions. While these modalities, in some fashion, may be employed with older patients, they are considered central to the pain management of neonates. These modalities include bundling, holding, and rocking the neonate, provision of a pacifier to alleviate distress, and minimization of environmental stimuli such as extraneous noise and unnecessary light.

POSTOPERATIVE PAIN CONTROL: REGIONAL ANALGESIA — Section 9 of 10

Regional pain control techniques are increasingly employed to manage postoperative pain in neonates. Regional techniques may include single-dose administration of local anesthetics into the caudal space, plexus blockade of the upper or lower extremity, extrapleural catheter placement, or neuraxial catheter placement for continuous pain control postoperatively. The most common regional techniques in neonates include single-dose caudal administration and placement of epidural catheters for prolonged pain management.

Caudal anesthesia is a highly effective simple technique associated with a high success rate and a low complication rate. Caudal anesthesia is neuraxial anesthesia and thus is associated with some of the risks inherent to neuraxial access. However, because the neuraxial space is accessed at its most caudad entry point, the risk of neural injury or even inadvertent dural puncture is reduced. Sterile technique is required and may be accomplished by wearing sterile gloves or palpating the caudal space anatomy through an alcohol swab (ie, no-touch technique) before instilling a single dose of medication into the caudal space.

Use a short beveled needle to minimize the likelihood of inadvertent intravascular or intramedullary injection of the local anesthetic medication. A caudal anesthetic can be successfully administered in 96% of pediatric patients. Once the sacrococcygeal ligament has been penetrated with the regional anesthetic needle, lower the angle of the needle, advance the needle no more than 3-5 mm, aspirate the syringe to ensure the absence of cerebral spinal fluid or heme, and administer the local anesthetic. Most commonly, bupivacaine is administered for single-dose caudal blocks. Effective concentrations range from 0.125-0.25% bupivacaine. Volumes of 0.75-1 mL/kg are administered. Supplemental analgesics may not be required for up to 12 hours postoperatively when the caudal is effective.

Placement of a caudal, lumbar, or even thoracic catheter for continuous postoperative pain management has also been proven safe and effective in neonates. An epidural catheter may be successfully placed via the caudal approach and advanced cephalad to the lumbar or thoracic level. Using superficial anatomic landmarks as a guide, the level of the catheter may be accurately predicted. This catheter may then be used for postoperative infusion of narcotics or local anesthetic infusions. Epidural catheters have been successfully used for postoperative management of many major neonatal surgical procedures that require laparotomy or thoracotomy, including hepatic resection, abdominal wall defects (gastroschisis and omphalocele), tracheoesophageal fistula, congenital diaphragmatic hernia, and coarctation of the aorta. After successful placement and an initial bolus dose of the epidural catheter, pain management may be maintained with a continuous infusion of analgesic medications.

Epidural infusions provide an acceptable alternative to the intermittent top-up technique. Epidural infusions are both safe and effective in term and preterm neonates. Postoperative epidural bupivacaine infusions result in significantly less sedation, less depression of the respiratory rate, and improvement in oxygenation without supplemental oxygen administration, while providing similar analgesia and similar complication and hemodynamic profiles to a morphine infusion.

In 1992, Berde reported recommendations to facilitate safe use of epidural analgesia in pediatric patients after analysis of more than 20,000 pediatric regional anesthetic procedures in 15 institutions. Berde recommended bolus dosing of epidural bupivacaine not to exceed 2-2.5 mg/kg. Infusion rates of 0.2-0.25 mg/kg/h were recommended for neonates. This paper cautioned that children are probably not more resistant to local anesthetic toxicity than adults, as had been previously thought. Neonates, in particular, may be at risk for local anesthetic toxicity because of diminished plasma alpha1-acid glycoprotein levels, which could result in a higher free fraction and slower clearance of bupivacaine. Premonitory symptoms or signs of local anesthetic toxicity may be absent in neonates. Reduce infusion rates for patients at risk for seizures.

When the epidural catheter level is too low to provide adequate analgesia at the incision site for a neonatal patient, increasing the rate of the epidural infusion cannot safely overcome this low catheter level. In one study, plasma bupivacaine levels continued to increase over a 48-hour infusion period, reaching the upper limits of the safe range before the end of this 48-hour period. In addition, plasma levels of bupivacaine were higher in neonates who were at higher risk for increased abdominal pressure postoperatively. Furthermore, as with all drugs administered during the neonatal period, interindividual variability in plasma bupivacaine levels were considerable in neonates receiving epidural infusions. While plasma clearance is lower in neonates than in adults receiving epidural infusions, this difference is even more dramatic in preterm neonates.

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Periventricular Hemorrhage-Intraventricular Hemorrhage

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Synonyms and related keywords: PVH, IVH, germinal matrix hemorrhage, intraventricular hemorrhage, periventricular hemorrhage

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INTRODUCTION	Section 2 of 11

Background: Families and caregivers of preterm infants and those threatened with preterm delivery must face 2 major unknowns regarding these newborns: Will this child survive? If the child survives, will this child be brain damaged? These questions are of particular importance because the answers can influence subsequent medical decisions, such as aggressiveness of care. Several acquired lesions of the central nervous system (CNS) specifically affect infants born prematurely and result in long-term disability. This chapter reviews one of the important CNS lesions, periventricular hemorrhage-intraventricular hemorrhage (PVH-IVH), which involves the periventricular white matter (motor tracts) and is associated with long-term disability.

PVH-IVH remains a significant cause of both morbidity and mortality in infants who are born prematurely. Sequelae of PVH-IVH include life-long neurological deficits, such as cerebral palsy, mental retardation, and seizures. PVH-IVH is diagnosed primarily through the use of brain imaging studies, usually cranial ultrasonography. As PVH-IVH can occur without clinical signs, serial examinations are necessary for the diagnosis.

Although classified according to anatomic involvement by Papile, a modified classification has recently emerged based on the pathophysiological processes that result in hemorrhage. Recent advances also have presented options for the prevention of such events. Still, PVH-IVH remains a serious problem, despite recent decreases in incidence, due to increased survival of extremely low birthweight infants (ie, <1000 g) as well as severity of sequelae.

Pathophysiology:
Site of origin

The site of origin of PVH-IVH is the subependymal germinal matrix, a region of the developing brain that regresses by term. During fetal development, the subependymal germinal matrix is a site of neuronal proliferation as neuroblasts divide and migrate into the cerebral parenchyma. By approximately 20 weeks' gestation, neuronal proliferation is completed; however, glial cell proliferation is still ongoing. The germinal matrix supports the division of glioblasts and differentiation of glial elements until approximately 32 weeks' gestation, at which time regression is nearly complete. Cells of the germinal matrix are rich in mitochondria and, therefore, are quite sensitive to ischemia.

Supplying this area of metabolically active differentiating cells is a primitive and fragile retelike capillary network. Arterial supply to the plexus is through the Heubner artery and the lateral striate arteries, which are within the distribution of the anterior and middle cerebral arteries, respectively. This fragile capillary network is the site at which PVH-IVH hemorrhage occurs. Venous drainage is through the terminal vein, which empties into the internal cerebral vein; this in turn empties into the vein of Galen. At the site of confluence of the terminal vein and the internal cerebral vein, blood flow direction changes from a generally anterior direction to a posterior direction.

Anatomic classification

PVH-IVH can be classified into 4 grades of severity. This classification, which is useful for prognostic reasons when counseling parents and caregivers, is described in Table 1. Note that this classification is based on radiological appearance rather than a pathophysiological description of events leading to PVH-IVH.

Table 1. Classification of PVH-IVH

Grade	Radiological Appearance – Site of Hemorrhage
I	Subependymal region and/or germinal matrix
II	Subependymal hemorrhage with extension into lateral ventricles without ventricular enlargement
III	Subependymal hemorrhage with extension into lateral ventricles with ventricular enlargement
IV	Intraparenchymal hemorrhage

Pathogenesis

PVH-IVH hemorrhage is now thought to be caused by capillary bleeding. Two major factors that contribute to the development of PVH-IVH are (1) loss of cerebral autoregulation and (2) abrupt alterations in cerebral blood flow and pressure. Most healthy infants who were born prematurely have some ability to regulate cerebral blood flow through a process called autoregulation. However, autoregulation is lost under some circumstances. Perlman and Volpe have demonstrated that the alteration from autoregulation to a pressure-passive circulatory pattern appears to be an important step in the development of PVH-IVH. When a pressure-passive circulatory pattern is challenged with fluctuations of cerebral blood flow and pressure, hemorrhage can occur.
The autoregulatory abilities of neonates vary proportionally to gestational age at time of birth. The range of perfusion pressures over which a premature neonate can control regional cerebral blood flow is narrower and lower than that of infants born at term. In the absence of autoregulation, the systemic blood pressure becomes the primary determinant of cerebral blood flow and pressure, a pressure-passive situation.

Multiple events can result in rapid changes in the cerebral circulation, potentially overwhelming the autoregulatory mechanisms of the neonate. These events include asynchrony between spontaneous and mechanical breaths; birth; noxious procedures of caregiving; instillation of mydriatics; tracheal suctioning; pneumothorax; rapid volume expansion (iso-osmotic or hyperosmotic as in sodium bicarbonate); rapid colloid infusion (eg, exchange transfusion); seizures; and changes in pH, $PaCO_2$, and PaO_2. Specific metabolic derangements (eg, hypocarbia, hypercarbia, hypoxemia, acidosis) also can disrupt the autoregulatory abilities in infants.

The loss of autoregulatory ability coupled with rapid alterations in cerebral blood flow and pressure can result in hemorrhage. The capillaries of the immature germinal matrix possess neither tight junctions between endothelial cells nor a strong basement membrane. Therefore, increased flow and pressure may rupture the delicate capillaries, leading to bleeding.

In a series of investigations, Perlman, McMenamin, and Volpe described the relationship between cerebral blood flow and respiratory pattern in preterm infants. Their findings suggest that when mechanical breaths are not synchronized with efforts of the patient, beat-to-beat fluctuations in blood pressure occur, resulting in fluctuations in cerebral perfusion and subsequent PVH-IVH. Interventions to reduce the fluctuations by suppressing the respiratory efforts of the infant by pharmacological muscle blockade prevented hemorrhage. Patients without asynchrony between mechanical ventilation and patient efforts had stable blood pressures, stable cerebral perfusion, and a lower incidence of hemorrhage. Similar experimental models have demonstrated a relationship between rapid volume expansion following ischemia or hemorrhagic shock and PVH-IVH.

Based on the above discussion, the development of PVH-IVH appears to occur in 2 steps; the loss of cerebral autoregulation is followed by rapid changes in cerebral perfusion. Additionally, because the range of arterial pressures over which a prematurely born neonate can maintain autoregulation is narrow, abrupt large changes in blood pressures can overwhelm the ability of the neonate to protect the cerebral circulation and result in PVH-IVH. Experimental models also describe this development. Host factors can modify mechanisms of PVH-IVH. Among others, such factors include coagulopathy, acid-base balance, hydration, and hypoxia-ischemia.

The above mechanisms account for grades I, II, and III PVH-IVH. The pathogenesis of grade IV hemorrhages differs. Grade IV hemorrhages appear to result from hemorrhagic venous infarctions surrounding the terminal vein and its feeders, probably primarily related to increased venous pressure following or associated with the development of lower-grade hemorrhages. Indeed, the use of the term periventricular hemorrhagic infarction has been suggested rather than using the term grade IV hemorrhage, resulting in the following modification of Table 1:

Table 2. Modification of Grade Descriptions of Table 1

Grade	Radiological Appearance – Site of Hemorrhage
Mild (approximates grade I)	Subependymal region and/or germinal matrix
Moderate (approximates grade II)	Subependymal hemorrhage with minimal filling (10-40%) of lateral ventricles with no or little ventricular enlargement
Severe (approximates grade III)	Subependymal hemorrhage with significant filling of lateral ventricles (>50%) with significant ventricular enlargement
Periventricular hemorrhagic infarction	Intraparenchymal venous hemorrhage

Pathogenesis of sequelae

The major sequelae of PVH-IVH relate to the destruction of cerebral parenchyma and the development of posthemorrhagic hydrocephalus. Furthermore, the sequelae of ventricular-peritoneal shunt placement (primarily infection) can contribute to poor neurodevelopmental outcomes.

Following parenchymal hemorrhages, necrotic areas form cysts that can become contiguous with the ventricles (porencephalic cysts). Cerebral palsy is the primary neurological disorder observed after PVH-IVH, though mental retardation and seizures can ensue as well. The occurrence of cerebral palsy is related to the anatomical structure of the periventricular region of the brain. The cortical spinal motor tracts run in this region. The white matter is arranged such that tracts innervating the lower extremities are nearest to the ventricles, followed by those innervating the trunk, the arm, and, finally, the face. This anatomical arrangement accounts for the greater degree of motor dysfunction of the extremities as compared to the face (spastic hemiplegia in unilateral lesions and spastic diplegia or quadriplegia in bilateral lesions). In addition to destruction of periventricular motor tracts, destruction of the germinal matrix itself can occur. The long-term effects of the loss of glial cell precursorsare unknown.

The second mechanism by which long-term neurological outcome can be altered is through the development of posthemorrhagic hydrocephalus. The mechanisms by which hydrocephalus develop include (1) decreased absorption of cerebral spinal fluid (CSF) secondary to obstruction of arachnoid villi by blood and debris or the development of obliterative arachnoiditis (ie, communicating hydrocephalus) and (2) obstruction to CSF circulation (ie, obstructive hydrocephalus).

Finally, because the development of PVH-IVH is related to alterations in cerebral blood flow, injury to other portions of the brain must be considered. Two disorders that may coexist with PVH-IVH are global hypoxic-ischemic injury and periventricular leukomalacia (PVL). PVL is a disorder of the periventricular white matter, similar to periventricular hemorrhagic infarction. However, the mechanism of PVL, nonhemorrhagic ischemic necrosis, differs substantially from that of all grades of PVH-IVH, including periventricular hemorrhagic infarction. Both PVL and global hypoxic-ischemic injury can significantly affect the neurologic outcome in infants affected with these disorders.

The significance of alterations in cerebral blood flow is perhaps of greater importance than previously recognized, not only in the generation of hemorrhage but in more diffuse brain injury as well. For example, numerous studies have demonstrated alterations in cerebral blood flow during rapid infusions of indomethacin, raising concern that prophylactic use might improve the risk of PVH-IVH while increasing the risk of periventricular leukomalacia. Fortunately, this has not been shown to be true. Indeed, in a large follow-up study of patients receiving indomethacin prophylaxis, Ment demonstrated that while indomethacin prophylaxis did not result in improved motor outcomes, cognitive and verbal outcomes were improved with prophylaxis. The pathophysiology described above might appear inconsistent with that observation; however poorly understood alterations in cerebral blood flow distribution and cellular energy utilization might beneficially be effected by indomethacin.

Frequency:

- **In the US:** Incidence of PVH-IVH in infants of very low birth weight (<1500 g) or infants of less than 35 weeks' gestation has been reported to be as high as 50%. This incidence appears to have fallen in recent years. Although no firm estimates of incidence can be made at this point, a multicenter study conducted by Ment et al in 1994 reported rates of 12-18% with and without indomethacin prophylaxis respectively, were observed. Reasons for the decline in incidence of PVH-IVH are not entirely clear but probably are related to improvements in obstetric care as well as improvements in neonatal respiratory and fluid management.
- **Internationally:** Because the incidence of PVH-IVH is inversely proportional to gestational age, and because resource availability appears to influence aggressiveness of intervention and survival, international incidences of PVH-IVH would be expected to vary dramatically. However, there is no reason to think that international rates of PVH-IVH differ from those reported above, provided similar resources are available.

Mortality/Morbidity: Mortality from PVH-IVH is 27-50%. An inverse relationship between extent of hemorrhage and survival exists.

Age:

- Although all infants who are born prematurely should be considered at risk for PVH-IVH, neonates delivered at less than 32 weeks' gestation are at significant risk. Beyond approximately 32 weeks' gestation, the germinal matrix has regressed to the point that hemorrhage is significantly less likely. Risk of developing PVH-IVH is inversely proportional to gestational age.
- Postnatally, most hemorrhages occur when the neonate is younger than 72 hours, with 50% of hemorrhages occurring on the first day of life. The extent of hemorrhage is greatest when the neonate is aged approximately 5 days. PVH-IVH can occur when the individual is older than 3 days, especially if a significant life-threatening illness arises.
- Although intraventricular hemorrhage is uncommon in infants who are born at term, the disorder has been reported, especially in association with trauma and asphyxia. The site of hemorrhage in term infants is usually the choroid plexus, a difference from the site of PVH-IVH in infants who are born prematurely.

History: History of the patient can be entirely noncontributory in PVH-IVH. Caregivers or parents might note nonspecific subtle signs. However, in some patients, events that result in loss of autoregulation of cerebral blood flow can be obtained.

Physical:

- The presentation of PVH-IVH varies significantly.
- Most infants are asymptomatic or demonstrate subtle signs that are easily overlooked. PVH-IVH subsequently is found on surveillance sonography.
- One subgroup of infants with PVH-IVH presents with the following:

  - A sudden unexplained drop in hematocrit
  - Possible physical findings related to anemia (eg, pallor, poor perfusion) or hemorrhagic shock

- Another subgroup of infants with PVH-IVH presents with extreme signs.

  - A sudden and significant deterioration associated with anemia, metabolic acidosis, glucose instability, respiratory acidosis, apnea, hypotonia, and stupor is present.
  - Physical findings related to these signs include poor perfusion, pallor or an ashen color, irregularities of respiratory pattern, signs of respiratory distress including retractions and tachypnea, hypotonia, and altered mental status (eg, decreased responsiveness, coma).
  - Additional neurological signs, such as fullness of the fontanels, seizures, and posturing, also may be observed.
  - Progression can be rapid and may result in shock and death.

- Between the 2 extremes of presentation, infants might demonstrate varying degrees of neurological and systemic signs.

Causes:

- Rapid volume expansion (eg, the correction of hypotension with volume infusions)
- Asynchrony between mechanically delivered and spontaneous breaths in infants on ventilation

- Hypertension or beat-to-beat variability of blood pressure
- Coagulopathy
- Hypoxic-ischemic insults
- Respiratory disturbances (eg, hypercarbia, hypocarbia pneumothorax, hypoxemia, rapid alterations in blood gasses)
- Acidosis
- Infusions of hypertonic solutions (eg, sodium bicarbonate)
- Anemia
- Vacuum-assisted delivery
- Frequent handling
- Tracheal suctioning

DIFFERENTIALS	Section 4 of 11

Apnea of Prematurity
Hypermagnesemia
Hypoglycemia
Neonatal Sepsis
Periventricular Leukomalacia

WORKUP	Section 5 of 11

Imaging Studies:

- Cranial sonography

  - Sonography is the diagnostic tool of choice for screening examination and follow-up of individuals with PVH-IVH. Screening is best performed when neonates are aged 3-7 days because most hemorrhages occur before that age. Late screening (ie, when individual is approximately aged 28 days) is useful to find the less common late hemorrhage and for surveillance with regard to PVL.
  - Sonography is also the diagnostic tool of choice for the follow-up of individuals with PVH-IVH and posthemorrhagic hydrocephalus. Serial sonography is indicated weekly to follow for progression of hemorrhage and the development of posthemorrhagic hydrocephalus.

- CT scan

  - Prior to the availability of sonography, CT scanning was used for diagnosis and follow-up.
  - CT scanning is no longer used for diagnosis and follow-up in view of the safety and cost effectiveness of sonography.

Other Tests:

- Although not as useful as sonography, frontal-occipital circumference can be used as an adjunct test in monitoring the progression of posthemorrhagic hydrocephalus.

Medical Care: Supportive care includes the correction of underlying medical disturbances that might be related to the development of PVH-IVH as well as cardiovascular, respiratory, and neurological support.

- Correction of anemia, acidosis, and hypotension, as well as ventilatory support, might be required in those neonates who present with acute deterioration.
- Serial lumbar puncture, though once used to prevent progressive hydrocephalus, is not indicated

Surgical Care: Surgical support for PVH-IVH is limited to intervention for posthemorrhagic hydrocephalus. Because most patients with hydrocephalus following PVH-IVH demonstrate spontaneous resolution within weeks of onset, surgical intervention is usually unnecessary.

- Serial lumbar punctures have been used to manage early hydrocephalus. However, because spontaneous resolution of hydrocephalus is usually observed, the utility of this intervention has been questioned. A multicenter evaluation of serial lumbar punctures demonstrated no benefit when the individual with PVH-IVH is aged 30 months. The role of serial lumbar punctures in the management of late or rapidly progressive hydrocephalus remains controversial.
- Acetazolamide may be used to diminish CSF production and limit late or rapidly progressive hydrocephalus. Its utility in the treatment of early ventricular dilatation is probably limited.
- Ventriculostomy placement may be required for the management of significant hydrocephalus while awaiting definitive surgical drainage.
- Ventriculoperitoneal and ventriculosubgaleal shunting remain the definitive treatments for posthemorrhagic hydrocephalus requiring surgical intervention.

Consultations:

- Consult neurosurgery in the event of rapidly progressive ventricular enlargement or prolonged (>4 wk) slowly progressive ventricular enlargement.
- Neurology consultation might be of value in the event of intractable seizures in an individual with PVH-IVH.
- A developmental interventionist might be of help with a patient with high-grade hemorrhages.

Pharmacological intervention in the prevention and treatment of PVH-IVH and posthemorrhagic hydrocephalus remains controversial.

Drug Category: *Prostaglandin inhibitors* -- Postulated to perform prostaglandin synthesis inhibition. Inhibit free radical formation and accelerates maturation of germinal matrix vasculature.

Drug Name	Indomethacin (Indocin) -- Controversial, but possibly indicated in patients at risk for PVH-IVH, including those <32 wk of gestation or weighing <1250 g at birth. Among its actions, indomethacin inhibits the formation of prostaglandins by decreasing the activity of cyclooxygenase. Additionally, through mechanisms poorly understood, indomethacin causes maturation of the germinal matrix microvasculature. It also is associated with decreased cerebral blood flow, cerebral blood flow velocity, and cerebral blood volume, especially when administered rapidly. Alterations of oxidative metabolism also are suggested.
Pediatric Dose	0.1 mg/kg/dose IV when aged 6h, then q24h for 2 d for a total of 3 doses
Contraindications	Thrombocytopenia or active bleeding; acute renal failure; pulmonary hemorrhage; oliguria; electrolyte disorders; premature infants with or

	suspected necrotizing enterocolitis (NEC)
Interactions	May interfere with renal excretion of drugs (eg, gentamicin); may increase serum potassium levels when administered with potassium-sparing diuretics
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Pregnancy category D if used for more than 48 h or after 34 wk of gestation; fluid and electrolyte imbalance including hyperkalemia; possible cerebral hypoperfusion and ischemia; alterations in regional blood flow including gastrointestinal and renal;acute renal failure; oliguria

Drug Category: *Carbonic anhydrase inhibitors* -- Suppress CSF production.

Drug Name	Acetazolamide (Diamox) -- The suppression of CSF production in slowly progressive ventricular dilation is controversial. Acetazolamide is a competitive and reversible inhibitor of carbonic anhydrase.
Pediatric Dose	5 mg/kg/dose PO/IV q6h initially; increase by 25 mg/kg/d; not to exceed 100 mg/kg/d
Contraindications	Patients with hyperchloremic acidosis; decreased serum sodium and/or potassium
Interactions	May increase the excretion of phenobarbital
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Hypercalciuria and nephrocalcinosis (especially in combination with furosemide); possible interference with CNS myelination; metabolic acidosis; hypokalemia; hepatic dysfunction

FOLLOW-UP Section 8 of 11

Further Inpatient Care: Developmental intervention programs
Further Outpatient Care:

- Neurological follow-up
- Developmental follow-up

Deterrence/Prevention:

- Prevention of PVH-IVH begins with avoidance of conditions that do the following:

    o Interfere with autoregulation (eg, hypocarbia, hypercarbia, hypoxia, acidosis
    o Overwhelm autoregulatory abilities (eg, hypertension)
    o Contribute to rapid fluctuations of cerebral blood flow (eg, ventilatory asynchrony, rapid volume expansion, noxious stimuli, frequent handling)

- Perform correction of host factors (eg, coagulopathy, acid-base balance, hydration, hypoxia-ischemia).
- Pharmacological prophylaxis can be accomplished through the use of indomethacin. Although the mechanism of action is currently unknown, indomethacin has been shown to reduce the incidence of PVH-IVH and, specifically, high-grade hemorrhages. Follow-up of patients enrolled in a multicenter prophylaxis study conducted by Ment is encouraging. Although motor skills are not different when patients are aged 4.5 years, cognitive and social skills appear better in patients receiving prophylaxis. However, because of complications, this therapy is not universally accepted and remains controversial.
- In addition to effects on pulmonary development, prenatal treatment with glucocorticoids has a protective effect with regard to PVH-IVH.

- The use of other pharmacological modalities to prevent PVH-IVH has been proposed; however, this use is not widely accepted. The other pharmacological modalities include prenatal treatment with vitamin K and phenobarbital and postnatal treatment with Ethamsylate, phenobarbital, and vitamin E. Although positive reports concerning the efficacy of these agents exist, further investigation is required to prove conclusive evidence of benefit.

Complications:

- Obstructive hydrocephalus
- Nonobstructive hydrocephalus
- Developmental impairment
- Cerebral palsy
- Seizures

Prognosis:

- Grade I and grade II hemorrhage: Neurodevelopmental prognosis is excellent (ie, perhaps slightly worse than infants of similar gestational ages without PVH-IVH).
- Grade III hemorrhage without white matter disease: Mortality is less than 10%. Of these patients, 30-40% have subsequent cognitive or motor disorders.
- Grade IV (severe PVH-IVH) IVH with either periventricular hemorrhagic infarction and/or periventricular leukomalacia: Mortality approaches 80%. A 90% incidence of severe neurological sequelae including cognitive and motor disturbances exists.

Patient Education:

- Prenatal

  o Specific risks of gestational age
  o Sequelae

- Postnatal

  o Provide postnatal education (if not provided previously) or reinforce prenatal education.
  o Provide results of sonography and expectations for short-term and long-term care.

MISCELLANEOUS	Section 9 of 11

Medical/Legal Pitfalls: Use of indomethacin

  o According to randomized controlled trials, the use of indomethacin appears to be effective in the prevention of PVH-IVH. However, this therapy is not accepted universally because of potential complications of treatment. Whether or not failure to use indomethacin (or the use of the drug with subsequent complications) could result in civil liability is not clear.
  o Additionally, in order to be effective, indomethacin must be administered within hours of birth. The number of at-risk premature patients who could conceivably receive the drug is large. Obtaining a pre-indomethacin echocardiogram to rule out an underlying cardiac condition in which patency of the ductus arteriosus is essential may be considered impractical and not cost effective. Whether or not legal risk is associated with the failure to diagnose a ductal-dependent lesion prior to administering indomethacin is not clear.

Special Concerns: In patients with posthemorrhagic ventricular dilation that regresses, provide close follow-up care because hydrocephalus can recur.
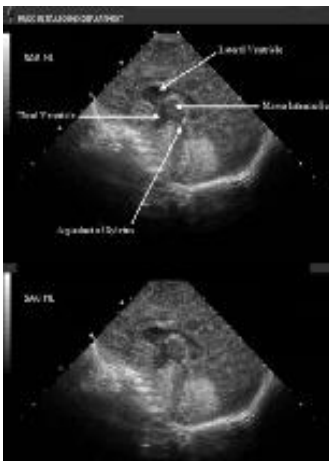
Picture 1. Periventricular hemorrhage, intraventricular hemorrhage. Sonographic appearance of a normal neonatal brain. Image is from a coronal midline scan.
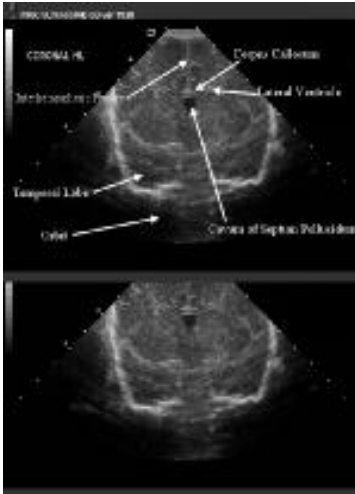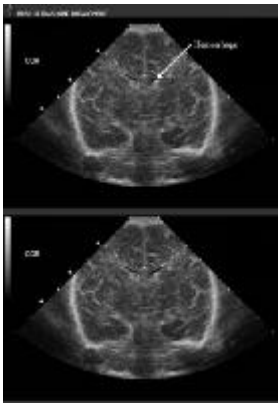

Picture 2. Periventricular hemorrhage, intraventricular hemorrhage. Normal neonatal brain shown with left sagittal scan.
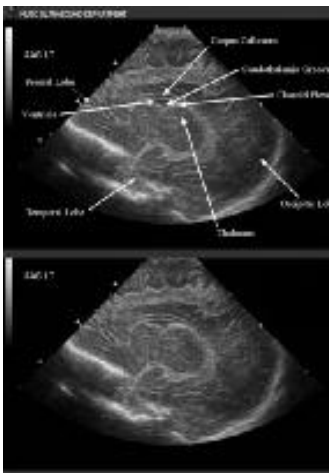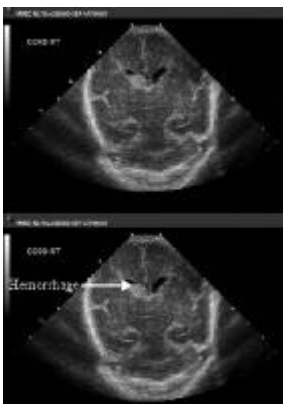

Picture 3. Periventricular hemorrhage, intraventricular hemorrhage. Normal neonatal brain shown with midline sagittal scan.
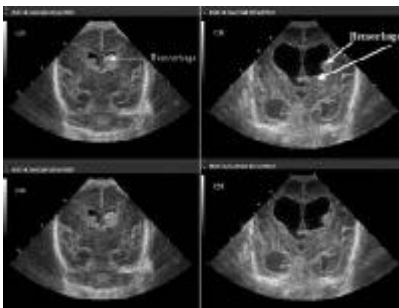
Picture 4. Periventricular hemorrhage, intraventricular hemorrhage. Grade I hemorrhage minimal or grade I periventricular hemorrhage (PVH).

Picture 5. Periventricular hemorrhage, intraventricular hemorrhage. Moderate or grade II hemorrhage (subependymal with no or little ventricular enlargement).

Picture 6. Periventricular hemorrhage, intraventricular hemorrhage. Severe or grade III hemorrhage (subependymal with significant ventricular enlargement).

Picture 7. Intraventricular hemorrhage (IVH) with periventricular hemorrhagic infarction (PVHI).
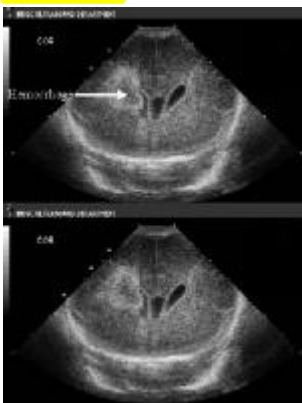
Picture 8. Periventricular hemorrhagic infarction (PVHI) with porencephalic cyst formation.
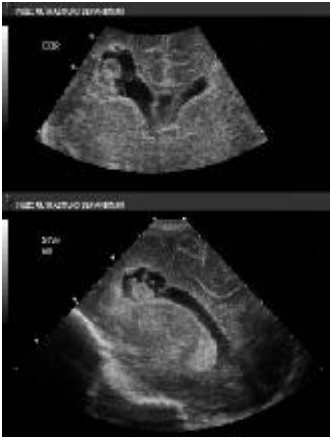
Picture 9. Periventricular hemorrhage, intraventricular hemorrhage. Periventricular hemorrhagic infarction (PVHI) on MRI.
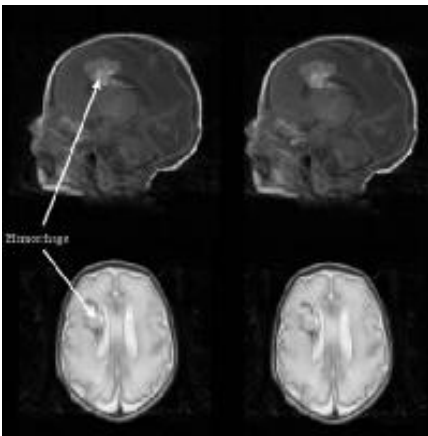
Picture 10. Periventricular hemorrhage, intraventricular hemorrhage. Hydrocephalus.
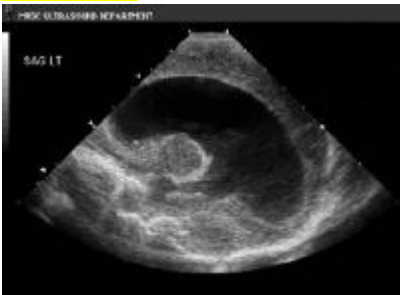
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Periventricular Hemorrhage-Intraventricular Hemorrhage excerpt

Periventricular Leukomalacia

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INTRODUCTION	Section 2 of 10

Background: Periventricular leukomalacia (PVL) is the most common ischemic brain injury in premature infants. The ischemia occurs in the border zone at the end of arterial vascular distributions. The ischemia of PVL occurs in the white matter adjacent to the lateral ventricles. The diagnostic hallmarks of PVL are periventricular echodensities or cysts detected by cranial ultrasonography. Diagnosing PVL is important because a significant percentage of surviving premature infants with PVL develop cerebral palsy (CP), intellectual impairment, or visual disturbances.

Pathophysiology: The two major theories propounded in the pathophysiology of PVL are: (1) Watershed injury to the periventricular area due to a vascular insult and/or (2) maternal chorioamnionitis or vasculitis with the production of cytokines leading to inflammatory damage to the periventricular area in the developing brain.

PVL is a bilateral white matter lesion of premature infants that may result from hypotension, ischemia, and coagulation necrosis at the border or watershed zones of deep penetrating arteries of the middle cerebral artery. Decreased blood flow affects the white matter at the superolateral borders of the lateral ventricles. The site of injury affects the descending corticospinal tracts, visual radiations, and acoustic radiations. Premature infants on mechanical ventilation may develop hypocarbia. Several studies have linked hypocarbia, particularly in the first few days of life, with the development of PVL. In addition to possible ischemic injury, PVL may be the result of edema fluid and hemorrhage causing compression of arterioles in the white matter. Premature infants have impaired cerebrovascular autoregulation and are susceptible to intracranial hemorrhage (ICH) as well as PVL. Many premature infants have both PVL and ICH detected on ultrasonography.

In a recent 1999 epidemiologic study, Leviton et al provided a detailed careful analysis of maternal infection, placental inflammation, and vasculitis and their relationship to PVL. They observed that fetal inflammatory response, as reflected by fetal vasculitis (polymorphonuclear leukocyte infiltration in the chorionic plate or umbilical cord), and not intra-amniotic infection damages the fetal brain. Maternal infection (as reflected by maternal antibiotic administration) is also associated with fetal brain damage, although not as a result of fetal brain infection. Furthermore, various maternal cytokines have also been implicated in the pathogenesis of PVL.

Following the initial insult, whether ischemia- or cytokine-mediated, white matter damage occurs. The white matter damage may occur because of selective loss of oligodendroglia. However, in 2001, Dammann and coworkers offered support that white matter damage involves axons as well as oligodendrocytes.

Frequency:

- **In the US:** Incidence of PVL ranges from 4-26% in premature infants in neonatal intensive care units (NICUs). Incidence of PVL is much higher in reports from autopsy studies of premature infants. As many as 75% of premature infants have evidence of PVL on postmortem examination.

Mortality/Morbidity:

- Cerebral palsy: Approximately 60-100% infants with PVL later develop signs of CP. Spastic diplegia is the most common form of CP following mild PVL. Severe PVL is frequently associated with quadriplegia.
- Intellectual impairment: Varying degrees of intellectual impairment, developmental impairment, or both have been reported in association with PVL.
- Visual dysfunction: Fixation difficulties, nystagmus, strabismus, and blindness have been associated with PVL. Some cases of visual dysfunction in association with PVL occur in the absence of retinopathy of prematurity, suggesting damage to optic radiations as causation.

Age: PVL occurs most commonly in premature infants younger than 32 weeks' gestation at birth.

CLINICAL	**Section 3 of 10**

History: PVL occurs most commonly in premature infants born at less than 32 weeks' gestation and less than 1500 g birth weight. Most infants have a history of cardiorespiratory problems, such as respiratory distress syndrome or pneumonia, in association with hypotension or patent ductus arteriosus.

Physical: Initially, most premature infants are asymptomatic. If symptoms occur, they usually are subtle. Symptoms may include the following:

- Decreased tone in lower extremities
- Increased tone in neck extensors
- Apnea and bradycardia events
- Irritability
- Pseudobulbar palsy with poor feeding
- Clinical seizures (may occur in 10-30% of infants)

Causes:

- Mechanically ventilated premature infants born at less than 32 weeks' gestation are at greatest risk for PVL.
- Hypotension, hypoxemia, and acidosis may result in ischemic brain injury and PVL.
- Marked hypocarbia in ventilated premature infants has been associated with increased risk of developing PVL.
- Other associated risk factors include the following:

  o Placental vascular anastomoses, twin gestation, antepartum hemorrhage
  o Chorioamnionitis and funisitis
  o Maternal cocaine abuse

Periventricular Hemorrhage-Intraventricular Hemorrhage
Periventricular Leukomalacia

Other Problems to be Considered:

Intraventricular hemorrhage
Periventricular hemorrhagic venous infarction

Imaging Studies:

- Cranial ultrasonography: Cranial ultrasonography is the modality of choice for the initial evaluation of hypoxic-ischemic damage of the CNS in premature infants. Sonography may be performed in the NICU without the need to transport fragile infants. The earliest ultrasonographic appearance of PVL is abnormal increased echotexture in the periventricular white matter. This is a nonspecific finding that must be differentiated from the normal periventricular halo and mild periventricular edema that may not result in permanent injury. The abnormal periventricular echotexture of PVL usually disappears at 2-3 weeks. Approximately 15% of infants experiencing PVL demonstrate periventricular cysts first appearing at 2-3 weeks after the initial increased echodensities. The severity of PVL is related to the size and distribution of these cysts. Cranial ultrasonographic findings may be normal in patients who go on to develop clinical and delayed imaging findings of PVL.
- CT scanning: CT scanning is not a first-line modality in evaluating these fragile premature infants in the first weeks of life. CT scanning may be helpful to better evaluate the extent and severity of PVL. Findings include ventriculomegaly involving the lateral ventricles with irregular margins of the ventricles and loss of deep white matter.
- MRI: Like CT scanning, MRI does not play a major role in the early evaluation of PVL. MRI is most helpful in monitoring infants with suspected PVL and evaluating infants who develop clinical signs suggestive of PVL. MRI demonstrates the loss of white matter, abnormal signal intensity of the deep white matter, and ventriculomegaly. MRI demonstrates thinning of the posterior body and splenium of the corpus callosum in severe cases of PVL.

Other Tests:

- Electroencephalography (EEG)

Histologic Findings: PVL lesions demonstrate widespread loss of oligodendrocytes and an increase in astrocytes.

Medical Care: No medical treatment currently exists for PVL. Free radical scavengers are being investigated to determine if they have a role in preventing oligodendrocyte injury in PVL.

Consultations: Infants with PVL require close neurodevelopmental follow-up after discharge from the hospital. Potential consultants include pediatricians, developmental specialists, and neurologists.

Further Outpatient Care:

- Developmental follow-up: Premature infants with evidence of PVL require close developmental follow-up because of the high association with CP.

Deterrence/Prevention:

- Prevention of premature birth is the most important means of preventing PVL.
- Prior to birth, diagnosing and managing chorioamnionitis may prevent PVL. In 1999, Baud et al reported that betamethasone administered to mothers at 24-31 weeks' gestation, before delivery, significantly reduced the risk of PVL, suggesting the possible effect of steroids on fetal inflammatory response.
- Avoiding maternal cocaine abuse and avoiding maternal-fetal blood flow alterations has been suggested to minimize PVL.
- Following delivery of a premature infant, attempts to minimize blood pressure (BP) swings and hypotension may also be beneficial in preventing PVL.
- Avoidance of prolonged hypocarbia in the mechanically premature infant may be useful in the prevention of PVL.

Prognosis:

- Infants with PVL are at risk for development of neurodevelopmental deficits. Mild PVL is often associated with spastic diplegia. Severe PVL is associated with quadriplegia. Severe PVL is also associated with a higher incidence of intelligence deficiencies and visual disturbances.

Medical/Legal Pitfalls:

- Timing of initial cranial ultrasonography can be useful in determining the timing of the insult. Cystic PVL has been identified on cranial ultrasounds on the first day of life, indicating that the event was prenatal rather than perinatal or postnatal.

Picture 1. Cranial ultrasound, coronal view, in 1-week-old premature infant. The periventricular echotexture is abnormally increased (greater than or equal to that of the choroid plexus), which is consistent with the early changes of periventricular leukomalacia (PVL). Courtesy of Matthew Omojola, MD.

Picture 2. Cranial ultrasound, coronal view, in 1-week-old premature infant without periventricular leukomalacia (PVL). The periventricular echotexture is normal. Compare to Image 1.


Picture 3. Cranial ultrasound, coronal view, in a 3-week-old premature infant. Multiple bilateral periventricular cysts are typical of this stage of periventricular leukomalacia (PVL).


Picture 4. Cranial ultrasound, sagittal view, in 3-week-old premature infant. Multiple periventricular cysts are typical of this stage of periventricular leukomalacia (PVL).
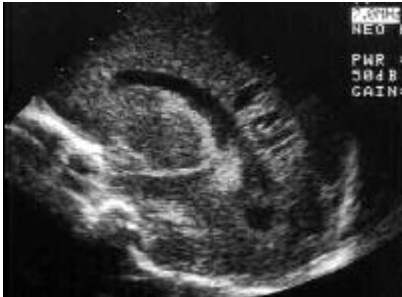

Picture 5. Cranial CT scan, axial image, in a 5-week-old premature infant with periventricular leukomalacia (PVL). The ventricular margins are irregular, which is consistent with incorporation of the periventricular cysts of PVL. Mild ventriculomegaly and loss of the periventricular white matter exists. Courtesy of Matthew Omojola, MD.
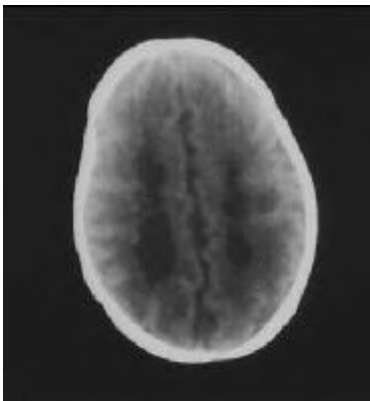
Picture 6. Cranial CT scan, axial image, in 14-month-old with periventricular leukomalacia (PVL). Ventriculomegaly is limited to the lat ventricles second to diffuse loss of periventricular white matter
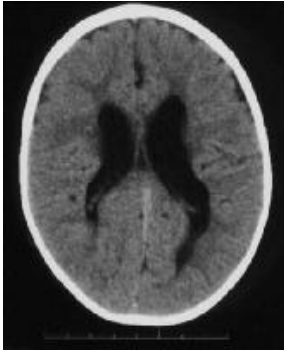

Picture 7. Cranial MRI, T1-weighted axial image, in an 18-month-old with periventricular leukomalacia (PVL). The lateral ventricles are enlarged without hydrocephalus. The periventricular white matter is diminished. Courtesy of Matthew Omojola, MD.
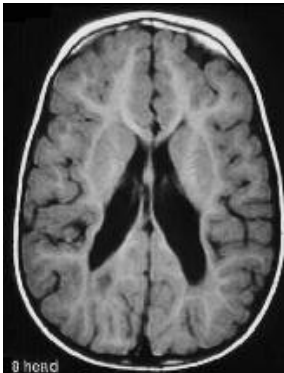
Picture 8. Cranial MRI, T2-weighted axial image, in an 18-month-old with periventricular leukomalacia (PVL). Again, enlarged ventricles and loss of white matter are demonstrated. Also noted is the abnormal increased signal in the periventricular regions on this T2-weighted image.
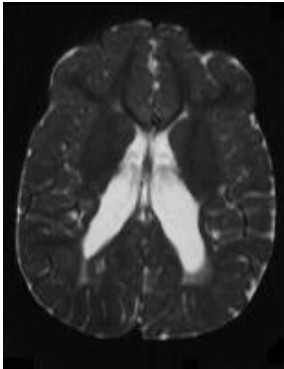
Picture 9. Cranial MRI, sagittal T1-weighted image in the midline, in an 18-month-old with periventricular leukomalacia (PVL). Hypoplasia of the corpus callosum is present and most evident involving the body (see Image 8). Courtesy of Matthew Omojola, MD.
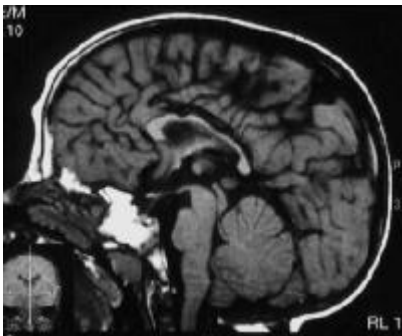
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Periventricular Leukomalacia excerpt

Polycythemia of the Newborn

Last Updated: June 3, 2005

Synonyms and related keywords: neonatal polycythemia, erythrocythemia, hematocrit, Hct, hyperviscosity, sludged blood, microthrombi, microthrombus

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INTRODUCTION	Section 2 of 9

Background: Polycythemia, defined as a venous hematocrit (Hct) of greater than 65%, is a relatively common disorder. The primary concern with polycythemia is related to hyperviscosity and its associated complications. Blood viscosity increases exponentially as the Hct rises above 42%. This associated hyperviscosity is thought to contribute to the symptom complex observed in approximately one half of infants with polycythemia. However, only 47% of infants with polycythemia have hyperviscosity, and only 24% of infants with hyperviscosity have a diagnosis of polycythemia.

Pathophysiology: As the central Hct increases, viscosity increases, resulting in abnormal blood flow kinetics. This condition manifests as poor flow or sludging of blood, which predisposes the infant to microthrombi and decreased tissue oxygenation. Many factors determine blood viscosity. As previously mentioned, viscosity increases as Hct rises. Plasma volume, plasma proteins, platelets, and endothelial factors also contribute to viscosity. Factors unique to the neonate (eg, increased RBC volume, decreased deformability of the fetal erythrocyte) also contribute to increased viscosity.

Frequency: In the US: Polycythemia occurs in 0.4-12% of neonates. It is more common in infants who are small for their gestational age (SGA) and in infants who are large for their gestational age (LGA). However, most infants with polycythemia are of appropriate size or weight for their gestational age (AGA). Infants of mothers with diabetes have an incidence of >40%, and those born to mothers with gestational diabetes have an incidence of >30%. Hyperviscosity occurs in 6.7% of infants.

Mortality/Morbidity:

- The central nervous, cardiopulmonary, gastrointestinal, and renal systems are at risk.
- Metabolic derangements are common.
- Coagulation also can be affected.

Age:

- The Hct peaks 2 hours after birth and then declines until the infant is aged 6 hours, at which time it equals the Hct in cord blood.
- Fewer than 40% of infants with a Hct greater than 64% at 2 hours still have a high value at 12 hours or later.

History: Neonates with polycythemia may have the following findings:

- Lethargy
- Irritability
- Jitteriness
- Tremors
- Seizures
- Cerebrovascular accidents
- Respiratory distress
- Cyanosis
- Apnea

Physical:

- General

  o The most obvious finding is plethora or ruddiness.
  o Evaluate the infant for dehydration (eg, sunken fontanelle, dry mucous membranes)
  o Priapism may be observed in male patients.

- Central nervous system

  o CNS manifestations are the most common problems observed with polycythemia and hyperviscosity.
  o Symptoms include lethargy, irritability, jitteriness, tremors, seizures, and cerebrovascular accidents.

- Cardiopulmonary: Manifestations include respiratory distress, tachypnea, cyanosis, apnea, and congestive heart failure.
- Gastrointestinal

  o Poor feeding is reported in more than one half of all infants with polycythemia and hyperviscosity.
  o Necrotizing enterocolitis (NEC) is a rare but devastating complication of polycythemia or hyperviscosity. Historically, about 44% of term infants with NEC have polycythemia. More recent data suggest that polycythemia may not have a large role in the development of NEC in the term infant.

- Renal: Manifestations include decreased glomerular filtration rates, oliguria, hematuria, proteinuria, and renal vein thrombosis.
- Metabolic

  o Metabolic alterations are frequent.
  o Hypoglycemia is the most common metabolic derangement and is observed in 12-40% of infants with polycythemia.
  o Hypocalcemia is the next most common metabolic derangement and is found in 1-11% of neonates with polycythemia.

- Coagulation

  o Coagulation can be affected.
  o Thrombocytopenia may occur secondary to consumption with thrombosis.
  o Disseminated intravascular coagulation (DIC) is rare.

Causes:

- Increased fetal erythropoiesis secondary to fetal hypoxia

  - Placental insufficiency can be secondary to preeclampsia, eclampsia, primary renovascular disease, chronic or recurrent abruptio placenta, cyanotic congenital heart disease, postdate pregnancy, maternal smoking, or intrauterine growth restriction (IUGR).
  - Endocrine abnormalities secondary to increased oxygen consumption resulting in fetal hypoxia may be due to congenital thyrotoxicosis, congenital adrenal hyperplasia, Beckwith-Wiedemann syndrome, or being the infant of a diabetic mother (IDM).
  - Genetics disorders (eg, trisomy 13, trisomy 18, trisomy 21) also may cause in utero hypoxia.

- Hypertransfusion

  - Delayed cord clamping allows for an increased blood volume to be delivered to the infant. When cord clamping is delayed more than 3 minutes after birth, blood volume increases 30%.
  - Gravity also may be a factor because of the position of the delivered infant in relation to the maternal introitus before cord clamping.
  - In the event of delayed cord clamping, blood flow to the infant is enhanced by oxytocin.
  - Twin-to-twin transfusion syndrome due to a vascular communication occurs in approximately 10% of monozygotic twin pregnancies.
  - Maternal-fetal transfusion may occur.
  - As a result of intrapartum asphyxia, the direction of blood flow in the umbilical cord tends to be toward the fetus.

- Dehydration may be due to decreased plasma volume in relation to RBC mass.

DIFFERENTIALS	Section 4 of 9

Dehydration
Polycythemia
Polycythemia Vera
Other Problems to be Considered:
Method of blood draw: Capillary Hct measurements depend on regional blood flow and can vary widely from central venous measurements.
Iatrogenic problems: These may be related to transfusion.

WORKUP	Section 5 of 9

Lab Studies:

- Along with symptoms attributable to neonatal hyperviscosity, the central venous Hct measurement is used as a surrogate for diagnosing hyperviscosity because it is a readily available.
- Other laboratory tests include measurements of the following:

  - Serum glucose and calcium levels: Measure these to determine if the patient has decreased levels that require treatment.
  - Bilirubin level: Measure this level in the infant with jaundice and polycythemia because the increased RBC mass leads to an increased load of bilirubin precursors that can result in hyperbilirubinemia.
  - Serum sodium level, blood urea nitrogen level, and specific gravity of urine: Measure these values to aid in the diagnosis of dehydration.

- o Arterial blood gases (ABG): Consider measuring ABG values to assess oxygenation in the symptomatic infant.
- o Platelet count: This count may demonstrate thrombocytopenia if thrombosis or DIC are present.

==Medical Care:== Therapy is based on both the measured central venous Hct and the presence or absence of symptoms.

Treatment of polycythemia with partial exchange transfusion remains controversial. Regarding treatment with partial exchange, the Committee of the Fetus and Newborn of the American Academy of Pediatrics states, "The accepted treatment of polycythemia is partial exchange transfusion (PET). However there is no evidence that exchange transfusion affects the long term outcome."

- Treatment for asymptomatic patients

  - o Hct 65-75%: Liberally give fluids, perform cardiorespiratory monitoring and monitoring of Hct and glucose levels every 6 hours, and observe the patient for symptoms.
  - o Hct >75% on repeated measurements: Consider partial exchange transfusion.
  - o If the etiology is dehydration: Rehydrate the patient over 6-8 hours.

- Treatment for symptomatic patients

  - o Hct 60-65%: Consider alternative explanations for the symptoms. Although hyperviscosity may be the etiology of the symptoms, other causes for the symptoms must be excluded.
  - o Hct >65% with symptoms attributable to hyperviscosity: Perform partial exchange transfusion.

- Partial exchange transfusion

  - o Perform a partial exchange transfusion by using an umbilical arterial or venous catheter to reduce the central Hct to 50-55%.
  - o The total blood volume to be exchanged is determined as follows: [blood volume(patient's Hct – desired Hct)]/(patient's Hct), where blood volume = the patient's weight in kilograms multiplied by 90 mL/kg.
  - o Normal saline is the replacement fluid of choice for exchange transfusions because it is effective and inexpensive. As alternatives, Plasmanate, 5% albumin, or fresh frozen plasma can be used. However, none of these is more effective than normal saline. In addition, both 5% albumin and fresh frozen plasma are blood products, and certain religious beliefs prohibit their use.
  - o Sterile technique is required.
  - o An exchange transfusion can be performed in 3 ways, depending on the type of vascular access that is available. Regardless of the method used, aliquots should not exceed approximately 5 mL/kg delivered or removed over 2-3 minutes.
    - If only a single umbilical arterial or venous catheter is in place, use a push-pull technique. With this technique, the withdrawal of blood is alternated with the administration of replacement fluid through the single catheter. Do not remove more than 5% of the patient's calculated blood volume in any single withdrawal.
    - If both umbilical venous and arterial catheters are in place, withdraw blood from the arterial catheter while administering the replacement fluid through the venous catheter
    - If a venous or arterial umbilical catheter and a peripheral venous catheter are in place, the former can be used for blood withdrawal, while the latter is used to simultaneously and continuously infuse the replacement fluid.

Further Inpatient Care:

- Carefully monitor vital signs and bilirubin, glucose, and electrolyte levels as needed
- Feedings may cautiously be introduced a number of hours after completing the partial exchange transfusion.

Further Outpatient Care:

- Perform routine newborn follow-up care.

Complications:

- Apnea
- Arrhythmia
- Vasospasm
- Vessel perforation
- Air embolus
- Thrombosis
- Infarction
- Thrombocytopenia
- Hemolysis
- Electrolyte abnormalitie
- Hypoglycemia
- Hypocalcemia
- Intrahepatic hematoma
- Necrotizing enterocolitis

Prognosis:

- Infants are at increased risk for neurological deficits including speech abnormalities, fine-motor delays, and gross-motor delays.
- Partial exchange transfusion has not been shown to reduce these problems.
-

Medical/Legal Pitfalls:

- Use of a blood product (eg, albumin) in an exchange transfusion may result in the transmission of infection. Infections related to blood products can be avoided by using normal saline, which is sterile and which has been shown to be as effective as albumin.

- Informed consent must be obtained as exchange transfusions have multiple risks (see Partial exchange transfusion).

- The question regarding the efficacy of partial exchange transfusion in improving neurologic outcomes has not been answered. However, polycythemia and neurologic abnormalities have been linked. With this in mind, a symptomatic infant who has not been treated with partial exchange transfusion and who subsequently develops neurologic abnormalities may be considered inadequately treated.

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Polycythemia of the Newborn excerpt

Polyhydramnios and Oligohydramnios

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INTRODUCTION	Section 2 of 9

Background: The amniotic fluid that bathes the fetus is necessary for its proper growth and development. It cushions the fetus from physical trauma, permits fetal lung growth, and provides a barrier against infection. Normal amniotic fluid levels vary; however, the average volume increases with gestational age, peaking at 800-1000 mL, which coincides with 36-37 weeks' gestation. An abnormally high level of amniotic fluid, polyhydramnios, alerts the clinician to possible fetal anomalies. Inadequate levels of amniotic fluid, oligohydramnios, results in poor development of the lung tissue and can lead to fetal death.

In pregnancies affected by polyhydramnios, approximately 20% of the neonates are born with a congenital anomaly of some type; therefore, the delivery of these newborns in a tertiary care setting is preferred. This article presents the causes, outcomes, and treatments of polyhydramnios and oligohydramnios, as well as their effects on the developing fetus and neonate.

Pathophysiology: Rupture of the membranes is the most common cause of oligohydramnios. However, because the amniotic fluid is primarily fetal urine in the latter half of the pregnancy, the absence of fetal urine production or a blockage in fetus' the urinary tract also can result in oligohydramnios. Fetal swallowing, which occurs physiologically, reduces the amount of fluid, and an absence of swallowing or a blockage of the fetus' gastrointestinal tract can lead to polyhydramnios.

Frequency: In the US: Oligohydramnios occurs in 4% of pregnancies, and polyhydramnios occurs in 1% of pregnancies.

Mortality/Morbidity:

- Chamberlin used ultrasonography to evaluate the perinatal mortality rate (PMR) in 7562 patients with high-risk pregnancies. The PMR of patients with normal fluid volumes was 1.97 deaths per 1000 patients. The PMR increased to 4.12 deaths per 1000 patients with polyhydramnios and 56.5 deaths per 1000 patients with oligohydramnios
- Preterm labor and delivery occurs in approximately 26% of mothers with polyhydramnios. Other complications are premature rupture of the membranes (PROM), abruptio placenta, malpresentation, cesarean delivery, and postpartum hemorrhage

- Studies show an increased risk of associated fetal anomalies in more severe forms of polyhydramnios. In series in 1990, 20% of cases of polyhydramnios involved associated fetal anomalies, including problems of the gastrointestinal system (40%), central nervous system (26%), cardiovascular system (22%), or genitourinary system (13%). Among these cases of polyhydramnios, multiple gestations occurred in 7.5%, 5% were due to maternal diabetes, and the remaining 8.5% were due to other causes. However, at least 50% of the patients had no associated risk factors.
- The mortality rate in oligohydramnios is high. The lack of amniotic fluid allows compression of the fetal abdomen, which limits movement of its diaphragm. In addition to chest wall fixation, this limitation leads to pulmonary hypoplasia. Oligohydramnios is also associated with meconium staining of the amniotic fluid, fetal heart conduction abnormalities, poor tolerance of labor, lower Apgar scores, and fetal acidosis. In cases of intrauterine growth restriction (IUGR), the degree of oligohydramnios is often proportional to growth restriction, and it is associated with a corresponding increase in the PMR.
- In twin gestation with twin-to-twin transfusion, polyhydramnios may exist in the recipient twin, and oligohydramnios may exist in the donor. This complication is associated with high morbidity and mortality rates.

Age: No age variables exist.

CLINICAL	Section 3 of 9

Physical:

- Amniotic fluid

  o The volume of the amniotic fluid is evaluated by visually dividing the mother's abdomen into 4 quadrants. The largest vertical pocket of fluid is measured in centimeters. The total volume is calculated by multiplying this value by 4.
  o Polyhydramnios is usually defined as an amniotic fluid index (AFI) more than 24 cm or a single pocket of fluid at least 8 cm in deep that results in more than 2000 mL of fluid.
  o Oligohydramnios is sonographically defined as an AFI less than 7 cm or the absence of a fluid pocket 2-3 cm in depth.

- Polyhydramnios

  o Visual inspection may reveal a rapidly enlarging uterus in the pregnant mother
  o Multiple gestations are associated with polyhydramnios.
  o Fetal abnormalities associated with polyhydramnios include neonatal macrosomia, fetal or neonatal hydrops with anasarca, ascites, and pleural or pericardial effusions.
  o Skeletal malformations also can occur; these include congenital hip dislocation, clubfoot, and limb reduction defect.
  o Attempt to identify abnormalities in fetal movement suggestive of neurologic abnormalities and obstruction of the gastrointestinal tract.

- Oligohydramnios

  o When the oligohydramnios is associated with renal agenesis, symptoms include a marked deformation of the fetus due to of intrauterine constraint (Potter syndrome).
  o Other obstructive uropathies cause similar deformations, including external compression with a flattened facies and epicanthal folds, hypertelorism, low-set ears, a mongoloid slant of the palpebral fissure, a crease below the lower lip, and micrognathia. Thoracic compression also may occur.
  o Oligohydramnios adversely affects fetal lung development, resulting in pulmonary hypoplasia that typically leads to death from severe respiratory insufficiency. Findings associated with pulmonary hypoplasia include bowed legs, clubbed feet, a single

umbilical artery, gastrointestinal atresias, and a narrow chest secondary to external compression. Infants are typically small for their stated gestational age (SGA). When an abdominal mass is found on examination of the infant in this clinical setting, it often represents multicystic-dysplastic kidney, enlarged urinary bladder, or prune-belly syndrome.

Causes:

- Polyhydramnios

  o Twin gestation with twin-to-twin transfusion (increased amniotic fluid in the recipient twin and decreased amniotic fluid in the donor) or multiple gestations, which can lead to twin-to-twin transfusion syndrome
  o Fetal anomalies, including esophageal atresia (usually associated with a tracheoesophageal fistula), tracheal agenesis, duodenal atresia, and other intestinal atresias
  o CNS abnormalities and neuromuscular diseases that cause swallowing dysfunction
  o Congenital cardiac-rhythm anomalies associated with hydrops, fetal-to-maternal hemorrhage, and parvovirus infection
  o Maternal type 2 diabetes mellitus (more often than in oligohydramnios)
  o Chromosomal abnormalities, most commonly trisomy 21, followed by trisomy 18 and trisomy 13.
  o Fetal akinesia syndrome with absence of swallowing

- Oligohydramnios

  o Fetal urinary tract anomalies, such as renal agenesis, polycystic kidneys, or any urinary obstructive lesion (eg, posterior urethral valves)
  o Maternal problems, including placental insufficiency, PROM, and chronic leakage of the amniotic fluid: The major maternal complication from oligohydramnios is chorioamnionitis, which has an incidence of 21-74%. The earlier chorioamnionitis occurs in pregnancy, the greater the fetal risk of bronchopulmonary dysplasia (BPD); neurologic complications; pulmonary hypoplasia; and, in severe cases, respiratory failure.
  o Maternal use of prostaglandin synthase inhibitors or angiotensin-converting enzyme (ACE) inhibitors
  o Postmaturity syndrome in infants when a pregnancy extends beyond 42 weeks' gestation (possibly caused by a decline in placental function)

WORKUP	Section 4 of 9

Lab Studies:

- Lecithin-sphingomyelin (L:S) ratio and phosphatidylglycerol (PG) levels in the amniotic fluid: If premature delivery is anticipated with either oligohydramnios or polyhydramnios, the amniotic fluid L:S ratio and PG concentration are helpful in determining the maturity of the fetal lungs and, therefore, in assessing the likelihood of respiratory distress syndrome.
- Polyhydramnios

  o Glucose tolerance test for mothers with suspected type 2 diabetes mellitus
  o If associated fetal hydrops is present, screening for maternal antibodies to D, C, Kell, Duffy, and Kidd antigens to determine the mother's immunity
  o Kleihauer-Betke test to evaluate fetal-maternal hemorrhage
  o Venereal Disease Research Laboratories (VDRL) test to screen for syphilis
  o Immunoglobulin G (IgG) and immunoglobulin M (IgM) titers to evaluate for exposure to rubella, cytomegalovirus (CMV), and toxoplasmosis
  o Hemoglobin Bart in patients of Asian descent (heterozygous for alpha-thalassemia)

- o Fetal karyotyping for trisomy 21, 13, and 18
- o Test for congenital viruses in the amniotic fluid by using the polymerase chain reaction

- Oligohydramnios - Test for systemic lupus erythematosus, which causes immune-mediated infarcts in the placenta and placental insufficiency

Imaging Studies:

- Prenatal ultrasonography and polyhydramnios

  - o Evaluate fetal swallowing. A decrease in fetal deglutition occurs in anencephaly, trisomy 18, trisomy 21, muscular dystrophy, and skeletal dysplasia.
  - o Evaluate the fetal anatomy; assess for diaphragmatic hernia, lung masses, and the absence of the stomach bubble (which is associated with esophageal atresia). The double-bubble sign or a dilated duodenum suggests the possibility of duodenal atresia.
  - o An abnormally large abdominal circumference may be observed with ascites and hydrops fetalis or a macrosomic fetus; these findings are also observed in association with poorly controlled maternal diabetes.

- Prenatal ultrasonography and oligohydramnios

  - o Perform serial measurements of the AFI during the pregnancy. If the mother is in the third trimester and if the volume is less than 8 cm, suspect oligohydramnios. Levels less than 5 cm indicate significant oligohydramnios.
  - o Visualize the fetal kidneys, collecting system, and bladder. If these are normal, suspect the chronic leakage of amniotic fluid.
  - o Assess fetal growth. If PROM or urinary tract anomalies are absent, consider placental insufficiency and IUGR. Uterine artery Doppler studies may aid in diagnosing placental insufficiency.

- Postnatal testing of the infant: Evaluate those organ systems that are likely to be involved on the basis of the pregnancy history and results of other prenatal evaluations.

Other Tests: Chromosome tests are recommended, depending on the results of postnatal evaluation of the infant.
Procedures:

- Polyhydramnios

  - o Reductive amniocentesis may be performed and has contributed to prolonged pregnancy in patients who are severely affected by hydramnios.
  - o This procedure can reduce the risk of preterm labor, PROM, umbilical cord prolapse, and placental abruption.
  - o However, if too much fluid is removed, the risk of placental abruption due to uterine compression increases.
  - o Other risks of the procedure include infection, bleeding, and trauma to the fetus.

- Oligohydramnios

  - o The transabdominal instillation of indigo carmine may be used to evaluate for PROM.
  - o The transcervical instillation of isotonic sodium chloride solution (ie, amnioinfusion) at the time of delivery reduces the risk of cord compression, fetal distress and meconium dilution. It also reduces the potential need for cesarean delivery.

Medical Care: The first step is identifying the etiology of the abnormal volume of amniotic fluid. Medical care includes use of steroids to enhance fetal lung maturity if preterm delivery is anticipated.

- Polyhydramnios

  - Patients with polyhydramnios tend to have a higher incidence of preterm labor secondary to overdistention of the uterus.
  - Schedule weekly or twice weekly perinatal visits and cervical examinations.
  - Place patients on bed rest to decrease the likelihood of preterm labor.
  - Perform serial ultrasonography to determine the AFI and document fetal growth.
  - In some cases of polyhydramnios associated with fetal hydrops, the direct intravascular transfusion of erythrocytes may increase the fetal survival rate.

- Oligohydramnios

  - Maternal bed rest and hydration promote the production of amniotic fluid by increasing the maternal intravascular space.
  - Studies show that oral hydration, by having the women drink 2 liters of water, increases the AFI by 30%.

Consultations:

- A specialist in maternal-fetal medicine may be helpful in significant oligohydramnios or polyhydramnios, especially when the condition is unexplained, involves hydrops fetalis, or is associated with congenital malformations.
- Genetic counseling may be helpful in cases in which congenital anomalies are identified.
- Consult a neonatologist, pediatric surgeon, pediatric cardiologist, pediatric nephrologist, or genetics other specialist as required to care for the infant.

Diet: In cases of polyhydramnios in which maternal diabetes is suspected, perform a glucose tolerance test. If the test results are positive, treat the mother with an American Diabetes Association (ADA) diet. Insulin is rarely needed.

Most cases of polyhydramnios respond in the first week of treatment with indomethacin. The approach appears to be highly effective (90-100% in some studies), provided that the cause is not hydrocephalus or a neuromuscular disorder that alter fetal swallowing.

Drug Category: *Prostaglandin inhibitors --* When administered to pregnant women with polyhydramnios, these drugs can reduce fetal urinary flow, decreasing the volume of amniotic fluid.

Drug Name	Indomethacin (Indocin) -- Rapidly absorbed; metabolism occurs in liver by demethylation, deacetylation, and glucuronide conjugation; inhibits prostaglandin synthesis.
Adult Dose	25 mg PO q6h
Contraindications	Documented hypersensitivity; GI bleeding; renal insufficiency
Interactions	Coadministration with aspirin increases risk of serious NSAID-related adverse effects; probenecid may increase concentrations and, possibly, toxicity of NSAIDs; may decrease effect of hydralazine,

	captopril, and beta-blockers; may decrease diuretic effects of furosemide and thiazides; monitor PT closely (instruct patients to watch for signs of bleeding); may increase risk of methotrexate toxicity; may increase phenytoin levels when administered concurrently
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Can cause fetal renal complications; associated with premature closure of the fetal ductus arteriosus when administered near term; acute renal insufficiency, hyperkalemia, hyponatremia, interstitial nephritis, and renal papillary necrosis may occur; increases risk of acute renal failure in patients with preexisting renal disease or compromised renal perfusion; reversible leukopenia may occur (discontinue if persistent leukopenia, granulocytopenia, or thrombocytopenia present)

Further Inpatient Care:

- Polyhydramnios: See recommendations for oligohydramnios below.
- Oligohydramnios

  - Consider hospitalizing and thoroughly evaluating the mother in cases diagnosed after 26-33 weeks' gestation.
  - If the fetus does not have an anomaly, delivery should be performed if the biophysical profile is nonreassuring.
  - The instillation of isotonic sodium chloride solution in the second trimester may be of benefit in some patients. Use transabdominal amnioinfusion to instill 400-600 mL, which may improve visualization for ultrasonography and increase volume of the amniotic fluid.
  - In cases associated with postmaturity, review pregnancy dating. If the gestation is truly longer than term, deliver the fetus by means of either induction or cesarean delivery.
  - If meconium is present during labor, administer amnioinfusion therapy to reduce the potential for fetal distress and prenatal aspiration.

Transfer:

- Transfer is indicated when the pregnant woman has a high likelihood of maternal illness, preterm delivery, or infant problems that may require the resources of a tertiary care facility.

Complications:

- Polyhydramnios

  - Risks and complications of amnioinfusion include amniotic fluid embolism, maternal respiratory distress, increased maternal uterine tone, and transient fetal respiratory distress. An increase in the risk of maternal or fetal infection is not substantiated.
  - Risks of amniocentesis include fetal loss (1-2%). Other complications are placental abruption, preterm labor, fetal-maternal hemorrhage, maternal Rh sensitization, and fetal pneumothorax. The risk of fetal infection is slightly increased.

- Oligohydramnios

  - The primary complications are those related to fetal distress before or during labor.
  - The risk of fetal infection is increased in the presence of prolonged rupture of the membranes.

- Polyhydramnios

  o If the condition is not associated with any other findings, the prognosis is usually good.
  o According Desmedt et al, the PMR in polyhydramnios associated with a fetal or placental malformation was 61%.
  o As mentioned in Background and Mortality/Morbidity 20% of infants with polyhydramnios have some anomaly; in these cases, the prognosis depends on the severity of the anomaly.
  o Studies show that, as the severity of polyhydramnios increases, so does the likelihood of determining the etiology.
  o In cases of mild polyhydramnios, the likelihood of finding a significant problem is only about 16.5%; this should be communicated to the parents.

- Oligohydramnios

  o In renal agenesis, the mortality rate is 100%.
  o Milder forms of renal dysplasia or obstructive uropathy can be associated with mild-to-severe forms of pulmonary hypoplasia and long-term renal failure.
  o In cases of pulmonary hypoplasia, the effectiveness of many treatments such as the administration of surfactant, high frequency ventilation, and nitric oxide has not been established. The prognosis in these cases is related to the volume of amniotic fluid and the gestational age at which oligohydramnios develops.

MISCELLANEOUS	Section 8 of 9

Medical/Legal Pitfalls:

- Failure to perform ultrasonography in a pregnancy complicated by either polyhydramnios or oligohydramnios to rule associated or contributory fetal anomalies
- The underlying anomalies may determine the outcome of the fetus, as well as the treatment and outcome of the neonate. As appropriate, specialists should be consulted and the patient should be transferred in a timely fashion to optimize the outcome of the pregnancy and to reduce the risk of perinatal mortality.

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Polyhydramnios and Oligohydramnios excerpt

Pulmonary Interstitial Emphysema

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INTRODUCTION	Section 2 of 10

Background: Pulmonary interstitial emphysema (PIE) is a collection of gases outside of the normal air passages and inside the connective tissue of the peribronchovascular sheaths, interlobular septa, and visceral pleura secondary to alveolar and terminal bronchiolar rupture. PIE is more frequent in premature infants who require mechanical ventilation for severe lung disease. Once PIE is diagnosed, intensive respiratory management is required to reduce mortality and morbidity.

Pathophysiology: PIE often occurs in conjunction with respiratory distress syndrome (RDS), but other predisposing etiologic factors include meconium aspiration syndrome (MAS), amniotic fluid aspiration, and infection.

Positive pressure ventilation (PPV) and reduced lung compliance are significant predisposing factors. However, in extremely premature infants, PIE can occur at low mean airway pressure and probably reflects increased sensitivity of the underdeveloped lung to stretch. The process of PIE is initiated when air ruptures from the alveolar airspace and small airways into the perivascular tissue of the lung.

Infants with RDS have an initial increase in interstitial and perivascular fluid that declines rapidly over the first few days of life. This fluid may obstruct the movement of gas from ruptured alveoli or airways to the mediastinum, causing an increase of PIE. Another possible mechanism for entrapment of air in the interstitium is the increased amount of pulmonary connective tissue in the immature lung. The entrapment of air in the interstitium may result in a vicious cycle causing compression atelectasis of the adjacent lung, which then necessitates a further increase in ventilatory pressure with still more escape of air into the interstitial tissues.

Plenat et al described two topographic varieties of air leak, intrapulmonary pneumatosis and intrapleural pneumatosis. In the intrapulmonary type, which is more common in premature infants, the air remains trapped inside the lung and frequently appears on the surface of the lung, bulging under the pleura in the area of interlobular septa. This phenomenon develops with high frequency on the costal surface and the anterior and inferior edges but can involve all of the pulmonary areas. In the intrapleural variety, which is more common in more mature infants with compliant lungs, the abnormal air pockets are confined to the visceral pleura, often affecting the mediastinal pleura. The air of PIE may be located inside the pulmonary lymphatic network.

The extent of PIE can vary. It can present as an isolated interstitial bubble, several slits, lesions involving the entire portion of one lung, or diffuse involvement of both lungs. PIE does not localize preferentially in any one of the 5 pulmonary lodes.

PIE compresses adjacent functional lung tissue and vascular structures and hinders both ventilation and pulmonary blood flow, resulting in impedance of oxygenation, ventilation, and blood pressure. This further compromises the already critically ill infant with a significant increase in mortality and morbidity. PIE can regress completely or decompress into adjacent spaces causing pneumomediastinum, pneumothorax, pneumopericardium, pneumoperitoneum, or subcutaneous emphysema.

Frequency:

- **In the US:** The prevalence of PIE varies widely with the population studied. In a study by Gaylord et al, PIE developed in 3% of infants admitted to the neonatal intensive care unit (NICU). No specific data are available on the prevalence of PIE in the postsurfactant era; reported incidence of PIE in published clinical trials can be useful. In a randomized trial of surfactant replacement therapy at birth, in premature infants of 25-29 weeks' gestation, Kendig et al found PIE in 8 of 31 (26%) control neonates and 5 of 34 (15%) surfactant-treated neonates.

  Another randomized controlled trial of prophylaxis versus treatment with bovine surfactant in neonates of less than 30 weeks' gestation included 2 of 62 (3%) early surfactant-treated, 5 of 60 (8%) late surfactant-treated, and 15 of 60 (25%) control neonates with PIE. Kattwinkel et al compared prophylactic surfactant administration versus the early treatment of RDS with calf lung surfactant in neonates of 29-32 weeks' gestation. Three of 627 neonates in the prophylaxis group and 3 of 621 neonates in the early treatment group developed PIE. This information suggests a higher incidence of PIE in more immature infants.

- **Internationally:** Studies reflecting international frequency demonstrated that 2-3% of all infants in NICUs develop PIE. When limiting the population studied to premature infants, this frequency increases to 20-30%, with the highest frequencies occurring in infants weighing fewer than 1000 g. In another study of low birth weight infants, the incidence of PIE was 42% in infants with birth weight of 500-799 g, 29% in those with birth weight of 800-899 g, and 20% in those with birth weight of 900-999 g. Minimal information is available about the prevalence of PIE in the postsurfactant era. In a recent prospective multicenter trial comparing early high-frequency oscillatory ventilation (HFOV) and conventional ventilation in preterm infants of fewer than 30 weeks' gestation with RDS, 15 of 139 (11%) infants in the high-frequency group and 15 of 134 (11%) infants in the conventional group developed PIE.

Mortality/Morbidity: The mortality rate associated with PIE is reported to be as high as 53-67%. Lower mortality rates of 24% and 39% reported in other studies could result from differences in population selection. Morisot et al reported an 80% mortality rate with PIE in infants with birth weight of fewer than 1600 g and severe RDS. The early appearance of PIE (<48 h after birth) is associated with increased mortality, but this may reflect the severity of the underlying parenchymal disease.

In survivors, morbidity also is high. PIE can predispose an infant to other air leaks. In a study by Greenough et al, 31 of 41 infants with PIE developed pneumothorax, compared to 41 of 169 infants without PIE. In addition, 21 of 41 babies with PIE developed intraventricular hemorrhage (IVH),

compared to 39 of 169 among infants without PIE. PIE may not resolve for 2-3 weeks; therefore, it can increase the length of time of mechanical ventilation and the incidence of bronchopulmonary dysplasia. Some infants may develop chronic lobar emphysema, which may require surgical lobectomies.

No specific mortality and morbidity data concerning PIE in the postsurfactant era are available.

Sex: In a study by Plenat et al, PIE developed equally in both sexes (21 males, 18 females). Although these data also included cases with intrapleural pneumatosis, no relationship between sex and type of interstitial pneumatosis exists.

Age: PIE is more frequent in infants of lower gestational age. PIE usually occurs within the first weeks of life. Development of PIE within the first 24-48 hours after birth often is associated with extreme prematurity, very low birth weight, perinatal asphyxia, and/or neonatal sepsis and frequently indicates a grave prognosis.

CLINICAL	Section 3 of 10

History: PIE is a radiographic and pathologic diagnosis. In most cases, the discovery of PIE may be preceded by a decline in the baby's clinical condition. Hypotension and difficulty in oxygenation and ventilation can suggest the development of PIE. Alternatively, the baby can present with the signs of one of the complications of PIE, such as pneumothorax. Sometimes, PIE becomes apparent following reexpansion of a collapsed lung after drainage of a pneumothorax.

Physical: No specific signs of PIE exist. Overinflation of the chest wall and crepitations on auscultation on the affected side may be present.

Causes:

- Risk factors

    o Prematurity
    o Respiratory distress syndrome
    o Meconium aspiration syndrome
    o Amniotic fluid aspiration
    o Infection - Neonatal sepsis, pneumonia, or both
    o Low Apgar score or need for PPV during resuscitation at birth
    o Use of high peak airway pressures on mechanical ventilation
    o Incorrect positioning of the endotracheal tube in one bronchus

DIFFERENTIALS	Section 4 of 10

Other Problems to be Considered:

The roentgenologic appearance of PIE can be confused with the following:

Air-bronchogram in RDS
Aspiration pneumonia
Pulmonary edema
Distended airways in patients on a ventilator

Lab Studies: Blood gases should be obtained to ensure adequate gas exchange.
Imaging Studies:

- Chest radiograph (see Images 1-3)

  o The classic radiologic appearance of PIE often provides a clear diagnosis. PIE is best visualized in the anteroposterior supine projection. PIE has two basic radiographic appearances, linear and cystlike radiolucencies, although both types often appear together.
  o Linear radiolucencies are coarse and nonbranching, measure from 3-8 mm, and vary in width but rarely exceed 2 mm.
  o Small cystlike radiolucencies extend in diameter from 1-4 mm, and, though generally round, they may appear oval or slightly lobulated.
  o Disorganized haphazard distribution of PIE in localized areas is unlike the anatomically organized pattern of the air-bronchogram. The air-bronchogram is a classic radiographic sign of RDS, which should not be confused with PIE. In RDS, long, smooth, branching, linear radiolucencies decrease in caliber from the hilum and frequently disappear at the lung periphery. PIE should be suspected when coarse radiolucencies appear in the lung periphery or when the lucencies do not branch in a pattern consistent with the normal bronchial tree.
  o In some patients receiving mechanical ventilation, distended airways and alveoli have a somewhat similar appearance to that of PIE on radiographs. Over time, it either progresses to a classic radiographic picture of PIE or resolves very rapidly as ventilator settings are decreased.
  o PIE rarely can be misinterpreted as normally aerated lung surrounded by exudate as in an aspiration syndrome or pulmonary edema.

Histologic Findings: The histology of PIE is well described by Plenat et al. Their histologic study demonstrates interstitial slits preferentially located in perivenous topography. Sometimes, the peribronchial arterial or arteriolar sheaths are involved. Air dissects through a plane just next to the arterial or arteriolar face, opposite the bronchus, which is pushed into adjoining parenchyma. The bronchoarterial solidarity most often is respected. Seldom, air can dissect arterioles and bronchioles and isolate them from the adjacent lobules. On the periphery of interstitial slits, the small vessels are compressed but never ruptured, while the collagen fibers constantly are broken and squeezed together.

Medical Care: Different treatment modalities have been used to manage PIE, with variable success.

- Lateral decubitus positioning

  o This conservative approach has been used with success and is most effective in infants with unilateral PIE. The infant is placed in the lateral decubitus position with the affected lung in a dependent position. This therapy can result in plugging of dependent airways and improved oxygenation of the nondependent lung. The latter allows for overall decreased ventilatory settings. The combination of the above factors helps in resolution of PIE.
  o In different case studies of lateral decubitus position as a treatment of unilateral PIE in infants, PIE resolved in 48 hours to 6 days with minimal recurrence and a low failure rate. Lateral decubitus positioning should be considered as an early first-line therapy in the management of unilateral PIE. Lateral decubitus positioning has been used successfully for patients with bilateral PIE when one side is affected more significantly.

- Selective main bronchial intubation and occlusion
  - Many case reports exist of successful treatment of severe localized PIE in infants with selective intubation of the contralateral bronchus to decompress the overdistended lung tissue and to avoid exposing it to high positive inflationary pressures. Selective bronchial intubation of the right main bronchus is not a difficult procedure; the left side may be more difficult. The endotracheal tube of the same diameter as for a regular intubation is inserted 2-4 cm beyond its usual position. It is introduced with the bevel on the end of the tube positioned so that the long part of the tube is toward the bronchus to be intubated. This increases the chance of entering the correct bronchus as the tube is advanced into the airway. Turning the infant's head to the left or right moves the tip of the endotracheal tube to the contralateral side of the trachea and may help in selective tube placement.
  - Weintraub et al have described a method for left selective bronchus intubation using a regular Portex endotracheal tube in which an elliptical hole 1 cm in length has been cut through half the circumference 0.5 cm above the tip of the oblique distal end. With the side with the elliptical hole directed to the left lung, left selective bronchus intubation can be accomplished easily and repeatedly. Another method of selective intubation is the use of a small fiberoptic bronchoscope to direct the endotracheal tube tip into the desired bronchus. Selective intubation under fluoroscopy also can be considered.
  - Potential complications of the selective intubation/ventilation are atelectasis in the affected lung, injury to bronchial mucosa with subsequent scarring and stenosis, acute hypoventilation or hypoxemia if ventilating one lung is inadequate, excessive secretions, hyperinflation of the intubated or nonoccluded lung, upper lobe collapse when intubating the right lung, and bradycardia. Despite potential risks, selective bronchial intubation is a desirable alternative to lobectomy in a persistent, severe, localized PIE causing mediastinal shift and compression atelectasis and not responding to conservative management. This procedure should be attempted before any surgical intervention.
- High-frequency ventilation

  - Keszler et al studied use of high-frequency jet ventilation (HFJV) in 144 newborns with PIE. They concluded that HFJV was safe and more effective than rapid-rate conventional ventilation in the treatment of newborns with PIE. With HFJV, similar oxygenation and ventilation was obtained at lower peak and mean airway pressures, suggesting that in infants with PIE a reduction in the amount of air leaking into the interstitial spaces would occur.
  - Similar effects can be achieved by use of HFOV.
    - In a study by Clark et al, 27 low birth weight infants who developed PIE and respiratory failure while on conventional ventilation were treated with HFOV. Surviving patients showed continued improvement in oxygenation and ventilation at an increasingly lower fraction of inspired oxygen (FiO_2) and proximal airway pressure with resolution of PIE, while nonsurvivors progressively developed chronic respiratory insufficiency with continued PIE from which recovery was not possible. Overall survival in nonseptic patients was 80%.
    - They found HFOV to be effective in the treatment of PIE and hypothesized that interstitial air leak is decreased during HFOV because adequate ventilation is provided at lower peak distal airway pressures. Although this mode of ventilation has inherent risks, it can be a very effective tool in experienced hands for the treatment of severe diffuse PIE. Care must be taken in smaller infants who require a high amplitude to ventilate because the active exhalation during HFOV may cause small airway collapse and exacerbate gas trapping.

- Other treatment modalities

  - Case reports and/or case series describe different approaches for the management of PIE, including 3-day course of dexamethasone (0.5 mg/kg/d), chest physiotherapy with intermittent 100% oxygen in localized and persistent compressive PIE, artificial pneumothorax, and multiple pleurotomies.
  - Despite success claimed by the authors, the efficacy of these treatment modalities seems questionable. With advancements in respiratory care, these treatment modalities rarely are used.

Surgical Care: Lobectomy is indicated in a small number of patients with localized PIE when spontaneous regression is not occurring and medical management has failed. Although clear guidelines for surgical intervention are difficult to establish, it should be reserved for infants in whom the risks of recurring complications outweigh those of surgery. It seems most helpful in infants who develop severe lobar emphysema.

Consultations: All infants with PIE need to be under the care of a neonatologist. In some cases, pediatric pulmonology and pediatric surgery consultations are appropriate.

Diet: The overall importance of appropriate nutritional management of ill newborns cannot be overstressed. Most of these infants are treated with total parenteral nutrition and require diligent attention.

FOLLOW-UP	Section 7 of 10

Further Inpatient Care:

- Admission/transfer to a NICU is indicated.
- Keep a thoracentesis set handy and keep the possibility of air leak, including pneumothorax and pneumopericardium, in mind.

Further Outpatient Care:

- Monitoring for physical and psychomotor development in a neonatal follow-up care program or equivalent program is important because most infants with PIE are premature and are at risk for developmental delay. In addition, PIE has been associated with increased risks of IVH and periventricular leukomalacia (PVL), which also increase the risks of developmental delay in these infants.
- Patients with chronic lung disease may need pediatric pulmonology follow-up care.

Deterrence/Prevention:

- Surfactant

  o Four of the 5 randomized controlled trials for the prophylactic use of surfactant in premature infants with RDS noted a significant reduction in the incidence of PIE.
  o Metaanalysis of the different trials suggests that prophylactic administration of surfactant leads to significant reduction in the risk of PIE.

- High-frequency ventilation

  o In a study comparing high-frequency positive pressure ventilation (HFPPV) to conventional ventilation, Pohlandt et al reported a reduction in the risk of PIE with HFPPV. Review of different trials of elective HFOV versus conventional ventilation for acute pulmonary dysfunction in preterm infants suggests an increase in the incidence of air leak syndromes including but not limited to PIE in the HFOV group
  o A recent prospective randomized multicenter study of HFOV versus conventional ventilation in premature infants with RDS showed no difference in the incidence of PIE. Limited data regarding rescue HFOV for pulmonary dysfunction in the preterm infant also showed no difference in the rate of PIE.
  o Cochrane reviews of trials of elective HFJV versus conventional ventilation for RDS demonstrated no significant difference in the incidence of air leak syndrome in the individual trials or in the overall analysis.
  o In summary, current literature suggests that elective or rescue high-frequency ventilation does not prevent the development of PIE.

- Other considerations

  - Avoid use of high peak inspiratory pressure (PIP).
  - Be careful (watch manometer) during manual ventilation.

Complications:

- Death
- Respiratory insufficiency
- Other air leaks

  - Pneumomediastinum
  - Pneumothorax
  - Pneumopericardium
  - Pneumoperitoneum
  - Subcutaneous emphysema (rare)

- Massive air embolism
- Chronic lung disease (CLD) of prematurity
- Intraventricular hemorrhage
- Periventricular leukomalacia

Prognosis:

- Long-term follow-up data are scarce.
- Gaylord et al demonstrated a high (54%) incidence of CLD in survivors of PIE compared with their nursery's overall incidence of 32%. In addition, 19% of the infants developed chronic lobar emphysema; 50% received surgical lobectomies.

MISCELLANEOUS	Section 8 of 10

Medical/Legal Pitfalls:

- Although the primary risk factor for PIE, prematurity, is rarely preventable, attention should be given to the use of as little mechanical ventilatory support as is necessary for the patient's very fragile lungs.
- Because pneumothorax is a known complication, anticipatory guidance for this possibility should be provided for all those caring for the infant. Appropriate personnel should be readily available to address this complication.

PICTURES	Section 9 of 10

Picture 1. This radiograph, obtained from a 1-day-old premature infant at 24 weeks' gestation, shows bilateral PIE. Linear radiolucencies extending up to the lung periphery are visible.

Picture 2. This radiograph, obtained from a premature infant at 26 weeks' gestation, shows characteristic radiographic changes of pulmonary interstitial emphysema (PIE) of the right lung.

Picture 3. This radiograph shows pneumothorax and pulmonary interstitial emphysema (PIE) on the right side. Interstitial air prevents collapse of the underlying lung by a tension pneumothorax. In such cases, extreme caution is required during drainage of a pneumothorax to avoid perforation of the underlying lung.

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Pulmonary Interstitial Emphysema excerpt

Respiratory Distress Syndrome

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Synonyms and related keywords: RDS, HMD, premature infant, surfactant therapy

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INTRODUCTION	Section 2 of 11

Background: Respiratory distress syndrome (RDS), also known as hyaline membrane disease (HMD), occurs almost exclusively in premature infants. The incidence and severity of RDS are related inversely to the gestational age of the infant. The outcome of RDS has improved in recent years with the increased use of antenatal steroids to improve pulmonary maturity, early postnatal surfactant therapy to replace surfactant deficiency, and gentler techniques of ventilation to minimize damage to the immature lungs. These therapies have also resulted in the survival of premature infants who are smaller and more ill. Although reduced, the incidence and severity of complications of RDS continue to present significant morbidities.

The sequelae of RDS include intracranial hemorrhage and/or periventricular leukomalacia with associated neurodevelopmental delay, septicemia, bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), and pulmonary hemorrhage. Direct attention to anticipating and minimizing these complications and also toward preventing premature delivery whenever possible are strategic goals.

Pathophysiology: A relative deficiency of surfactant, which leads to decrease in lung compliance (see Image 1) and functional residual capacity with increased dead space, causes RDS. The resulting large ventilation-perfusion mismatch and right-to-left shunt may involve as much as 80% of cardiac output. Macroscopically, the lungs appear airless and ruddy (ie, liverlike). Thus, the lungs of these infants require a higher critical opening pressure to inflate (see Image 1). Diffuse atelectasis of distal airspaces along with distension of some distal airways and perilymphatic areas are observed microscopically. With progressive atelectasis along with barotrauma or volutrauma and oxygen toxicity, endothelial and epithelial cells lining these distal airways are damaged, resulting in exudation of fibrinous matrix derived from blood.

Hyaline membranes that line the alveoli (see Image 2) are formed within a half hour after birth. At 36-72 hours after birth, the epithelium begins to heal, and surfactant synthesis begins. The healing process is complex (see Image 3); in infants who are extremely immature and critically ill and in infants born to mothers with chorioamnionitis, a chronic process often ensues, resulting in BPD.

Surfactant is a complex lipoprotein (see Image 4) comprised of 6 phospholipids and 4 apoproteins. Functionally, dipalmitoyl phosphatidylcholine (DPPC), or lecithin, is the principle phospholipid. DPPC along with apoproteins SP-B and SP-C or with the addition of other substances (eg, nonionic detergent tyloxapol, C16:0 alcohol hexadecanol [Exosurf]) facilitates adsorption and spreading of DPPC as a monolayer, which lowers the surface tension at the alveolar air-fluid interface in vivo.

The components of pulmonary surfactant are synthesized in the Golgi apparatus of the endoplasmic reticulum of the type II alveolar cell (see Image 5). The components are packaged in multilamellar vesicles in the cytoplasm of the type II alveolar cell and are secreted by a process of exocytosis, the daily rate of which may exceed the weight of the cell. Once secreted, the vesicles unwind to form bipolar monolayers of phospholipid molecules that are dependent on the apoproteins SP-B and SP-C to configure properly in the alveolus. The lipid molecules are enriched in dipalmitoyl acyl groups attached to a glycerol backbone that pack tightly and generate low surface pressures.

Tubular myelin stores surfactant and may depend on SP-B. Corners of the myelin lattice appear to be glued together with the larger apoprotein SP-A, which may also have an important role in phagocytosis. Hypoxia, acidosis, hypothermia, and hypotension may impair surfactant production and/or secretion of surfactant.

Frequency:

- **In the US:** While the greatest risk factor for developing RDS is prematurity, maternal diabetes and asphyxia are also risk factors. Not all premature infants develop RDS. Approximately half of infants born at 28-32 weeks' gestation develop RDS.

  In the United States, RDS occurs in approximately 40,000 infants each year and in 14% of low birth weight infants. Incidence of RDS increases with decreasing gestational age and may occur in as many as 45-80% of infants born when younger than 28 weeks' gestation.

- **Internationally:** RDS has been reported in all races worldwide, occurring more often in premature infants of Caucasian ancestry.

CLINICAL	Section 3 of 11

History:

- RDS frequently occurs in the following individuals:

  - Male infants
  - Infants born to mothers with diabetes
  - Infants delivered via cesarean without maternal labor
  - Second-born twins
  - Infants with a family history of RDS

- In contrast, the incidence of RDS decreases with the following:

  - Use of antenatal steroids
  - Pregnancy-induced or chronic maternal hypertension
  - Prolonged rupture of membranes
  - Maternal narcotic addiction

- Secondary surfactant deficiency may occur in infants with the following:

  - Intrapartum asphyxia
  - Pulmonary infections
  - Pulmonary hemorrhage
  - Meconium aspiration pneumonia
  - Oxygen toxicity along with barotrauma or volutrauma to the lungs

- Physical findings are consistent with the infant's maturity assessed by Dubowitz examination or its modification by Ballard.
- Progressive signs of respiratory distress are noted soon after birth and include the following:

  - Tachypnea
  - Expiratory grunting (from partial closure of glottis)
  - Subcostal and intercostal retractions
  - Cyanosis
  - Nasal flaring

- Extremely immature infants may develop apnea and/or hypothermia.

Causes: Surfactant deficiency and risk factors are outlined in History.

DIFFERENTIALS	Section 4 of 11

Anemia, Acute
Aspiration Syndromes
Gastroesophageal Reflux
Hypoglycemia
Hypothermia, Circulatory Arrest and Cardiopulmonary Bypass
Pneumomediastinum
Pneumonia
Pneumothorax
Polycythemia
Sudden Infant Death Syndrome
Transient Tachypnea of the Newborn
Other Problems to be Considered:
Several diagnoses may coexist and further complicate the course of RDS, including the following:
Pneumonia is often secondary to group B beta hemolytic streptococci (GBBS) and often coexists with RDS.
Metabolic problems (eg, hypothermia, hypoglycemia) may occur.
Hematologic problems (eg, anemia, polycythemia) may occur.
Transient tachypnea of the newborn usually occurs in term or near-term infants, usually after cesarean delivery. The chest radiograph of an infant with transient tachypnea exhibits good lung expansion and, often, fluid in the horizontal fissure.

Aspiration syndromes may result from aspiration of amniotic fluid, blood, or meconium. Aspiration syndrome is also observed in more mature infants and is differentiated by obtaining a history and by viewing the chest radiograph findings.

Pulmonary air leaks (eg, pneumothorax, interstitial emphysema, pneumomediastinum, pneumopericardium) may occur. In premature infants, these complications may occur from excessive positive pressure ventilation, or they may be spontaneous.

Congenital anomalies of the lungs (eg, diaphragmatic hernia, chylothorax, congenital cystic adenomatoid malformation of the lung, lobar emphysema, bronchogenic cyst, pulmonary sequestration) and heart (eg, cardiac anomalies) are rare in premature infants. These entities can be diagnosed based on chest radiograph or ultrasound examination findings and, on rare occasion, may coexist with RDS.

Lab Studies:

- Blood gases are usually obtained as clinically indicated from either an indwelling arterial (umbilical) catheter or an arterial puncture. Blood gases exhibit respiratory and metabolic acidosis along with hypoxia.

  - Respiratory acidosis occurs because of alveolar atelectasis and/or overdistension of terminal airways.
  - Metabolic acidosis is primarily lactic acidosis, which results from poor tissue perfusion and anaerobic metabolism.
  - Hypoxia occurs from right-to-left shunting of blood through the pulmonary vessels, PDA, and/or foramen ovale. Pulse oximetry is used as a noninvasive tool to monitor oxygen saturation, which should be maintained at 90-95%.

Imaging Studies:

- Chest radiographs of an infant with RDS exhibit bilateral diffuse reticular granular or ground glass appearance, air bronchograms, and poor lung expansion (see Image 6).

  - The prominent air bronchograms represent aerated bronchioles superimposed on a background of collapsed alveoli.
  - The cardiac silhouette may be normal or enlarged. Cardiomegaly may be the result of prenatal asphyxia, maternal diabetes, PDA, an associated congenital heart anomaly, or simply poor lung expansion.
  - These findings may be altered with either early surfactant therapy (see Image 6) or indomethacin treatment with mechanical ventilation.
  - The radiologic findings of RDS cannot be differentiated reliably from those of pneumonia, which is caused most commonly by GBBS.

- Echocardiographic evaluation is performed in selected infants to assist the clinician in diagnosing PDA and determine the direction and degree of shunting. It is also useful in making the diagnosis of pulmonary hypertension and excluding structural heart disease.

Other Tests:

- Pulmonary mechanics testing

  - Although pulmonary mechanics testing (PMT) has been used primarily as a research tool in the past, newer ventilators are equipped with PMT capabilities to assist the neonatologist in adequately managing the changing pulmonary course of RDS.
  - Constant PMT monitoring may be helpful in preventing volutrauma from alveolar and airway overdistension. Monitoring may also facilitate weaning the infant from the ventilator after surfactant therapy or determining if the infant can be extubated.
  - Infants with RDS have significant decrease in lung compliance with a range of 0.0005-0.0001 L/cm H_2O. Therefore, for the same pressure gradient (compared to healthy lungs), the delivered tidal volume is reduced in infants with RDS. The resistance (airway and tissues) may be normal or increased. The time constant and the corresponding pressure and volume equilibration are shorter. The anatomic dead space and the functional residual capacity are increased.

Procedures:

- Sedation, analgesia, or anesthesia whenever feasible
- Arterial puncture, venous puncture, and capillary blood sampling
- Vascular access

    o Intravenous line placement
    o Umbilical arterial catheterization
    o Umbilical artery cut down
    o Peripheral artery cannulation
    o Umbilical venous catheterization

- Tracheal intubation or tracheostomy
- Bronchoscopy
- Thoracotomy tubes
- Pericardial tubes
- Gastric tubes
- Transfusion of blood, blood products, and exchange transfusion
- Lumbar puncture
- Suprapubic bladder aspiration and bladder catheterization

Histologic Findings: See Pathophysiology and Image 2.

TREATMENT	Section 6 of 11

Medical Care:

- Prenatal prevention and prediction of RDS: Obstetricians with experience in fetal medicine should care for mothers whose infants are at an increased risk for developing RDS, preferably at a tertiary perinatal center. Strategies to prevent premature birth (eg, bed rest, tocolytics, appropriate antibiotics) and the prudent use of antenatal steroids to mature fetal lungs may decrease the incidence and severity of RDS. Fetal lung maturity can be predicted by estimating the lecithin-to-sphingomyelin ratio and the presence of phosphatidylglycerol in the amniotic fluid obtained via amniocentesis.
- Delivery and resuscitation: A neonatologist experienced in the resuscitation and care of premature infants should attend deliveries of fetuses when younger than 28 weeks' gestation. They are at a high risk of maladaptation, which further inhibits surfactant production.
- Surfactant replacement therapy: The mortality rate of RDS has decreased 50% during the last decade with the advent of surfactant therapy.

    o Infants diagnosed with RDS who require assisted ventilation with more than 0.40 fraction of inspiratory oxygen (FIO_2) should receive intratracheal surfactant as soon as possible, preferably within 2 hours after birth.
    o Because surfactant is protective of delicate lungs, several investigators have recommended prophylactic use following resuscitation in extremely premature infants (<27 weeks' gestation). However, prophylactic surfactant is expensive and unnecessary in most instances because 40-60% of premature infants do not have surfactant deficiency and, thus, are intubated with its inherent risks.
    o Premature infants with surfactant deficiency and RDS have an alveolar pool size of approximately 5 mg/kg. Full-term animal models have pool sizes with a range of 50-100 mg/kg. The recommended dose of the clinically available surfactant preparations has a range of 50-200 mg/kg, which is an approximation of the surfactant pool of term newborn lungs. Rapid bolus administration of surfactant after adequate lung recruitment using 2-4 cm positive end-expiratory pressure (PEEP) and adequate positive pressure may lead to its more homogenous distribution. Most infants require 2 doses; however, as many as 4 doses at 6- to 12-hour intervals have been used in several clinical trials. If the infant improves rapidly after only 1 dose, the infant most likely does not have RDS. Conversely,

in infants who respond poorly or are nonresponders to surfactant, exclude PDA, pneumonia, and complications of ventilation (air leak), especially prior to using third and subsequent doses.

- o Some of the complications from a meta-analysis of several clinical trials conducted worldwide are listed in Tables 1-6. Clinical trials with protein-containing natural surfactants result in fewer complications and a more rapid improvement in the infant's respiratory status. The currently marketed natural surfactants have varying amounts of phospholipids (mostly desaturated phosphatidylcholine) and apoprotein B and C but not apoprotein A. Apoprotein A may be important for host defense. The source, composition, and dosages of several surfactant preparations are outlined in Table 7. In 2 recent reviews, Notter and Kresch et al summarized data from extensive biophysical studies, in vitro and whole animal biochemical studies, molecular and physiologic studies, and several large international clinical trials.

- Oxygen and continuous positive airway pressure: In 1971, continuous positive airway pressure (CPAP) was introduced as the primary therapeutic modality when Gregory et al demonstrated a marked reduction in RDS mortality. Oxygen was the primary therapeutic modality prior to the introduction of CPAP.
  - o Oxygen via hood still is used for treating infants with mild RDS.
  - o CPAP keeps the alveoli open at the end of expiration, thereby decreasing the right-to-left pulmonary shunt.
  - o CPAP may be administered via the endotracheal tube, nasal prongs, or nasopharyngeal tubes (in larger infants).
  - o CPAP is an adjunct therapy following surfactant administration, if prolonged assisted ventilation is not required.
  - o CPAP may be used following extubation in individuals with RDS to prevent atelectasis and/or prevent apnea in premature infants.
  - o The goal of therapy for patients with RDS is to maintain a pH of 7.25-7.4, an arterial oxygen (PaO_2) of 50-70 mm Hg, and a carbon dioxide pressure (PCO_2) of 40-65 mm Hg, depending on the infant's clinical status.

- Kirby and deLemos introduced assisted ventilation 2 decades ago. Assisted ventilation further decreased RDS-related mortality; however, earlier ventilators were associated with complications, such as air leaks, BPD (secondary to barotrauma or volutrauma), airway damage, and intraventricular hemorrhage. Advances in microprocessor-based technology, transducers, and real-time monitoring have enabled patient-driven ventilator control and synchronization of mechanical ventilation with patient effort. The novelty of the newer ventilation techniques has generated several controversies that remain to be resolved. Among these controversies are signal detection and transduction, optimal volume delivery (ventilation modes), and weaning from mechanical ventilation.
- Consider ventilation as a necessary physiologic support while the infant recovers from RDS. Several investigators have suggested that permissive hypercapnia with arterial carbon dioxide ($PaCO_2$) with a range of 45-55 mm Hg (with adequate lung volume), may facilitate weaning during recovery from RDS. To minimize the complications of conventional intermittent mandatory ventilation, newer ventilation techniques have been introduced, including the following:

  - o Synchronous intermittent mandatory ventilation is a technique wherein some of the patient's respirations are synchronized with breaths delivered by the ventilator. In a recent randomized controlled trial, the incidence of BPD (defined as oxygen requirement at corrected gestational age of 36 wk) was reduced significantly when compared with standard intermittent mandatory ventilation (47% vs 72%; $p < 0.05$).
  - o Assist-control ventilation has also been suggested to improve outcome.
  - o Some physicians use pressure-support ventilation to wean the infants who have developed chronic lung changes.
  - o High-frequency ventilation (HFV) is a technique wherein small tidal volumes (less than anatomic dead space) are usually delivered at rapid frequencies. HFV was originally designed to treat patients with air leak. Numerous studies in animal models of RDS demonstrate that HFV promotes more uniform lung inflation, improves lung mechanics

and gas exchange, and reduces exudative alveolar edema, air leak, and lung inflammation. Although animal studies are unequivocal, human data are less clear. Some clinical trials demonstrate that HFV can reduce the occurrence of chronic lung disease, whereas other studies have demonstrated no effect. Adequate clinical trials controlling for techniques of resuscitation, surfactant therapy, and comparing HFV with synchronous intermittent mandatory ventilation are awaited. HFV techniques have a learning curve, and the optimal ventilator strategy varies with the stage of RDS. These ventilators include the following:

- High-frequency oscillatory ventilation (10-15 Hz): Because expiration occurs actively, monitor patients for hypocarbia in order to prevent periventricular leukomalacia. Controlled trials of the use of high-frequency oscillatory ventilation (HFOV) in reducing BPD in infants with RDS have been controversial. Perhaps the unfavorable outcome of HFOV in some of these studies can be attributed to (1) having very low incidence of BPD with antenatal steroid use and, therefore, inadequate sample size to detect a difference, (2) not using an optimal lung volume strategy in patients treated with HFOV, (3) definition and differences in chorioamnionitis, or (4) differences in resuscitation techniques at birth.
- High-frequency jet ventilation: Its frequency range is 4-11 Hz (usually 7 Hz), but it has to be used in tandem with a conventional ventilator to provide PEEP and sigh breaths. It has been demonstrated to decrease air leaks. Because the solenoid valves open intermittently to provide jet breaths, high-frequency jet ventilation may be preferred by some neonatologists to treat infants with air leaks.
- High-frequency flow interrupter: Its frequency range is 6-15 Hz, with the advantages of a built-in conventional ventilator and an ability to provide sigh breaths. Its use is also associated with a decrease in the incidence of air leaks in infants with RDS.

- Supportive therapy includes the following:
  o Temperature regulation: Hypothermia increases oxygen consumption, thereby further compromising infants with RDS who are born prematurely. Therefore, prevent hypothermia in infants with RDS during delivery, resuscitation, and transport. Care for these infants in a neutral thermal environment with the use of a double-walled incubator or radiant warmer.
  o Fluids, metabolism, and nutrition: In infants with RDS, initially administer 5% or 10% dextrose intravenously at 60-80 mL/kg/d. Closely monitor blood glucose (Dextrostix), electrolytes, calcium, phosphorous, renal function, and hydration (determined by body weight and urine output) to prevent any imbalance. Add calcium at birth to the initial intravenous fluid. Start electrolytes as soon as the infant voids and as indicated by electrolytes. Gradually increase the intake of fluid to 120-140 mL/kg/d. Extremely premature infants occasionally may require fluid intake of as much as 200-300 mL/kg or more because of insensible water loss occurring from their large body surfaces.
  Once the infant is stable, add intravenous nutrition with amino acids and lipid. After the respiratory status is stable, initiate a small volume of gastric feeds (preferably breast milk) via a tube to initially stimulate gut development and, thereafter, provide nutrition as intravenous nutritional support is being decreased.
  o Circulation and anemia: Assess the baby's circulatory status by monitoring heart rate, peripheral perfusion, and blood pressure. Administer blood or volume expanders, and use vasopressors to support circulation. Monitor blood withdrawn for laboratory tests closely in tiny infants and replace the blood by packed cell transfusion when it has reached 10% of the infant's estimated blood volume or if the hematocrit level is less than 40-45%.
  o Antibiotic administration: Start antibiotics in all infants who present with respiratory distress at birth after obtaining blood cultures; discontinue antibiotics after 3-5 days if blood cultures are negative. Exceptions to the use of antibiotics include a recent negative maternal cervical culture for GBBS or an infant delivered by a mother with intact amniotic membranes, no clinical or laboratory findings suggestive of chorioamnionitis, and adequate antenatal care.
  o Support of parents and family: Often parents undergo much emotional and/or financial stress with the birth of a critically ill premature infant with RDS and the associated complications. The parents may feel guilty, be unable to relate to the infant in the

intensive care setting, and be anxious about the prognosis for the infant. In addition, the infant may provide inadequate cues to arouse mothering. These factors interact to prevent maternal-infant bonding. Hence, provide adequate support for these parents and other family members to prevent or minimize these problems.

Staff members (preferably a physician and a nurse) should keep the parents well informed by frequently talking to them, especially during the acute stage of RDS. Encourage parents and assist them in frequently visiting their child. Explain the equipment and procedures to the parents, and encourage them to touch, feed, and care for their infant as soon as possible. Prior to discharge from the hospital, the infant is immunized ,and follow-up care is arranged with a multidisciplinary team and coordinated by a pediatrician experienced in the care of problems of premature infants.

Table 1. **Results of Meta-Analysis of Separate Clinical Trials in the Treatment of Respiratory Distress Syndrome With Natural or Synthetic Surfactant Preparations***

	Natural Surfactant Treatment		Synthetic Surfactant Treatment	
Outcome	Number of trials	RR (95% CI) RD (95% CI)	Number of trials	RR (95% CI) RD (95% CI)
Pneumothorax	12	0.43 (0.35, 0.52) -17% (-21%, -13%)	5	0.64 (0.55, 0.76) -9% (-12%, -6%)
BPD	9	0.94 (0.72, 1.22) -2% (-9%, 4%)	5	0.75 (0.61, 0.92) -4% (-6%, -1%)
Mortality	12	0.68 (0.57, 0.80) -9% (-13%, -5%)	6	0.73 (0.61, 0.88) -5% (-7%, -2%)
BPD or death	10	0.76 (0.65, 0.90) -14% (-21%, -7%)	4	0.73 (0.65, 0.83) -8% (-11%, -5%)

*RR, relative risk; RD, relative difference; CL, confidence interval; BPD, bronchopulmonary dysplasia.

Table 2. **Results of Meta-Analysis of Separate Clinical Trials With Prophylactic Use of Natural or Synthetic Surfactant Preparations***

	Prophylactic Natural		Prophylactic Synthetic	
Outcome	Number of trials	RR (95% CI) RD (95% CI)	Number of trials	RR (95% CI) RD (95% CI)
Pneumothorax	8	0.35 (0.26, 0.49) -13% (-20% -11%)	6	0.67 (0.50, 0.90) -5% (-9%, -2%)
BPD	7	0.93 (0.80, 1.07) -4% (-9%, -3%)	4	1.06 (0.83, 1.36) 1% (-4%, 6%)
Mortality	7	0.60 (0.44, 0.83) -7% (-12%, -3%)	7	0.70 (0.58, 0.85) -7% (-11%, -3%)
BPD or death	7	0.84 (0.75, 0.93) -10% (-16%, -4%)	4	0.80 (0.77, 1.03) -4% (-10%, 1%)

Table 3. Meta-Analysis of Head-to-Head Trials With Natural Versus Synthetic Surfactants*

Outcome	Number of trials	Relative Risk (95% CI)	Relative Difference (95% CI)
Pneumothorax	5	0.68 (0.56, 0.83)	-4.1% (-6.3%, -2.0%)
BPD	4	0.97 (0.88, 1.07)	-1.2% (-5.4%, -2.9%)
Mortality	7	0.88 (0.76, 1.02)	-2.2% (-4.7%, 0.4%)
BPD or death	2	0.94 (0.87, 1.01)	-3.6% (-8.0%, 0.8%)

Table 4. Meta-Analysis of Clinical Trials Comparing Prophylactic Use of Surfactant Versus Rescue Treatment of Infants With Respiratory Distress Syndrome*

Outcome	Number of trials	Relative Risk (95% CI)	Relative Difference (95% CI)
Pneumothorax	6	0.62 (0.42, 0.89)	-2.1% (-3.7%, -0.55)
BPD	7	0.95 (0.81, 1.11)	-0.9% (-3.5%, 1.7%)
Mortality	6	0.59 (0.46, 0.76)	-4.6% (-6.8%, -2.5%)
BPD or death	7	0.85 (0.76, 0.95)	-4.5% (-7.4%, -1.5%)
Infants <30 Weeks' Gestation			
Mortality	6	0.60 (0.47, 0.77)	-6.5% (-9.6%, -3.4%)
BPD or death	7	0.86 (0.77, 0.96)	-5.5% (-9.6%, -1.5%)

Table 5. Meta-Analysis of Early Versus Delayed Treatment of Respiratory Distress Syndrome*

Outcome	Number of trials	Relative Risk (95% CI)	Relative Difference (95% CI)
Pneumothorax	3	0.70 (0.59, 0.82)	-5.2% (-7.5%, -2.9%)
BPD	3	0.97 (0.88, 1.06)	-1.2% (-4.6%, 2.2%)
Mortality	4	0.87 (0.77, 0.99)	-2.8% (-5.5%, 0.0%)
BPD or death	3	0.94 (0.88, 1.00)	-3.7% (-7.2%, 0.0%)

Table 6. Meta-Analysis of Clinical Trials Comparing Multiple Doses With a Single Dose of Surfactant*

Outcome	Number of trials	Relative Risk (95% CI)	Relative Difference (95% CI)
Pneumothorax	2	0.51 (0.30, 0.88)	-8.7% (-15.4%, -2.0%)
BPD	1	1.10 (0.63, 1.93)	1.2% (-5.8%, 8.3%)
Mortality	2	0.63 (0.57, 1.11)	-7.0% (-14%, 0%)
BPD or death	1	0.80 (0.57, 1.11)	-6.6%, (-16.2%. 3%)

Table 7. Type, Source, Composition, Dosages, and Other Information on Currently Available Surfactant Preparations*

Type	Source	Composition	Dosage	Comments
Survanta / Surfactant AT	Bovine lung mince	DPPC, tripalmitin SP (B<0.5%, C99% of TP wt/wt)	4 mL (100 mg)/kg, 1-4 doses q6h	Refrigerate
Alveofact	Bovine lung lavage	99% PL, 1% SP-B and SP-C	45 mg/mL	Federal Republic of Germany
bLES	Bovine lung lavage	75% PC and 1% SP-B and SP-C		Canadian
Infasurf	Calf lung lavage	DPPC, tripalmitin, SP (B290 g/mL, C360 g/mL)	3 mL (105 mg)/kg, 1-4 doses, q6-12h	6 mL vials, refrigerate
Calf lung surfactant extract (CLSE)	Similar to Infasurf			
Curosurf	Minced pig lung	DPPC, SP-B and SP-C (?amount)	2.5 mL (200 mg)/kg $\Rightarrow$ 1.25 mL (100 mg)/kg	1.5 and 3 mL
Exosurf	Synthetic	85% DPPC, 9% hexadecanol, 6% tyloxapol	5 mL (67.5 mg)/kg, 1-4 doses, q12h	Lyophilized; dissolve in 8 mL
Surfaxan (KL$_4$)	Synthetic	DPPC, synthetic peptide		
ALEC	Synthetic	70% DPPC, 30% unsaturated PG		Possibly discontinued

*DPPC indicates dipalmitoyl phosphatidyl choline; PG, phosphatidylglycerol; SP-B and SP-C, surfactant proteins B and C; bLES, bovine lipid extract surfactant; ALEC, artificial lung expanding compound.

Consultations: Premature infants with RDS are prone to various complications. Appropriate consultations may be obtained as indicated.

Diet: See fluids, metabolism, and nutrition in the Medical Care section.

MEDICATION	Section 7 of 11

The goals of pharmacotherapy are to reduce morbidity and prevent complications.

Drug Category: *Lung surfactants* -- Exogenous surfactant can be helpful in treatment of airspace disease (eg, RDS). Following inhaled administration, surface tension is reduced and alveoli are stabilized, thus decreasing the work of breathing and increasing lung compliance.

Drug Name	Beractant (Survanta, Alveofact) -- Natural bovine lung extract that lowers surface tension on alveolar surfaces during respiration and stabilizes alveoli against collapse at resting transpulmonary pressures. For ET use only.
Pediatric Dose	ET: 4 mL/kg (100 mg/kg) divided in 4 aliquots administered at least 6 h apart for 1-4 doses
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Must be warmed to room temperature; administer only under carefully supervised conditions because of risk of acute airway obstruction Marked improvement in oxygenation may occur after administration, hence, decrease oxygen and ventilator pressures (expired tidal volume) as suggested by blood gases; monitor systemic oxygenation to avoid hyperoxia or hypoxia; surfactant may reflux into ET tube (hence, administer it rapidly followed by positive pressure ventilation); monitor heart rate and blood pressure; because ET may rarely become occluded, suction infant's ET tube (preferably using closed suction system) prior to administering surfactant; pulmonary hemorrhage may occur in extremely premature infants (exclude PDA); apnea and nosocomial sepsis may also occur
Drug Name	Calfactant (Infasurf) -- A natural calf lung extract containing phospholipids, fatty acids, and surfactant-associated proteins B (260 mcg/mL) and C (390 mcg/mL). For ET use only.
Pediatric Dose	ET: 3 mL/kg (105 mg/kg) q6-12h for 1-4 doses
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Administer only under carefully supervised conditions, because of risk

	of acute airway obstruction Marked improvement in oxygenation may occur within minutes, hence, wean infant's inspired oxygen and/or ventilator pressure (expired tidal volume) as indicated by blood gases; monitor systemic oxygenation by pulse oxymetry to avoid hypoxia and/or hyperoxia; surfactant may reflux into ET (hence, administer rapidly followed by positive pressure ventilation); cyanosis, bradycardia, or changes in blood pressure have occurred during dosing procedures; because ET rarely may become occluded, suction infant's tube (preferably using a closed system) before administering surfactant
Drug Name	Poractant (Curosurf) -- Lowers surface tension on alveolar surfaces during respiration and stabilizes alveoli against collapse at resting transpulmonary pressures. Indicated to treat RDS in premature infants. For ET use only.
Pediatric Dose	ET: 2.5 mL/kg (200 mg/kg); then 1.25 mL/kg (100 mg/kg) at 12-h intervals prn in 2 subsequent doses
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Correction of acidosis, hypotension, anemia, hypoglycemia, and hypothermia recommended before administration; marked improvement in oxygenation may occur within minutes; monitor systemic oxygenation to avoid hyperoxia
Drug Name	Colfosceril (Exosurf Neonatal) -- Lowers surface tension on alveolar surfaces during respiration and stabilizes alveoli against collapse at resting transpulmonary pressures. For ET use only.
Pediatric Dose	ET: 5 mL/kg (67.5 mg/kg) q12h for 1-4 doses
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Rapidly affects oxygenation and lung compliance; only for instillation into trachea; surfactant may reflux into ET, hence, administer rapidly followed by ventilation; because ET rarely may become blocked, suction ET (preferably using closed suction system) before surfactant administration; pulmonary hemorrhage may occur in infants weighing <700 g; nosocomial sepsis and apnea also may occur

FOLLOW-UP	Section 8 of 11

Further Inpatient Care: See the Treatment section.
Further Outpatient Care: See the Treatment section.
In/Out Patient Meds: See the Medication section.
Transfer: Transfer the following to a tertiary care center:

- o Mothers with high-risk pregnancy
- o Mothers in premature labor
- o Newborn infants with respiratory failure

Deterrence/Prevention: See Medical Care section.

- Acute complications include the following:

  - Alveolar rupture: Suspect air leak (ie, pneumothorax [see Tables 1-6], pneumomediastinum, pneumopericardium, interstitial emphysema) when an infant with RDS suddenly deteriorates with hypotension, apnea, or bradycardia or when metabolic acidosis is persistent.
  - Infections may complicate the management of RDS and may manifest in a variety of ways, including failure to improve, sudden deterioration, or a change in white blood cell count or thrombocytopenia. Also, the use of invasive procedures (eg, venipunctures, catheter insertion, use of respiratory equipment) and the use of postnatal steroids provide access for organisms that may invade the immunologically compromised host. With the advent of surfactant therapy, infants who are smaller and more ill are surviving with an increase in the incidence of septicemia secondary to staphylococcal epidermidis and/or infection by *Candida* species. When septicemia is suspected, obtain blood cultures from 2 sites and place the infant on appropriate antibiotics until the culture results are obtained.
  - Intracranial hemorrhage and periventricular leukomalacia: Intraventricular hemorrhage is observed in 20-40% of premature infants with greater frequency in infants with RDS who require mechanical ventilation. Cranial ultrasound is performed within the first week and thereafter as indicated in premature infants younger than 32 weeks' gestation. Prophylactic indomethacin therapy and antenatal steroids have decreased the frequency of intracranial hemorrhage in these patients with RDS. Hypocarbia and chorioamnionitis are associated with an increase in periventricular leukomalacia.
  - PDA with increasing left-to-right shunt may complicate the course of RDS, especially in infants weaned rapidly after surfactant therapy. Suspect PDA in any infant who deteriorates after initial improvement or has bloody tracheal secretions. Although helpful in the diagnosis of PDA, cardiac murmur and wide pulse pressure are not always apparent in critically ill infants. An echocardiogram enables the clinician to confirm the diagnosis. Treat PDA with indomethacin, which can be repeated during the first 2 weeks if the PDA reopens. In refractory incidents of RDS or in infants in whom indomethacin is contraindicated, surgically close the PDA.
  - Occurrence of pulmonary hemorrhage increases in tiny premature infants, especially following surfactant therapy. Increasing PEEP on the ventilator and administering intratracheal epinephrine manages pulmonary hemorrhage. In some patients, pulmonary hemorrhage may be associated with PDA; treat pulmonary hemorrhage promptly in such individuals. In a retrospective study, intratracheal surfactant therapy has been used successfully, with the rationale that blood is an inhibitor of pulmonary surfactant.
  - Suspect necrotizing enterocolitis and/or gastrointestinal perforation in any infant with abnormal abdominal findings on physical examination. A radiograph of the abdomen assists in confirming their presence. Spontaneous perforation (not necessarily as part of necrotizing enterocolitis) may occasionally occur in critically ill premature infants and has been associated with the use of steroids and/or indomethacin.
  - Apnea of prematurity is common in immature infants, and its incidence has increased with surfactant therapy, possibly due to early extubation. Manage apnea of prematurity with methylxanthines (theophylline, caffeine) and CPAP or assisted ventilation in refractory incidents. Exclude septicemia, seizures, gastroesophageal reflux, and metabolic and other causes in infants with apnea of prematurity.

- Chronic complications include the following:

  - Bronchopulmonary dysplasia: BPD is a chronic lung disease and is defined as oxygen requirement at a corrected gestational age of 36 weeks. BPD is related directly to high volume and/or pressures that are used in mechanical ventilation, infections, inflammation, and vitamin A deficiency. BPD increases with decreasing gestational age.

The postnatal use of surfactant therapy, gentler ventilation, vitamin A, and steroids reduces the severity of BPD.

- o Clinical studies have demonstrated varying incidence of BPD, which has been attributed to an increase in the survival of smaller and more ill infants with RDS following the introduction of the above therapies (see Tables 1-6). BPD may also be associated with Gastroesophageal Reflux or Sudden Infant Death Syndrome; hence, consider these entities in infants with unexplained apnea prior to discharge from the hospital.
- o Retinopathy of prematurity (ROP): Infants with RDS and a PaO_2 greater than 100 mm Hg are at a greater risk of developing ROP; hence, monitor PaO_2 closely and maintain at 50-70 mm Hg. Although used in all premature infants, pulse oximetry is not helpful in preventing ROP in tiny infants because of the flat portion of the oxygen-hemoglobin dissociation curve. Eyes of all premature infants are examined at 34 weeks' gestation by an ophthalmologist and thereafter as indicated. If ROP progresses, laser therapy or cryotherapy is used to prevent retinal detachment and blindness. Monitor infants with ROP closely for refractive errors.
- o Neurologic impairment: Neurologic impairment occurs in approximately 10-70% of infants and is related to the infant's gestational age, the extent and type of intracranial pathology, the presence of hypoxia, and the presence of infections. Hearing and visual handicaps further may compromise the development of these infants. They may develop a specific learning disability and aberrant behavior. Therefore, follow up periodically with these infants to detect those with neurologic impairment, and undertake appropriate interventions.
- o Familial psychopathology: Infants with RDS are at a greater risk of child abuse and failure to thrive; therefore, obtain home clearance in conjunction with a nurse and social worker prior to discharge from the hospital. Encourage and document parental visits and the parent's interaction with the infant. Advise parents to spend time with their infants with RDS in a separate room prior to discharge, especially parents who are at high social risk (eg, teenagers) who also have extremely premature infants. Advise parents of infants who are discharged on oxygen and/or on an apnea monitor, with gastrostomy or requiring tube feeding, or with a tracheostomy or other special needs to spend time with their infants with RDS in a separate room prior to discharge. Physicians who are skilled in recognizing the problems encountered in these infants should be involved with their ongoing care because of the high risk of morbidity and mortality in infancy.

Prognosis: See Tables 1-6.

Patient Education:

- Because an increased risk of prematurity and RDS exists for subsequent pregnancies, counsel parents.
- Promptly manage high-risk factors, such as diabetes, hypertension, incompetent cervix, and chorioamnionitis.
- Educate and counsel parents, caregivers, and families of premature infants regarding the potential problems infants with RDS may encounter during and after the nursery stay. Supplement such education with audiovisual aids and handouts.

| MISCELLANEOUS	Section 9 of 11

Medical/Legal Pitfalls:

- Trained and experienced professionals at a tertiary care facility should treat infants with RDS whenever possible, because complications of premature births, RDS, and the procedures performed on infants with RDS are associated with an increase in medicolegal action against health care professionals and institutions. To minimize such actions, adequately document the infant's clinical progress, including discussions with the families and/or caregivers. Obtain written informed consent prior to elective procedures or blood product transfusions.

Picture 1. The lower curve indicates lungs obtained at postmortem from an infant with HMD; these lungs require far more pressure to achieve a given volume of inflation than do those obtained from an infant dying of a nonrespiratory cause. The arrows depict the inspiratory and expiratory limbs of the pressure volume curves. Note the decrease in lung compliance and the higher critical opening and closing pressures respectively in the premature infant with hyaline membrane disease.
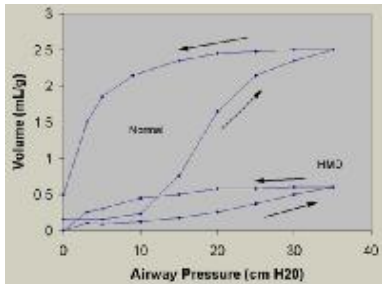

Picture 2. Microscopic appearance of lungs of an infant with respiratory distress syndrome. Hematoxylin and eosin stain exhibits the presence of hyaline membranes (pink areas).
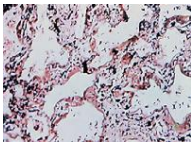
Picture 3. A schematic outlining of the pathology of respiratory distress syndrome. Infants may recover completely or develop chronic lung damage, resulting in bronchopulmonary dysplasia.


Picture 4. The bar chart below demonstrates the composition of lung surfactant. Of the 10% proteins, approximately 1% comprises surfactant apoproteins; the remaining proteins are derived from alveolar exudate.
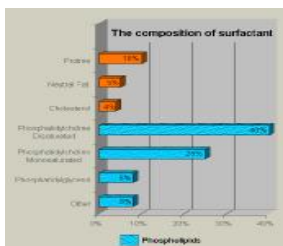
Picture 5. A schematic diagram of the surfactant metabolism. A single alveolus is shown with the location and movement of surfactant components depicted. Surfactant components are synthesized from precursors (1) in the endoplasmic reticulum (2) and transported through the Golgi apparatus (3) via multivesicular bodies. The components are ultimately packaged in lamellar bodies (4), which are intracellular storage granules for surfactant before secretion. After secretion (exocytosis) into the liquid lining of the alveolus, the surfactant phospholipids are organized into a complex lattice called tubular myelin (5). The tubular myelin is believed to generate the phospholipid that provides material for a monolayer (6) at the air-liquid interface in the alveolus, which lowers surface tension. Subsequently, surfactant phospholipids and proteins are taken back into type II cells, possibly in the form of small vesicles (7), apparently by a specific pathway that involves endosomes (8), and probably transported for storage into lamellar bodies (9) for recycling. Some surfactant in the liquid layer is also taken up by alveolar macrophages (10). A single transit of the phospholipid components of surfactant through the alveolar lumen normally requires a few hours. The phospholipid in the lumen is taken back into type II cell and is reused 10 times before being degraded. Surfactant proteins are synthesized in polyribosomes and extensively modified in endoplasmic reticulum, Golgi apparatus, and multivesicular bodies. Surfactant proteins are detected within lamellar bodies or in secretory vesicles closely associated with lamellar bodies before secretion into the alveolus.
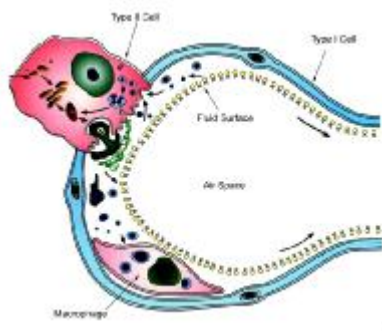
Picture 6. Chest radiograph of a premature infant with respiratory distress syndrome before and after surfactant treatment. Initially, radiograph exhibits poor lung expansion, air bronchogram, and reticular granular appearance. The chest radiograph repeated when the neonate is aged 3 hours following surfactant therapy demonstrates marked improvement.
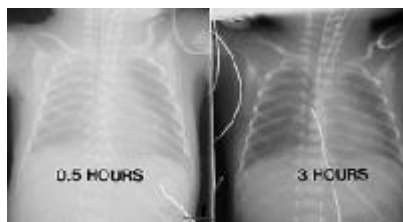
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Respiratory Distress Syndrome excerpt

Retinopathy of Prematurity

Last Updated: October 29, 2002

Synonyms and related keywords: ROP, retrolental fibroplasia, retinal neovascularization

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INTRODUCTION	Section 2 of 10

Background: Retinopathy of prematurity (ROP) is a serious vasoproliferative disorder affecting extremely premature infants. ROP often regresses or heals, but it can lead to severe visual impairment or blindness. Significant ROP can lead to lifelong disabilities for the smallest survivors of neonatal intensive care units. ROP remains a serious problem despite striking advances in neonatology.

Pathophysiology: ROP primarily occurs in extremely low birth weight (ELBW) infants. Most research suggests that a low birth weight, a young gestational age (GA), and the severity of the illness (eg, days the patient receives supplemental oxygen) are associated factors. Recently, other associations have been described. However, the severity of the illness appears to be a major predictor of severe disease. The smallest, sickest, and most immature infants are at the highest risk for serious disease. African American infants appear to have less severe ROP.

Retinal vasculature begins to develop around the 16th week of gestation. It grows circumferentially and becomes fully mature at term. Premature birth results in the cessation of normal retinal vascular maturation. Blood vessels constrict and can become obliterated, resulting in delays of normal retinal vascular development. Early on, oxygen and nutrients can be delivered to the retina by means of diffusion from the underlying choroid. The retina continues to grow in thickness and eventually outgrows its vascular supply. Over time, retinal hypoxia occurs and results in an overgrowth of vessels. This process is mediated in part by vascular endothelial growth factor (VEGF). These problems result in ROP.

Frequency:

- **In the US:** The incidence varies with birth weight, but it is reported to be approximately 50-70% in infants whose weight is less than 1250 g at birth.

  Hussain et al reviewed the incidence and the need for surgery in neonates with ROP who were born at 22-36 weeks' GA between July 1989 and June 30, 1997. The incidences were 21.3% (202 of 950) for ROP of any stage and 4.6% (44 of 950) for ROP at stage 3 or worse. No ROP was noted in infants born after 32 weeks' GA. No

infant born after 28 weeks needed retinal surgery. Despite the increased survival of ELBW infants, they found a considerable reduction in the incidence and severity of ROP compared with reports from an earlier period. However, infants before 28 weeks' GA and those with birth weights less than 1000 g were still likely to need retinal surgical treatment for ROP.

Investigators from the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) multicenter trial concluded that maintaining oxygen saturation in the high 90-percent range did not reduce the severity of the retinopathy when compared with the saturations in the low 90-percent range. However, it did result in more pulmonary adverse events. In a subanalysis of infants who did not have plus disease (ie, tortuosity of vessels) at the time of study entry, the progression to threshold was significantly decreased when compared with the progression in infants with plus disease. Thus, a critical window for oxygen administration may exist.

Mortality/Morbidity: Long-term outcomes for serious disease include severe visual impairment and blindness. In addition, myopia, amblyopia, and strabismus may occur. Recently, Repka et al described the need for subsequent ophthalmic intervention.

Race: Some reports indicate a decreased incidence of progression to threshold disease in black infants. Most evidence comes from the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study. Further evidence that African American race is protective against the development of severe ROP has been reported in studies of candidemia in very low birth weight infants. The exact mechanism for the decreased incidence of progression to surgery in black infants has not been described.

Sex: Although some reports indicate a male predilection, the CRYO-ROP study reveals no differences based on sex.

CLINICAL	Section 3 of 10

History:

- Infants at highest risk for ROP are those with the lowest birth weights and youngest GAs. In tiny infants, the PaO_2 in room air may be toxic to their retinal vessels.
- Prolonged exposure to supplemental oxygen is also a risk factor.
- The severity of illness (including sepsis), blood transfusions, days receiving mechanical ventilation, a patent ductus arteriosus, and intraventricular hemorrhage are also associated with ROP.
- The effect of blood transfusion on ROP is controversial. The smallest, sickest infants receive more transfusions than their healthy counterparts, and they may have more frequent or severe ROP. However, theoretical risks associated with factors such as volume and iron load may place infants who receive more transfusions at higher risk for ROP.

Physical:

- Screening: An ophthalmologist experienced in evaluating infants for ROP should perform a screening examination.
- International classification

  - To standardize examinations, a group of physicians organized an international classification of ROP (ICROP) in 1984 and updated the classification in 1987.
  - ROP is characterized by 3 parameters: stage, zone, and plus disease (ie, tortuosity of vessels).

- Examination recommendations

  o The American Academy of Pediatrics and the American Academy of Ophthalmology have joint recommendations for infants who should be screened for ROP. These guidelines include a birth weight less than or equal to 1500 g and a GA less than or equal to 28 weeks. In addition, infants with birth weights greater than 1500 g who are believed to be at high risk for ROP should also be examined. An experienced ophthalmologist should perform the examination, which should occur at 4-6 weeks of age or by 31-33 weeks' postconceptional age.
  o Screening guidelines have been the focus of recent studies. The issue of cost-effectiveness versus missing cases of ROP is controversial. In addition, Subhani et al recently suggested that infants should be examined by the age of 4-6 weeks, contrary to the standard postconceptional age criteria.
  o Follow-up examinations are based on initial examination findings.

Other Tests:

- Ophthalmologic evaluation

  o Record the vascular maturity (how far out the vessels have grown), as indicated by zone, stage of disease, and the presence or absence of plus disease.
  o The eyes can be divided into 3 zones (1, 2, and 3), and the ROP is quantified on the basis of the number of clock hours during which the disease is present in the retina.

Staging:

- The ICROP describes 5 stages of ROP, as follows:

  o Stage 1 is characterized by a line of demarcation. Extra vessels can be seen growing at the leading edge of the retinal vasculature. The line of demarcation separates the vascularized portion of the retina from the anteriorly positioned avascular retina.
  o Stage 2 is characterized by a ridge that has extra vessels plus the elevation of tissue, which can be seen on examination.
  o Stage 3 refers to extra retinal neovascularization or vessels that are growing into the vitreous toward the examiner.
  o Stage 4 refers to partial retinal detachment.
  o Stage 5 is total retinal detachment.

- Plus disease refers to the tortuosity of vessels. Rapidly progressing plus disease is sometimes referred to as Rush disease.
- In addition, the zone of disease is designated, as follows:

  o Zone 1 is the innermost area of the retina surrounding the macula.

  o Zone 2 is the middle third of the retina nasally extending to the edge of the retina
  o Zone 3 is the most peripheral area of the retina on the temporal side.

Medical Care:

- Medical care consists of ophthalmologic screening of appropriate infants.
- No specific medical therapies are available at this time.

Surgical Care:

- Ablative surgery

  - If threshold disease is present, perform ablative surgery.
  - Ablative therapy currently consists of cryotherapy or laser surgery to destroy the avascular areas of the retina.

- Cryotherapy

  - A randomized prospective trial of cryotherapy showed a 50% reduction in retinal detachment in treated eyes versus nontreated eyes.
  - Beneficial effects were observed in infants with threshold disease, defined as 5 contiguous clock hours of stage 3 disease with plus disease or 8 noncontiguous clock hours of stage 3 disease with plus disease.

- Laser surgery

  - Currently, laser surgery is preferred to cryotherapy because it may be more effective in treating zone 1 disease. Laser photocoagulation appears to be associated with outcomes in structure and function that are at least as good as those of cryotherapy 7 years after therapy. In addition, visual acuity and refractive error data suggest that laser surgery may have an advantage over cryotherapy, and evidence suggests that laser surgery is easier to perform and better tolerated by the infants.
  - Laser surgery has been used more recently than cryotherapy, and whether the slightly improved outcomes with laser surgery are attributable to changes in the care of high-risk neonates (eg, antenatal glucocorticoid therapy, surfactant use) is unclear. However, cryotherapy has been rigorously evaluated in a multicenter prospective randomized fashion, and the 10-year follow-up data show long-term value in preserving visual acuity in eyes with threshold ROP (CRYO-ROP group, 2001).

If a patient has prethreshold disease, maintain normal serum levels of vitamin E. Vitamin E use was evaluated in a meta-analysis, and levels should be maintained in the normal range in patients at high risk for severe ROP.

Further Inpatient Care:

- Base follow-up examinations on previous examination results. The more immature the retinal vasculature or the more serious the disease, the shorter the follow-up interval must be to enable the detection of disease. These examinations allow the physician to offer treatment if threshold disease develops in the eye.
- After surgical intervention, an ophthalmologist should perform an examination to determine if additional surgery is indicated.
- Patients who are medically monitored must undergo examinations until the retinal vasculature is mature. Ensuring appropriate follow-up for infants is critical if they are discharged from the nursery before retinal vascular maturity is attained.

Further Outpatient Care:

- Patients require yearly ophthalmologic follow-up evaluations. More frequent evaluation may be necessary, depending on the severity of the disease.
- The long-term outcome for infants with ROP continues to be problematic. Patients with ROP are at significant risk for myopia. In addition, strabismus, amblyopia, and late retinal detachment continue to be problems for these infants. Long-term follow-up findings from the CRYO-ROP cooperative group indicate that refractive errors in eyes with mild ROP are associated with the same risk of myopia as that in eyes without ROP. In patients with moderate-to-severe ROP, the prevalence of severe myopia is increased. As previously stated, laser surgery offers some advantage over cryotherapy in treating zone 1 disease.

Deterrence/Prevention:

- The only known deterrent measure is to prevent preterm birth. The more mature a neonate is at birth, the less likely ROP is to occur.
- Recent studies regarding the effects of antenatal corticosteroids on ROP revealed that this treatment has a protective effect against severe ROP.

Complications:

- Late complications include myopia, amblyopia, strabismus, nystagmus, retinal breaks, and retinal detachment.
- Follow-up by an ophthalmologist is required on a long-term basis.

Medical/Legal Pitfalls:

- The timing of examination and follow-up are important factors in the diagnosis and treatment ROP. If a patient misses an examination, it should be rescheduled as soon as possible.
- Ensuring that parents are aware of the significance of ROP and appropriate follow-up is also important.
- Because of the risk of rush retinopathy, premature infants with immature retina and/or progressive ROP who come from a high-risk social environment should stay in the hospital and undergo retinal examinations every 1-2 weeks.
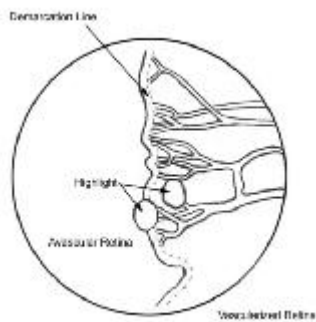
Picture 1. Retinopathy of prematurity.
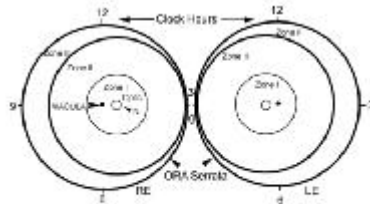
Scheme of retina of right eye (RE) and left eye (LE) showing borders and clock hours employed to describe location and extent of retinopathy of prematurity
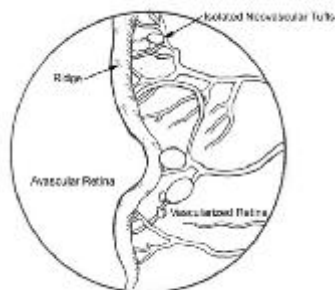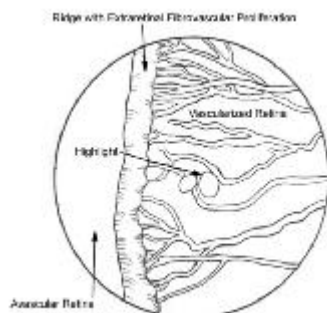
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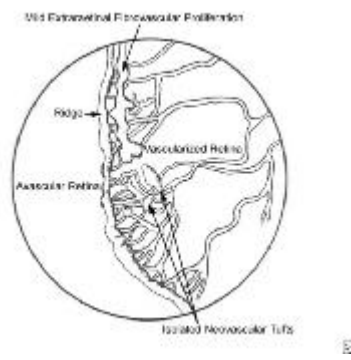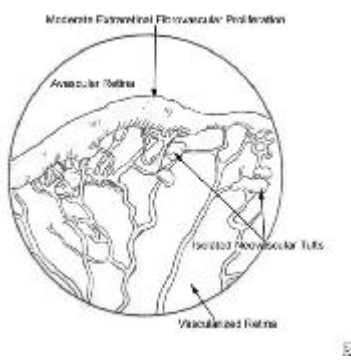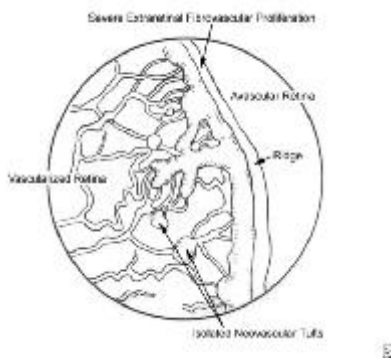

Picture 3. Retinopathy of prematurity.

Picture 4. Retinopathy of prematurity.
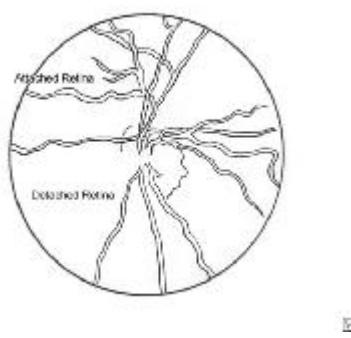
Picture 5. Retinopathy of prematurity.

Picture 6. Retinopathy of prematurity.

Picture 7. Retinopathy of prematurity.

Picture 8. Retinopathy of prematurity.

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Retinopathy of Prematurity excerpt

Shock and Hypotension in the Newborn

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INTRODUCTION	Section 2 of 10

Background: Shock is a complex clinical syndrome caused by an acute failure of circulatory function and is characterized by inadequate tissue and organ perfusion. When this occurs, inadequate amounts of oxygen and nutrient substrate are delivered to body tissues, and removal of metabolic waste products is inadequate. This results in cellular dysfunction, which may eventually lead to cell death. Failure of perfusion may involve isolated organs or the entire organism. Hypotension (ie, lower than expected blood pressure) frequently, but not always, accompanies shock.

Pathophysiology: Maintenance of adequate tissue perfusion depends on a combination of 3 major factors: (1) cardiac output; (2) integrity and maintenance of vasomotor tone of local vascular beds, including arterial, venous, and capillary; and (3) the ability of the blood to carry out its necessary delivery of metabolic substrates and removal of metabolic wastes.

Cardiac output is the product of heart rate and stroke volume. Neonatal cardiac output is more dependent upon heart rate than stroke volume; therefore, both very high (>160/min) and very low (<120/min) heart rates are likely to compromise cardiac output if prolonged, although not all infants with subnormal heart rates have impaired perfusion. At higher rates, ventricular filling time and end-diastolic volume are diminished, and myocardial oxygen consumption is increased. Because myocardial perfusion itself occurs during diastole, further increases in heart rate may produce undesirable cardiac ischemia and ventricular dysfunction. Stroke volume, the other major determinant of cardiac output, is influenced by 3 factors, which are preload, afterload, and myocardial contractility.

- Preload corresponds to the myocardial end-diastolic fiber length and is determined by the amount of blood filling the ventricles during diastole. Increases in preload increase stroke volume up to a maximum value, beyond which stroke volume falls according to the Starling Law.
- Afterload is the force that the myocardium generates during ejection against systemic and pulmonary vascular resistances (for the left and right ventricles, respectively). Reductions in afterload increase stroke volume if other variables remain constant.

- Contractility is a semiquantitative measure of ventricular function. An increase in contractility produces an increase in stroke volume if preload and afterload are unchanged.
- Clinically significant alterations in preload, afterload, and contractility may be achieved by the use of vasoactive pharmacologic agents, administration of inotropic agents, or changes in blood volume.

Blood flow to tissues and organs is influenced by their vascular beds, which are under the control of central and local vasoregulation, also referred to as autoregulation. This provides different organs with the ability to maintain internal blood flow over a wide range of arterial blood pressure fluctuations. When autoregulation is lost, blood flow becomes pressure passive, and this may lead to ischemic or hemorrhagic consequences. The biochemical mediators of vasomotor tone for each vascular bed are different, and their complex interactions are not yet fully understood.

The ability of the blood to impart delivery of oxygen and nutrients and to remove metabolic excretory products is largely determined by adequate lung ventilation and perfusion, oxygen-carrying capacity, and oxygen extraction by the tissues. Although each gram of hemoglobin can bind 1.36 mL of oxygen, fetal hemoglobin binds oxygen more tightly than adult hemoglobin and thus has a relatively reduced oxygen-unloading capacity at the tissue level. This results in a leftward shift of the oxygen-hemoglobin dissociation curve. Other factors that may also cause a significant leftward shift of this curve frequently accompany shock and include hypothermia and hypocarbia. Under these circumstances, oxygen extraction by tissues may be inappropriate despite adequate oxygen delivery.

Inadequate tissue perfusion may result from defects of the pump (cardiogenic), inadequate blood volume (hypovolemic), abnormalities within the vascular beds (distributive), flow restriction (obstructive), or inadequate oxygen-releasing capacity (dissociative). These are summarized in History.

Hypotension refers to a blood pressure that is lower than the expected reference range. Although normal physiologic range for the blood pressure, defined by the presence of normal organ blood flow, is not well studied in the newborn population, in clinical practice, the reference range blood pressure limits are defined as the gestational and postnatal age–dependent blood pressure values between the fifth (or 10th) and 95th (or 90th) percentiles. Usually, mean blood pressure rather than systolic pressure is used when judging the normality of data obtained from the indwelling arterial line because it is thought to be free of the artifact caused by resonance, thrombi, and air bubbles, but this may not always be true. Based on these data, the statistically defined lower limits of mean blood pressure during the first day of life are approximately numerically similar to the gestational age of the infant. However, by the third day of life, most preterm infants, even with 24-26 weeks' gestation, have a mean blood pressure of 30 mm Hg or greater.

A linear relationship exists between blood pressure and both gestational age or birthweight and postnatal age; however, only preliminary data are available on the gestational and postnatal age–dependent organ blood flow autoregulatory range and on the relation between blood pressure and systemic blood flow, cardiac output, and neonatal mortality and morbidity. Oxygen delivery to the tissues is influenced by cardiac output and blood flow more so than blood pressure, and, hence, values of blood pressure that are statistically abnormal are not necessarily pathologic. This is true for systolic, diastolic, and mean arterial blood pressures. Similarly, hypotension is not synonymous with shock, but it may be associated with the later stages of shock.

Frequency: In the US: The true frequency of neonatal shock is unknown because it is primarily a clinical syndrome.

Mortality/Morbidity: Shock remains a major cause of neonatal morbidity and mortality. Because shock is an accompaniment of other primary conditions, specific figures are unavailable. Morbidity as a consequence of end-organ injury and dysfunction is similar.
Race: No predilection based on race exists.

Sex: No predilection based on sex exists.

History: Many conditions and pathophysiologic disturbances are associated with shock and hypotension.

- Causes of neonatal shock include the following:
    - Hypovolemic shock is caused by acute blood loss or fluid/electrolyte losses.
    - Distributive shock is caused by sepsis, vasodilators, myocardial depression, or endothelial injury.
    - Cardiogenic shock is caused by cardiomyopathy, heart failure, arrhythmias, or myocardial ischemia.
    - Obstructive shock is caused by tension pneumothorax or cardiac tamponade.
    - Dissociative shock is caused by profound anemia or methemoglobinemia.

- Risk factors for neonatal shock include the following:

    - Umbilical cord accident
    - Placental abnormalities
    - Fetal/neonatal hemolysis
    - Fetal/neonatal hemorrhage
    - Maternal infection
    - Maternal anesthesia/hypotension
    - Intrauterine and/or intrapartum asphyxia
    - Neonatal sepsis
    - Pulmonary air leak syndromes
    - Lung overdistension during positive pressure ventilation
    - Cardiac arrhythmias

Physical: Clinical manifestations of hypotension include prolonged capillary refill time, tachycardia, mottling of the skin, cool extremities, and decreased urine output. Give attention to heart sounds, peripheral pulses, and breath sounds.

The physical examination should carefully assess these factors, as well as accurately assess blood pressure. Measurement of neonatal blood pressure can be completed directly through invasive techniques or indirectly through noninvasive techniques. Invasive methods include direct manometry using an arterial catheter or use of an in-line pressure transducer and continuous monitor. Noninvasive methods include manual oscillometric techniques and automated Doppler techniques. A good correlation exists between mean pressures with some variability between systolic and diastolic pressures.

Causes: Shock is a progressive disorder, but it can generally be divided into 3 phases: compensated, uncompensated, and irreversible. Each phase has characteristic clinicopathologic manifestations and outcomes, but, in the neonatal setting, distinguishing them may be impossible. Initiate aggressive treatment in all cases where shock is suspected.

- Compensated: In compensated shock, perfusion to vital organs, such as the brain, heart, and adrenal glands, is preserved by sympathetic reflexes, which increase systemic arterial resistance. Derangement of vital signs, such as heart rate, respiratory rate, blood pressure, and temperature, is absent or minimal. Increased secretion of angiotensin and vasopressin allows the kidneys to conserve water and salt, the release of catecholamines enhances myocardial contractility, and decreased spontaneous activity reduces oxygen consumption. Clinical signs at this time include pallor, tachycardia, cool peripheral skin, and prolonged capillary refill time. As these homeostatic mechanisms are exhausted or become inadequate to meet the metabolic demands of the tissues, the uncompensated stage ensues.

- Uncompensated

  o During uncompensated shock, delivery of oxygen and nutrients to tissues becomes marginal or insufficient to meet demands. Anaerobic metabolism becomes the major source of energy production, and production of lactic acid is excessive, which leads to systemic metabolic acidosis. Acidosis reduces myocardial contractility and impairs its response to catecholamines. Numerous chemical mediators, enzymes, and other substances are released, including histamine, cytokines (especially tumor necrosis factor and interleukin-1), xanthine oxidase (which generates oxygen free radicals), platelet-aggregating factor, and bacterial toxins in the case of septic shock. This cascade of metabolic changes further reduces tissue perfusion and oxidative phosphorylation.

  o A further result of anaerobic metabolism is the failure of the energy-dependent sodium-potassium pump, which maintains the normal homeostatic environment in which cells function. The integrity of the capillary endothelium is disrupted, and plasma proteins leak, with the resultant loss of oncotic pressure and intravascular fluids in the extravascular space.

  o Sluggish flow of blood and chemical changes in small blood vessels lead to platelet adhesion and activation of the coagulation cascade, which may eventually produce a bleeding tendency and further blood volume depletion. Clinically, patients with uncompensated shock present with falling blood pressure, very prolonged capillary refill time, tachycardia, cold skin, rapid breathing (to compensate for the metabolic acidosis), and reduced or absent urine output. If effective intervention is not promptly instituted, progression to irreversible shock follows.

- Irreversible: A diagnosis of irreversible shock is actually retrospective. Major vital organs, such as the heart and brain, are so extensively damaged that death occurs despite adequate restoration of the circulation. Early recognition and effective treatment of shock are crucial.

DIFFERENTIALS	Section 4 of 10

Acidosis, Metabolic
Acute Tubular Necrosis
Adrenal Insufficiency
Alkalosis, Respiratory
Anemia, Acute
Birth Trauma
Coarctation of the Aorta
Congenital Adrenal Hyperplasia
Consumption Coagulopathy
Dehydration
Enteroviral Infections
Escherichia Coli Infections
Hemorrhagic Disease of Newborn
Myocarditis, Viral
Necrotizing Enterocolitis
Neonatal Sepsis
Oliguria
Outflow Obstructions
Periventricular Hemorrhage-Intraventricular Hemorrhage
Shock
Supraventricular Tachycardia, Atrial Ectopic Tachycardia
Supraventricular Tachycardia, Atrioventricular Node Reentry
Supraventricular Tachycardia, Junctional Ectopic Tachycardia
Supraventricular Tachycardia, Wolff-Parkinson-White Syndrome

- Take the opportunity to sample blood for hematocrit, electrolytes, blood culture, and glucose as soon as vascular access is obtained.
- Among laboratory investigations, supportive data include metabolic acidosis in the face of reasonable oxygenation on an arterial blood specimen.
- Mixed venous blood gases may be more helpful because this reflects oxygen extraction and waste products at the tissue level, compared to arterial blood, which reflects lung function and the composition of blood before it is delivered to the tissues.
- Comparison of simultaneous arterial and mixed venous blood gas determinations may be more useful in assessing cardiac output, tissue oxygenation, and acid-base balance.
- The value of capillary blood gas determinations is severely limited because they may only reflect diminished perfusion to the periphery and not reflect central perfusion.
- Elevated plasma lactate with a normal pyruvate also suggests anaerobic metabolism triggered by tissue hypoxia-ischemia.
- Specific studies must be performed to rule out both the causes (eg, sepsis, cardiac lesions, anemia) as well as the sequelae (eg, renal, hepatic, endocrine) of shock.

Imaging Studies:

- Echocardiography and Doppler flow velocimetry may provide semiquantitative and semiqualitative noninvasive analysis of myocardial function.
- Automated Doppler provides blood pressure readings through a noninvasive method.

Other Tests: Manual oscillometric techniques for noninvasive blood pressure testing

Procedures: Infant blood pressure testing through invasive methods includes direct manometry using an arterial catheter or use of an in-line pressure transducer and continuous monitor.

Medical Care: Once shock is suspected in a newborn, appropriate supportive measures must be instituted as soon as possible. These include securing the airway and assuring its patency, providing supplemental oxygen and positive-pressure ventilation, achieving intravascular or intraosseous access, and infusing 20 mL/kg of colloid or crystalloid. Use of crystalloid or colloid solutions is appropriate, unless the source of hypovolemia has been hemorrhage, in which case whole or reconstituted blood is more appropriate.

Take the opportunity to sample blood for hematocrit, electrolytes, blood culture, and glucose as soon as vascular access is obtained. At this stage, attempt to determine the type of shock, eg, hypovolemic, cardiogenic, or maldistributive, because each requires a different therapeutic approach. In any neonate who is hypotensively compromised, the authors encourage the early use of a bladder catheter because hourly urine output is one of the few objective methods of evaluating specific organ failure and perfusion and it prevents the assumption that low urine output (which often happens in babies receiving narcotics) is always a problem.

Hypovolemic shock is the most common cause of shock in infancy, and the key to successful resuscitation is early recognition and controlled volume expansion with the appropriate fluid. (The Table below lists agents commonly used in the treatment of neonatal shock.) The estimated blood volume of a newborn is 80-85 mL/kg of body weight. Clinical signs of hypovolemic shock depend on the degree of intravascular volume depletion, which is estimated to be 25% in compensated shock, 25-40% in uncompensated shock, and over 40% in irreversible shock. Initial resuscitation with 20

mL/kg of volume expansion should replace a quarter of the blood volume. If circulatory insufficiency persists, this dose should be repeated.

Once half of the blood volume has been replaced, further volume infusion should be titrated against central venous pressure (CVP), if possible, measured through an appropriately placed umbilical venous or other central catheter. This requires careful interpretation because of inherent technical difficulties. In the absence of CVP, titration against clinical parameters should be completed. Use of crystalloid or colloid solutions is appropriate, unless the source of hypovolemia has been hemorrhage, in which case whole or reconstituted blood is more appropriate. If blood is needed in an emergent situation, type-specific or type O (Rh negative) blood can be administered. Frequent and careful monitoring of the infant's vital signs with repeated assessment and reexamination are mandatory.

Cardiogenic shock usually occurs following severe intrapartum asphyxia, structural heart disease, or arrhythmias. Global myocardial ischemia reduces contractility and causes papillary muscle dysfunction with secondary tricuspid valvular insufficiency. Clinical findings suggestive of cardiogenic shock include peripheral edema, hepatomegaly, cardiomegaly, and a heart murmur suggestive of tricuspid regurgitation. Inotropic agents, with or without peripheral vasodilators, are warranted in most circumstances. Structural heart disease or arrhythmia often requires specific pharmacologic or surgical therapy. Excessive volume expansion may be potentially harmful.

The most common form of maldistributive shock in the newborn is septic shock, and it is a source of considerable mortality and morbidity. In sepsis, cardiac output may be normal or even elevated, but it still may be too small to deliver sufficient oxygen to the tissues because of the abnormal distribution of blood in the microcirculation, which leads to decreased tissue perfusion. In septic shock, cardiac function may be depressed (the left ventricle is usually affected more than the right). The early compensated phase of septic shock is characterized by an increased cardiac output, decreased systemic vascular resistance, warm extremities, and a widened pulse pressure. If effective therapy is not provided, cardiovascular performance deteriorates and cardiac output falls. Even with normal or increased cardiac output, shock develops. The normal relationship between cardiac output and systemic vascular resistance breaks down, and hypotension may persist as a result of decreased vascular resistance.

Newborns, who have little cardiac reserve, often present with hypotension and a picture of cardiovascular collapse. These critically ill infants are a diagnostic and therapeutic challenge, and sepsis must be presumed and treated as quickly as possible. Survival from septic shock depends upon maintenance of a hyperdynamic circulatory state. In the early phase, volume expansion with agents that are likely to remain within the intravascular space is needed, whereas inotropic agents with or without peripheral vasodilators may be indicated later. In early-onset neonatal sepsis, ampicillin and either gentamicin or cefotaxime are the antimicrobials of choice until a specific infectious agent is identified.

During and following restoration of circulation, varying degrees of organ damage may remain and should be actively sought out and managed. For example, acute tubular necrosis may be a sequela of uncompensated shock. Once hemodynamic parameters have improved, consider fluid administration according to urine output and renal function as assessed by serum creatinine and electrolytes and blood urea nitrogen concentrations.

Despite adequate volume restoration, myocardial contractility may still be a problem as a consequence of the prior poor myocardial perfusion, in which case inotropic agents and intensive monitoring may need to be continued. During the process of shock, production of chemical mediators may initiate disseminated intravascular coagulopathy (DIC), which requires careful monitoring of coagulation profiles and management with fresh frozen plasma, platelets, and/or cryoprecipitate. The liver and bowel may be damaged by shock, leading to gastrointestinal bleeding and increasing the risk for necrotizing enterocolitis, particularly in the premature infant. However, the extent of irreversible brain damage is probably most anxiously monitored following shock because the brain is so sensitive to hypoxic-ischemic injury once compensation fails.

In circumstances where volume expansion and vasoactive/inotropic agents have been unsuccessful, glucocorticoids, such as dexamethasone or hydrocortisone, have been shown to be effective. The findings that steroids rapidly up-regulate cardiovascular adrenergic receptor expression and serve as hormone replacement therapy in cases of adrenal insufficiency explain their effectiveness in stabilizing the cardiovascular status and decreasing the requirement for pressure support in the critically ill newborn with volume- and pressure-resistant hypotension.

Agents Used to Treat Neonatal Shock

Agent Type	Agent	Dosage	Comments
Volume expanders	Isotonic sodium chloride solution	10-20 mL/kg IV	Inexpensive, available
	Albumin (5%)	10-20 mL/kg IV	Expensive
	Plasma	10-20 mL/kg IV	Expensive
	Lactated Ringer solution	10-20 mL/kg IV	Inexpensive, available
	Isotonic glucose	10-20 mL/kg IV	Inexpensive, available
	Whole blood products	10-20 mL/kg IV	Limited availability
	Reconstituted blood products	10-20 mL/kg IV	Use O neg
Vasoactive drugs	Dopamine	5-20 mcg/kg/min IV	Never administer intra-arterially
	Dobutamine	5-20 mcg/kg/min IV	Never administer intra-arterially
	Epinephrine	0.05-1 mcg/kg/min IV	Never administer intra-arterially
	Hydralazine	0.1-0.5 mg/kg IV q3-6h	Afterload reducer
	Isoproterenol	0.05-0.5 mcg/kg/min IV	Never administer intra-arterially
	Nitroprusside	0.5-8 mcg/kg/min IV	Afterload reducer
	Norepinephrine	0.05-1 mcg/kg/min IV	Never administer intra-arterially
	Phentolamine	1-20 mcg/kg/min IV	Afterload reducer

Surgical Care: Structural heart disease or arrhythmias often require specific pharmacologic or surgical therapy. The liver and bowel may be damaged by shock, leading to gastrointestinal bleeding and increasing the risk for necrotizing enterocolitis, particularly in the premature infant.

Consultations: Depending upon the type of shock, potential consultants might include the following pediatric subspecialists: neonatologist, cardiologist, nephrologist, infectious disease specialist, and hematologist.

Diet: Infants in shock should not be fed, and feedings should not be resumed until gastrointestinal function has recovered. Initiate total parenteral nutrition as soon as possible.

Drug Category: *Adrenergic agonists --* Cardiovascular performance deteriorates and cardiac output falls if effective therapy is not administered. These agents improve the hemodynamic status by increasing myocardial contractility and heart rate, resulting in increased cardiac output. They also increase peripheral resistance by causing vasoconstriction. Increased cardiac output and increased peripheral resistance lead to increased blood pressure.

Drug Name	Dopamine (Intropin) -- Stimulates both adrenergic and dopaminergic receptors. Hemodynamic effect is dependent on the dose. Lower doses predominantly stimulate dopaminergic receptors that in turn produce renal and mesenteric vasodilation. Cardiac stimulation and renal vasodilation produced by higher doses.
Adult Dose	5-20 mcg/kg/min IV
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity;pheochromocytoma;ventricular fibrillatio
Interactions	Phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong effects
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Closely monitor urine flow, cardiac output, pulmonary wedge pressure, and blood pressure during infusion; prior to infusion, correct hypovolemia with either whole blood or plasma, as indicated; monitoring central venous pressure or left ventricular filling pressure may be helpful in detecting and treating hypovolemia
Drug Name	Dobutamine (Dobutrex) -- Produces vasodilation and increases inotropic state. At higher dosages, may cause increased heart rate, exacerbating myocardial ischemia.
Adult Dose	5-20 mcg/kg/min IV
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; idiopathic hypertrophic subaortic stenosis; atrial fibrillation or flutter
Interactions	Beta-adrenergic blockers antagonize effects of dobutamine; general anesthetics may increase toxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Following MI, use with extreme caution; correct hypovolemic state before using drug
Drug Name	Epinephrine (Adrenaline) -- Has alpha-agonist effects that include increased peripheral vascular resistance, reversed peripheral vasodilatation, systemic hypotension, and vascular permeability. Beta-agonist effects include bronchodilatation, chronotropic cardiac activity, and positive inotropic effects.
Adult Dose	1-10 mcg/min IV
Pediatric Dose	0.05-1 mcg/kg/min IV
Contraindications	Documented hypersensitivity; cardiac arrhythmias; angle-closure glaucoma; local anesthesia in areas such as fingers or toes (vasoconstriction may produce sloughing of tissue); use during labor (may delay second stage of labor)
Interactions	Increases toxicity of halogenated inhalational anesthetics and beta- and alpha-blocking agents

Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in elderly patients, prostatic hypertrophy, hypertension, cardiovascular disease, diabetes mellitus, hyperthyroidism, and cerebrovascular insufficiency; rapid IV infusions may cause death from cerebrovascular hemorrhage or cardiac arrhythmias
Drug Name	Hydralazine (Apresoline) -- Decreases systemic resistance through direct vasodilation of arterioles.
Adult Dose	10-20 mg IV prn q4-6h
Pediatric Dose	0.1-0.5 mg/kg IV q3-6h
Contraindications	Documented hypersensitivity; mitral valve rheumatic heart disease
Interactions	MAOIs and beta-blockers may increase toxicity; pharmacologic effects may be decreased by indomethacin
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Implicated in MI; caution in suspected coronary artery disease
Drug Name	Isoproterenol (Isuprel) -- Has beta1- and beta2-adrenergic receptor activity. Binds beta-receptors of heart, smooth muscle of bronchi, skeletal muscle, vasculature, and alimentary tract. Has positive inotropic and chronotropic actions.
Adult Dose	2-10 mcg/min IV; titrate to desired heart rate and blood pressure
Pediatric Dose	0.05-0.5 mcg/kg/min IV
Contraindications	Documented hypersensitivity; tachyarrhythmias; tachycardia or heart block caused by digitalis intoxication; ventricular arrhythmias that require inotropic therapy; angina pectoris
Interactions	Bretylium increases action of vasopressors on adrenergic receptors, which may in turn result in arrhythmias; guanethidine may increase effect of direct-acting vasopressors, possibly resulting in severe hypertension; tricyclic antidepressants may potentiate pressor response of direct-acting vasopressors
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	By increasing myocardial oxygen requirements while decreasing effective coronary perfusion, may have a deleterious effect on the injured or failing heart; in patients with organic disease of the AV node and its branches, paradoxically worsens heart block or precipitates Adams-Stokes attacks; caution in coronary artery disease, coronary insufficiency, diabetes or hyperthyroidism, and sensitivity to sympathomimetic amines; if heart rate >110 bpm, may decrease infusion rate or temporarily discontinue infusion
Drug Name	Nitroprusside (Nitropress) -- Produces vasodilation and increases inotropic activity of the heart. At higher dosages, may exacerbate myocardial ischemia by increasing heart rate.
Adult Dose	Begin infusion at 0.3-0.5 mcg/kg/min IV, titrate to desired effect using increments of 0.5 mcg/kg/min; average dose is 1-6 mcg/kg/min
Pediatric Dose	0.5-8 mcg/kg/min IV
Contraindications	Documented hypersensitivity; subaortic stenosis; idiopathic hypertrophic and atrial fibrillation or flutter
Interactions	Effects are additive when administered with other hypotensive agents
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in increased intracranial pressure, hepatic failure, severe renal impairment, and hypothyroidism; in renal or hepatic insufficiency, nitroprusside levels may increase and can cause

	cyanide toxicity; sodium nitroprusside has the ability to lower blood pressure and should use only in patients with mean arterial pressures >70 mm Hg
Drug Name	Norepinephrine (Levophed) -- For protracted hypotension following adequate fluid-volume replacement. Stimulates beta1- and alpha-adrenergic receptors, increasing cardiac muscle contractility and heart rate as well as vasoconstriction, resulting in systemic blood pressure and coronary blood flow increases. After obtaining a response, the rate of flow should be adjusted and maintained at a low-normal blood pressure, such as 80-100 mm Hg systolic, sufficient to perfuse vital organs.
Adult Dose	4 mcg/min IV; titrate to desired response
Pediatric Dose	0.05-1 mcg/kg/min IV
Contraindications	Documented hypersensitivity; peripheral or mesenteric vascular thrombosis (ischemia may be increased and the area of the infarct extended)
Interactions	Enhances the pressor response by blocking reflex bradycardia
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Correct blood-volume depletion, if possible, before administration; extravasation may cause severe tissue necrosis, administer into a large vein; caution in occlusive vascular disease
Drug Name	Phentolamine (Regitine) -- Alpha1- and alpha2-adrenergic blocking agent that blocks circulating epinephrine and norepinephrine action, reducing hypertension resulting from catecholamine effects on alpha-receptors.
Adult Dose	5-20 mg IV
Pediatric Dose	1-20 mcg/kg/min IV
Contraindications	Documented hypersensitivity; coronary or cerebral arteriosclerosis; renal impairment
Interactions	Concurrent administration of epinephrine or ephedrine may decrease effects; ethanol increases toxicity
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in tachycardia, peptic ulcer, and gastritis; cerebrovascular occlusions and myocardial infarctions can occur following administration

Drug Category: *Volume expanders* -- Use of crystalloid or colloid solutions is appropriate, unless the source of hypovolemia is hemorrhage, in which case whole or reconstituted blood is more appropriate.

Drug Name	Sodium chloride (Adsorbonac, Salinex) -- Isotonic sodium chloride solution is a low-cost alternative that is readily available.
Pediatric Dose	10-20 mL/kg IV
Contraindications	Fluid retention; hypernatremia
Interactions	May decrease levels of lithium when administered concurrently
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in congestive heart failure, hypertension, edema, liver cirrhosis, renal insufficiency, and sodium toxicity

Drug Name	Albumin 5% (Albumisol, Buminate) -- Useful for plasma volume expansion and maintenance of cardiac output.
Pediatric Dose	10-20 mL/kg IV; not to exceed 6 g/kg/d (120 mL/kg/d)
Contraindications	Documented hypersensitivity; pulmonary edema; protein load of 5% albumin
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	While theoretically attractive, no proven benefit of colloid resuscitation over isotonic crystalloids exists
Drug Name	Lactated Ringer (lactated Ringer with isotonic sodium chloride solution) -- Both fluids are essentially isotonic and have equivalent volume restorative properties. Although some differences between metabolic changes are observed with administration of large quantities of either fluid, for practical purposes and in most situations, differences are clinically irrelevant. Importantly, no demonstrable difference exists in hemodynamic effect, morbidity, or mortality exists with resuscitation using either one.
Pediatric Dose	10-20 mL/kg IV
Contraindications	Pulmonary edema (added fluid promotes more edema and may lead to the development of ARDS)
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Major complication of isotonic fluid resuscitation is interstitial edema; edema of extremities is unsightly but is not a significant complication; edema in the brain or lungs is potentially fatal; fluids should be stopped when desired hemodynamic response is observed or pulmonary edema develops

Drug Category: *Antimicrobials* -- In early-onset neonatal sepsis, ampicillin and either gentamicin or cefotaxime are the antimicrobials of choice, until a specific infectious agent is identified.

Drug Name	Ampicillin (Principen, Omnipen) -- Bactericidal activity against susceptible organisms.
Adult Dose	1-2 g IV q4-6h
Pediatric Dose	50-100 mg/kg IV/IM q6-8h
Contraindications	Documented hypersensitivity
Interactions	Probenecid and disulfiram elevate levels; allopurinol decreases effects and has additive effects on ampicillin rash; may decrease effects of PO contraceptives
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Adjust dose in renal failure; evaluate rash and differentiate from hypersensitivity reaction
Drug Name	Cefotaxime (Claforan) -- It is a third-generation cephalosporin. It possesses antimicrobial effect on a predominantly gram-negative spectrum. It has a lower efficacy against gram-positive organisms.
Adult Dose	1-2 g IV/IM q4h
Pediatric Dose	150 mg/kg/d IV divided q8h
Contraindications	Documented hypersensitivity
Interactions	Probenecid may increase cefotaxime levels; coadministration with

	furosemide and aminoglycosides may increase nephrotoxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Adjust dose in severe renal insufficiency (high doses may cause CNS toxicity); superinfections and promotion of nonsusceptible organisms may occur with prolonged use or repeated therapy; has been associated with severe colitis
Drug Name	Gentamicin (Garamycin) -- Aminoglycoside antibiotic for gram-negative coverage. Used in combination with both an agent against gram-positive organisms and one that covers anaerobes. Dosing regimens are numerous; adjust dose based on CrCl and changes in volume of distribution. May be administered IV/IM. Follow each regimen by at least a trough level drawn on the third dose (0.5 h before dosing). Peak levels may be drawn 0.5 h after 30-min infusion. If trough level >2mg/L, increase dosing interval.
Adult Dose	1-1.5 mg/kg IV q8h
Pediatric Dose	<5 years: 2.5 mg/kg/dose IV q8h >5 years: 1.5-2.5 mg/kg/dose IV q8h or 6-7.5 mg/kg/d
Contraindications	Documented hypersensitivity; non–dialysis-dependent renal insufficiency
Interactions	Coadministration with other aminoglycosides, cephalosporins, penicillins, and amphotericin B may increase nephrotoxicity; aminoglycosides enhance effects of neuromuscular blocking agents, thus prolonged respiratory depression may occur; coadministration with loop diuretics may increase auditory toxicity of aminoglycosides; possible irreversible hearing loss of varying degrees may occur (monitor regularly)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Narrow therapeutic index (not intended for long-term therapy); caution in renal failure (not on dialysis), myasthenia gravis, hypocalcemia, and conditions that depress neuromuscular transmission; adjust dose in renal impairment

FOLLOW-UP	Section 8 of 10

Further Inpatient Care: Infants recovering from neonatal shock are at risk for multiple sequelae and should be intensively screened for neurodevelopmental abnormalities, using brain imaging and brainstem audiometric evoked responses. Other tests are determined by the clinical course and complications.

Further Outpatient Care: Outpatient care should include neurodevelopmental follow-up testing and other studies as indicated by the neonatal course.

Transfer: Infants presenting with evidence of shock should be transferred immediately to a full-service neonatal intensive care unit with adequate support, personnel, and expertise.

Deterrence/Prevention: Early recognition and treatment is essential to maximizing outcome in neonatal shock.

Complications: Complications of neonatal shock are related to both the underlying cause (eg, sepsis, heart disease) and the injury sustained during the period of inadequate tissue perfusion. Frequent sequelae include pulmonary, renal, endocrine, gastrointestinal, and neurologic dysfunction

Prognosis: Prognosis following neonatal shock is also related to both the underlying cause (eg, sepsis, heart disease) and the injuries sustained during the period of inadequate perfusion.

Patient Education: Parents should be informed of the risk for neurodevelopmental handicaps as well as the need for intensive follow-up care of both medical and neurologic problems.

Medical/Legal Pitfalls:

- The major medicolegal pitfall is delayed diagnosis and treatment, leading to permanent neurologic sequelae such as cerebral palsy, epilepsy, and mental retardation.
- Another potential pitfall is the misclassification of shock and subsequent inappropriate treatment.
- Failure to transfer an affected infant to a level III neonatal intensive care unit in a timely manner is another pitfall.

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Shock and Hypotension in the Newborn excerpt

Transient Tachypnea of the Newborn

Synonyms and related keywords: RDS type II, retained lung fluid syndrome, wet lung, TTN

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INTRODUCTION	Section 2 of 11

Background: Transient tachypnea of the newborn (TTN) is a disease common in infants throughout the world and has been encountered by all physicians who care for newborn infants. Infants with TNN present within the first few hours of birth with tachypnea, increased oxygen requirement, and occasional hypoxia noted on arterial blood gases without concomitant carbon dioxide retention. When managing an infant with TTN, it is important to observe for signs of clinical deterioration that may suggest other diagnoses and to observe closely for the development of fatigue.

Pathophysiology: Noninfectious acute respiratory disease develops in approximately 1% of all newborn infants and results in admission to a critical care unit. TTN is the result of a delay in clearance of fetal lung liquid. Respiratory distress typically was thought to be a problem of relative surfactant deficiency, but it is now characterized by an airspace-fluid burden secondary to the inability to absorb fetal lung liquid.

In vivo experiments have demonstrated that lung epithelium secretes Cl^- and fluid throughout gestation but only develops the ability to actively reabsorb Na^+ during late gestation. At birth, the mature lung switches from active Cl^- (fluid) secretion to active Na^+ (fluid) absorption in response to circulating catecholamines. Changes in oxygen tension augment the Na^+-transporting capacity of the epithelium and increase gene expression for the epithelial Na^+ channel (ENaC). The inability of the immature fetal lung to switch from fluid secretion to fluid absorption results, at least in large part, from an immaturity in the expression of ENaC, which can be upregulated by glucocorticoids.

Both pharmacologic blockade of the lung's EnaC channel and genetic knockout experiments using mice deficient in the ENaC pore-forming subunit have demonstrated the critical physiologic importance of lung Na^+ transport at birth. When Na^+ transport is ineffective, newborn animals develop respiratory distress; hypoxemia; fetal lung liquid retention; and, in the case of the ENaC knockout mice, death. Bioelectrical studies of human infants' nasal epithelia demonstrate that both TTN and respiratory distress syndrome (RDS) have defective amiloride-sensitive Na^+ transp

These results suggest that infants with neonatal RDS have, in addition to a relative deficiency of surfactant, defective Na^+ transport, which plays a mechanistic role in the development of the disease. An infant born by cesarean delivery is at risk of having excessive pulmonary fluid as a result of having not experienced all of the stages of labor and subsequent low release of counter-regulatory hormones at the time of delivery.

Frequency: In the US: Frequency is equivalent universally. Approximately 1% of infants have some form of respiratory distress that is not associated with infection. Respiratory distress

includes both RDS (ie, hyaline membrane disease) and TTN. Of this 1%, approximately 33-50% is TTN.

Mortality/Morbidity: TTN is generally a self-limited disorder without significant morbidity. TNN resolves over a 24- to 72-hour period.

Race: No racial predilection exists.

Sex: Risk is equal in both males and females.

Age: Clinically, TTN presents as respiratory distress in full-term or near-term infants.

History: Signs of respiratory distress (eg, tachypnea, nasal flaring, grunting, retractions, cyanosis in extreme cases) become evident shortly after birth. The disorder is indeed transient, with resolution occurring usually by age 72 hours.

Physical: Physical findings include tachypnea, with variable grunting, flaring, and retracting. Extreme cases also may exhibit cyanosis.

Causes: The disorder results from delayed absorption of fetal lung fluid following delivery. TNN commonly is observed following birth by cesarean delivery because infants do not receive the thoracic compression that accompanies vaginal delivery.

- Cesarean delivery

  ο Studies utilizing lung mechanic measurements were performed on infants born by either cesarean or vaginal delivery. Milner et al noted that the mean thoracic gas volume was 32.7 mL/kg for infants born vaginally and 19.7 mL/kg for infants born via cesarean delivery. Importantly, chest circumferences were the same. Milner et al noted that the infants born via cesarean delivery had higher volumes of interstitial and alveolar fluid compared to those born vaginally, even though the overall thoracic volumes were within the normal range.

  ο Epinephrine release during labor has an effect on fetal lung fluid. In the face of elevated epinephrine levels, the chloride pump responsible for lung liquid secretion is inhibited, and the sodium channels that absorb liquid are stimulated. As a result, net movement of fluid from the lung into the interstitium occurs. Therefore, in the lack of this normal surge in counter-regulatory hormones in the infant, excursion of pulmonary fluid is limited.

- Maternal asthma and smoking

  ο In a recent study, Demissie et al performed a historical cohort analysis on singleton live deliveries in New Jersey hospitals during 1989-1992. After controlling for confounding effects of important variables, infants of mothers with asthma were more likely to exhibit TTN than infants of mothers in the control group.

  ο Schatz et al studied a group of 294 pregnant women with asthma and a group of 294 pregnant women without asthma with normal pulmonary function test results. The groups of women were matched for age and smoking status. TTN was found in 11 infants (3.7%) of the women with asthma and in 1 infant (0.3%) of the women from the control group. No significant differences between asthmatic and matched control subjects in other TTN risk factors were observed.

- Prolonged labor

  ο Other recent studies have found that obstetric histories of mothers of newborns with TTN were characterized by longer labor intervals and a higher incidence of failure to progress in labor leading to cesarean delivery.

  ο Excessive maternal sedation, perinatal asphyxia, and elective cesarean delivery without preceding labor are not frequently associated with TTN.

Pneumomediastinum
Pneumonia
Pneumothorax
Respiratory Distress Syndrome
Respiratory Failure
Other Problems to be Considered:

Cerebral hyperventilation
Metabolic acidosis

Lab Studies:

- Arterial blood gas

  o   An ABG is important to ascertain the degree of gas exchange and acid-base balance.

  o   Consider an intraarterial catheter if the infant's inspired fraction of oxygen exceeds 40%.

  o   Hypoventilation is very uncommon, and partial carbon dioxide tensions are usually low because of the tachypnea. However, a rising carbon dioxide tension in an infant with tachypnea may be a sign of fatigue and impending respiratory failure.

- Pulse oximetry

  o   Continuously monitor infants by pulse oximetry for assessment of oxygenation.

  o   Pulse oximetry allows the clinician to adjust the level of oxygen support needed to maintain appropriate saturation.

Imaging Studies:

- Chest x-ray

  o   The chest x-ray (CXR) is the diagnostic standard for TTN.

  o   The characteristic findings are prominent perihilar streaking, which correlates with the engorgement of the lymphatic system with retained lung fluid, and fluid in the fissures. Patchy infiltrates also have been described.

  o   A follow-up CXR may be necessary if the clinical history suggests meconium aspiration syndrome or neonatal pneumonia. In these cases, the CXR shows persistent infiltrates. Abnormalities resolve by 72 hours of life in cases of TTN.

Medical Care:

- Medical care is supportive. As the retained lung fluid is absorbed by the infant's lymphatic system, the pulmonary status improves.

- Supportive care includes intravenous fluids and gavage feedings (until the respiratory rate has decreased enough to allow oral feedings). Supplemental oxygen to maintain adequate arterial oxygen saturation, maintenance of thermoneutrality, and an environment of minimal stimulation are the therapies necessary for these infants.

- As TTN resolves, the infant's tachypnea improves, oxygen requirement decreases, and the CXR shows resolution of the perihilar streaking.

- Infants with TTN may have signs that last from a few hours to several days. Rarely, an infant may develop a worsening picture of respiratory distress after several days. This may require more aggressive support including the use of continuous positive airway pressure (CPAP) by nasal prongs or endotracheal tube, or mechanical ventilation.

Consultations: Infants with TTN occasionally may require consultation by a neonatologist. Consider this consultation if the fraction of inspired oxygen exceeds 40%, if metabolic or respiratory acidosis is present, if CPAP or mechanical ventilation is required, if the infant begins to display fatigue (periodic breathing or apnea), or if the infant fails to improve by age 48-72 hours.

Diet: Infants with TTN generally are supported by intravenous fluids or gavage feedings. Oral feedings are withheld until the respiratory rate is consistently normal (<60 bpm).

The use of medications for TTN is minimal. Aside from the use of antibiotics for a period of 36-48 hours after birth until sepsis has been ruled out, no further pharmacotherapy generally is prescribed. Diuretics have not been shown to be beneficial.

Drug Category: *Antibiotics* -- Used when sepsis is clinically suggested. Antibiotics generally consist of a penicillin (usually ampicillin) and an aminoglycoside (usually gentamicin) or a cephalosporin (usually cefotaxime). Choices are based on local flora and antibiotic sensitivities.

Drug Name	Ampicillin (Omnipen-N) -- A penicillin antibiotic with activity against gram-positive and some gram-negative bacteria. Ampicillin binds to penicillin-binding proteins (PBPs), inhibiting bacterial cell wall growth.
Pediatric Dose	<2000 g: 50 mg/kg/d IV/IM divided q12h >2000 g: 75 mg/kg/d IV/IM divided q8h
Contraindications	Documented hypersensitivity
Interactions	Probenecid increases the serum concentration of ampicillin
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Dose adjustments may be necessary in patients diagnosed with renal failure

Drug Name	Gentamicin (Garamycin) -- Provides gram-negative aerobic coverage. Gentamicin also provides synergistic activity with penicillins against gram-positive bacteria including enterococcus. Gentamicin inhibits protein synthesis by irreversibly binding to bacterial 30S and 50S ribosomes.
Pediatric Dose	<29 weeks' gestational age: 2.5 mg/kg/dose IV/IM q24h 30-36 weeks' gestational age: 3 mg/kg/dose IV/IM q24h >37 weeks' gestational age: 2.5 mg/kg/dose IV/IM q12h
Contraindications	Documented hypersensitivity
Interactions	Amphotericin B, cyclosporine, cephalosporins, and furosemide may increase the risk of renal toxicity
Pregnancy	D - Unsafe in pregnancy
Precautions	Nephrotoxicity and ototoxicity may be associated with prolonged elevated trough concentrations; monitor levels to minimize the risk of toxicity and to optimize therapy

FOLLOW-UP Section 8 of 11

Further Inpatient Care:

- After resolution of TNN, focus further inpatient care on routine newborn management.

- No further medical therapy concerning the infant's pulmonary function is required.

Transfer:

- When managing an infant with TTN, it is important to have appropriately trained support staff. Infants with TTN and pneumonia or meconium aspiration may have similar clinical presentations. Therefore, staff members must be competent in recognizing worsening respiratory distress or impending failure and must be able to appropriately resuscitate the infant.

- Transfer generally is indicated by the need for a higher level of observation and/or care.

Complications:

- Few potential complications exist.

- Gross et al noted a population of 55 pregnancies after which newborns developed TTN compared to 355 pregnancies after which respiratory distress did not occur. Neonatal complications and procedures often associated with prematurity were found to be significantly increased in the infants who developed TTN. Therefore, potential complications can occur in these patients. Carefully monitor infants for signs of worsening respiratory distress.

Prognosis:

- Prognosis is excellent.

- Asthma: Schaubel et al looked at neonatal characteristics as risk factors for preschool asthma. The study demonstrated that infants with TTN are at an increased risk for hospitalization from asthma during the preschool years.

Patient Education: Inform parents that TTN is usually a self-limited disorder and is not life threatening.

Medical/Legal Pitfalls: The major pitfall is assuming that respiratory distress is solely TTN and not a more serious disorder, such as sepsis/pneumonia, persistent pulmonary hypertension, or cyanotic congenital heart disease.

Picture 1. A supine anteroposterior chest radiograph of an infant with transient tachypnea of the newborn (TTN). Note the reticular appearance of the film with mild cardiomegaly and obvious interstitial fluid.
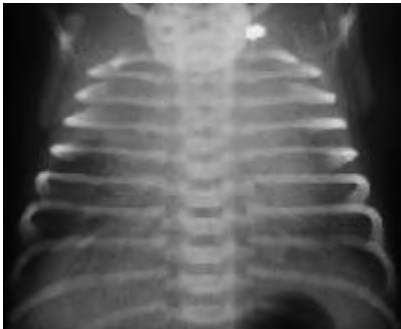
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Transient Tachypnea of the Newborn excerpt

Transport of the Critically Ill Newborn

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INTRODUCTION AND HISTORICAL PERSPECTIVE	Section 2 of 11

Critically ill neonates are often born in specialized centers either because of prenatal detection of a problem or because the referral center routinely delivers care to at-risk perinatal populations. These babies are called inborn. A large number of outborn neonates, however, require emergent transfer to a tertiary care center, often because of medical, surgical, or rapidly emerging postpartum problems. Studies show that shortened interfacility transport time leads to improved outcomes for the smallest and most critically ill neonates.

Medical transport of this high-risk and fragile population requires skilled personnel and specialized equipment. Ideally, neonatal transport teams form a single component associated with a larger system of perinatal care composed of a tertiary care neonatal intensive care unit (NICU), the perinatal care unit, the cadres of medical and surgical pediatric subspecialists, and the neonatal outreach program. This chapter reviews the issues related to transport of this specialized population, including personnel, medical control, equipment, policy development, and transport administration. Discussion of the medical and surgical problems of the newborn are discussed in other articles.

Because the outcome of an outborn neonate with major medical or surgical problems (including extreme prematurity) remains worse than for an inborn infant, primary emphasis should always remain on prenatal diagnosis and subsequent maternal transfer whenever possible. Despite advanced training and technology, mothers usually make the best transport incubators.

Development of neonatal transport, perinatal regionalization, and neonatal intensive care unit referral centers

The emergence of skills to care for ill or premature newborns often is traced to exhibits of premature infant care at public expositions, such as the 1933 World's Fair in Chicago. These exhibits preceded the emergence of neonatal intensive care units and the transport of ill infants.

After establishment of centers to care for ill neonates, attention shifted to caring for infants who were either born at home or in inadequately equipped centers. Transport of outborn neonates to these centers initially utilized clever adaptations of incubators otherwise carried in an automobile. Butterfield has written an excellent and personal review of these beginnings.

The next evolution in transport developed from the lessons in aeromedical transport of the wounded in World War II, Korea, and Vietnam. The need for rapid evacuation of trauma patients from the scene of accidents led to the development of a system of trauma centers and aeromedical transport services.

In 1976, the Committee on Perinatal Health, sponsored by the March of Dimes, proposed a system for regionalized perinatal care and defined three levels of hospital care, which served throughout the 1970s and 1980s as a national model for the rapid development of neonatal referral centers. This model required the development of a neonatal transport system, which was associated with a significant reduction in the US neonatal mortality rate.

Because neonatal transport was required for NICU referral centers and because pediatric transports to pediatric intensive care units (PICUs) were increasing, the American Academy of Pediatrics (AAP) formed a Task Force on Interhospital Transport and subsequently developed guidelines.

Appearance of a variety of commercial products for care of the neonatal patient in the transport environment paralleled the proliferation of neonatal transport programs.

ADMINISTRATIVE ASPECTS OF NEONATAL TRANSPORT SERVICES	Section 3 of 11

Program director

As health care financing becomes increasingly problematic, pressure increases to achieve efficiency. However, transport scheduling is an intrinsically unpredictable and inefficient process, especially for a low-volume/high-acuity specialty team such as that required for the neonatal population.

A committed hospital administration should provide an experienced manager or program director for a transport service and encourage communication between the hospital administration, the transport team personnel, and the medical director.

Medical control physician

The on-call medical control physician is immediately available to provide advice before and during transport. The medical control physician has the appropriate knowledge to manage critically ill neonatal patients and must be familiar with the capabilities and procedures of the neonatal transport team.

Medical director

The neonatal transport team medical director, preferably a licensed physician who is familiar with air and ground emergency medical services, supervises and evaluates the quality of medical care. Ideally, this physician is a board-certified subspecialist in neonatal-perinatal medicine. However, as an alternative, an adult-oriented medical director of a transport team may use specialty physicians as consultants.

The medical director should be actively involved in (1) selection of appropriate personnel, (2) continuing team education and training, (3) development and review of policies, (4) the quality management program, and (5) selection, orientation, and supervision of medical control physicians.

Communications

To initiate the transport process, a mechanism is needed for contacting the appropriate medical control physician immediately upon receiving a transport request. The medical control physician decides whether transfer is appropriate, discusses stabilization issues with the referring physician, and, in some cases, authorizes or recommends a mode of transport. Additional communication occurs between referring physicians, accepting physicians, medical control physicians, transport team members, and pilots or drivers.

Ideally, a dedicated communications center operates 24 hours a day, 7 days a week to allow for constant communication during the triage process and transport. A dedicated communications center is especially valuable for rotor-wing aircraft transport or for teams with multiple ground units. Several viable models are available for communications but in order to increase efficiency, the trend is to consolidate communications centers and share resources.

Medical transport systems appropriately focus on rapid arrival of the transport team and medical direction of the team upon arrival at bedside. However, prior to the arrival of the transport team, medical direction and advice to the stabilizing personnel at the referring hospital may be invaluable.

Upon being informed of a transfer request, the medical control physician is put in contact with the referring physician to discuss the case. Such discussion is essential to allow for adequate preparation of the accepting hospital and transport team and to provide direction on pretransport stabilization prior to the arrival of the transport team. Communication of vital signs, laboratory values, and previous therapies allows for effective comanagement of the patient.

Procedures and protocols

The Commission on Accreditation of Medical Transport Systems (CAMTS) develops standards that address patient care and safety in the transport environment and is an excellent resource for the transport industry. CAMTS strives to maintain accreditation standards in accordance with current medical research and transport industry developments and publishes these standards in order to define quality issues.

The medical director is responsible for the development and supervision of transport protocols. The process involves the input of the medical control physicians, transport team personnel, and any applicable subspecialty services (eg, surgery, cardiology), who are encouraged to create a wide spectrum of protocols that cover the most common clinical scenarios encountered in this neonatal population, especially those requiring immediate recognition and action.

Protocols usually include care guidelines for transport team configurations that require a physician (see Neonatal Team Configuration). However, with the more common team configurations the protocols may serve as standing orders to allow the transport team personnel to expedite the care of a critically ill neonate in the absence of direct physician input. The medical director should review protocols annually and distribute them to all medical personnel involved in the transport process.

Skills required for neonatal transport

Airway

- Most critically ill neonates who require transfer to an NICU have existing or impending respiratory failure, either as a primary diagnosis or secondary to their primary disease process. For this reason, transport teams commonly include respiratory therapists.

- Team competence in neonatal airway management is imperative. The team should be capable of (1) recognizing impending respiratory failure, (2) performing effective bag-valve-mask ventilation, (3) performing atraumatic intubation with appropriate endotracheal tubes, (4) instillation of artificial surfactant, and (4) management of ventilator settings.

Intravenous access

- Nearly all ill neonates require peripheral or central intravascular access during transport. The team must have the necessary equipment and skills for routinely and reliably securing IV access in these tiny and difficult patients.

Advanced procedures

- Staff competency also is required in percutaneous needle aspiration of the chest, chest tube insertion, umbilical catheter insertion, and intraosseous vascular access.

Other important skills

- Independent thought and action.

- Extensive experience in the rapid performance of advanced clinical skills under less than ideal conditions.

- Experience in other areas of patient care.

Neonatal team

Paramedics, nurses, respiratory therapists, nurse practitioners, and physicians have the role of rapidly stabilizing critically ill newborn patients for immediate transfer.

A number of transport team configurations are used for neonatal transport. Traditionally, adult advanced life support (ALS) ground transport units are staffed by an emergency medical technician (EMT) and a paramedic (EMT-P), using the military transport configuration. A registered nurse (RN) working with another nurse, a paramedic, a respiratory therapist, or a physician, often comprise a critical care transport team. The most common crew configuration is an RN and EMT-P. The 2-RN configuration is the second most common. In many programs, a respiratory therapist (RT) is the second crew member because of airway management expertise. Each kind of specialist, however, has advantages and disadvantages. These attributes, in reference to neonatal transport, are listed in Table 1.

Within a perinatal system, the transport team should be regarded as serving several other functions, including on-site teaching, communicating strengths and weaknesses of the referral hospital to the outreach personnel at the tertiary center, and public relations.

Table 1. Advantages and disadvantages of potential transport team staff. Data are used to determine crew configuration for a neonatal transport team.

	Availability	Knowledge Base	Airway Skills	Versatility	Costs
Paramedic (EMT-P)	Good	Low	Fair	Low	Low
Nurse (RN)	Good	Fair	Low	Fair	High
Respiratory therapist (RT)	Good	Fair	Excellent	Good	Moderate
Nurse practitioner (NNP)	Low	Good	Good	High	High
Physician resident (MD)	Fair	High	Good	Good	Moderate
Physician attending (MD)	Low	Excellent	Variable	High	Very high

Team recruitment, training, and orientation

Team configuration is determined largely by local availability of personnel, patient characteristics, and tradition. Little published data is available on these issues to assist in the decision process.

Applicants should be informed of any mandatory outreach educational roles and expectations as well as any public relations aspects of the job. Potential team members must be informed of the precise job requirements, especially if additional training, such as EMT or paramedic certification, is required. Continuing education, which includes practice labs, should be undergone at least annually, recognizing that in the field some skills are rarely used.

Cross-training issues

Schedule a structured series of skill sessions to ensure competency. Sessions may occur in the clinical realm (ie, neonatal intensive care units, delivery room suites, or operating room suites) or in practice labs with models, animals, or cadaveric material.

Often the critically ill neonatal patient cannot be adequately stabilized and managed in an outlying referring hospital, leading to time pressures in arranging for transport team arrival. One alternative to long delays and increasing costs is to use seasoned cross-trained personnel, including cross-trained NICU personnel, to perform transports. The feasibility of this alternative is dependent on adequate planning and training and a carefully defined triage mechanism. Since personnel cross-training necessitates more training, demands should be carefully evaluated.

Ground ambulance

This mode is employed for relatively short-distance transport (up to 25 miles) when surface transportation is more probable than air transport.

Advantages

- Lowest transport costs
- Relative immunity to weather (Table 2 summarizes weather and other considerations for each mode of transport.)
- Roomy interior space allowing for improved patient access (See Image 1)

Disadvantages

- Slowest mode of transport
- Necessity of physically securing neonatal incubator inside the transport vehicle and ensuring that neonatal-specific equipment is available if the ambulance is not dedicated to neonatal transport

Rotor-wing aircraft (helicopter) transport

This mode is used for medium-distance transfers (up to 150 miles).

Advantages

- Speed and versatility
- Rapid departure and arrival of the team to the patient, decreased out-of-hospital time space

Disadvantages

- Need for a landing zone in close proximity to the hospital
- Likelihood of grounding due to adverse weather conditions
- Higher costs
- Restricted patient access during flight
- Compromised patient assessment and/or interventions during flight due to high environmental noise and vibration levels (See Image 2)

Fixed-wing aircraft (airplane) transport

This mode's defined use is for long-distance transportation (typically farther than 150 miles).

Advantages

- Efficient fuel costs over long distances
- Interior space allowed for patient transport is adequate
- Reasonable access to patient during flight

Disadvantages

- Requires an airport for landing and takeoff operations(Image 3)
- Increased time with subsequent team ground transfer

Table 2. A comparison of the advantages and disadvantages of various modes of transport used in transport of the critically ill neonate.

	Ground Ambulance	Rotor-wing Aircraft	Fixed-wing Aircraft
Departure times	Excellent	Excellent	Poor to fair
Arrival times	Fair to poor	Excellent	Good
Out-of-hospital time	Poor	Excellent	Fair to excellent
Patient accessibility	Good	Poor	Fair
Weather issues	Excellent	Poor	Fair to good
Cost	Low	High	High

Method one

The transport team assumes patient care and rapidly loads the neonatal patient for transport, thereby reducing out-of-hospital time and maximizing access to NICU management. For neonates with rapidly progressing disease processes, this reduces the potential for progression of the disease prior to arrival. Method 1 more often is used with less experienced team personnel and/or with rotor-wing transfer. This approach leads to shorter out-of-hospital intervals.

Method two

The neonate is maximally stabilized prior to departure from the referring hospital. This minimizes the need for interventions en route to the NICU in the relatively uncontrolled transport environment but results in longer stabilization times and may lead to more time for disease progression. Method 2 more often is used with transport teams incorporating physicians and/or with longer ground or fixed-wing transports.

Combination method

Each neonatal patient undergoes a careful assessment (eg, vital signs), a rapid blood glucose determination, and establishment of intravenous access. Since respiratory distress is such a frequent problem with a large proportion of critically ill neonates, special effort should be paid to assessing the airway and the competence of oxygenation and ventilation.

Following this initial rapid assessment, most neonates who are not stable or are deteriorating rapidly are stabilized quickly and then expediently transferred. Alternatively, some clinical situations require more extensive and immediate interventions in the field, including artificial surfactant administration for extreme respiratory failure, and evacuation of a pneumothorax, among others.

Thermal control

The critically ill neonate often is extremely premature with a very low birthweight (less than 1 kg) and markedly immature skin that is prone to massive insensible fluid losses. The low fat stores render this patient vulnerable to hypothermia.

In the NICU, infants are managed with specially designed neonatal radiant warmers or incubators, which decrease and/or compensate for these fluid and heat losses. During transport, thermal control becomes very difficult due to the less controlled environment, cold weather, high winds, high elevations, travel over a long period of time, and less efficient equipment.

A hypothermic neonate should be rewarmed in a highly controlled fashion (approximately 1°C/h), which is extremely difficult to accomplish during transport. Rapid rewarming of hypothermic neonates is associated with increased mortality and increased severe morbidities.

Ventilation and airway management

In those patients who require positive pressure ventilatory assistance, the first level of intervention is bag-valve-mask ventilation, although it is unacceptable for prolonged airway management during transport.

Intubation in the neonate requires an uncuffed endotracheal tube of appropriate size, varying from 2.5-4.0 French external diameter. The neonatal transport team must know how to perform rapid, atraumatic intubation, with subsequent tube positioning and securing.

Positive pressure ventilation can be accomplished by hand-bag ventilation for transports of short duration, but transport ventilators are generally utilized for most transports. Transport ventilators often are different from those models used in the receiving NICU; therefore, the transport personnel must be experienced in the setup and use of the ventilator. Due to limitations in current technology, transport ventilators currently are not capable of patient synchronization, patient-triggered ventilation modes, heated ventilation circuits, or high-frequency ventilation modes.

Monitoring issues

Routine NICU care involves patient monitoring with cardiorespiratory monitors that utilize adhesive chest leads and pulse oximetry monitors that utilize pulse-detecting extremity probes. Continuous monitoring of blood pressure often uses transducers that require indwelling central lines (eg, umbilical catheters). The increased vibration and electromechanical interference associated with transport environment frequently interferes with or precludes such monitoring.

The premature neonate's small size and small signals complicate electronic interference issues. These interference problems are greatest during aircraft takeoff and landing, when the crew typically is distracted by a flurry of tasks, is restrained for flight safety reasons, or may be unable to assess the patient. The highest probability of monitoring failure, therefore, occurs during the periods when the patient is most likely to become destabilized and require intervention.

Flight physiology

Increasing altitude affects physiology in a number of ways, including decreased partial pressure of gasses, expansion of trapped gas compartments (eg, pneumothorax), lowered environmental temperatures, and altered drug metabolism. Flight crew members and medical control physicians must be familiar with these concepts.

Flight team personnel also are affected by the transport environment and need to be familiar with how their own performances are altered. For example, if a flight team member with a head cold and upper airway congestion experiences a sinus squeeze upon takeoff, they need to recognize and deal with this phenomenon quickly so that patient care and team safety is not compromised.

Neonatal pharmacology issues

Neonatal patients are not simply scaled-down adults with respect to pharmacologic issues. An example of this is chloramphenicol, which, if given to an infant in a dose that is simply proportional to the infant's smaller size, will cause shock and possibly death from "gray baby syndrome," due to decreased hepatic elimination.

For hepatically eliminated drugs, such as chloramphenicol, the neonate may have either a reduced or a totally absent capacity for certain enzymatic degradation pathways. Thus, a drug that is metabolized by one enzymatic pathway in adults (eg, glucuronidation) may instead be metabolized in infants via a completely different pathway (eg, sulfation); this can result in unpredictable drug metabolism. The enzymatic processes develop in the fetal liver progressively, with more complex enzymatic processes requiring more gestational development (ontogeny of development).

Use caution when administering drugs excreted by the kidney, since the neonate, especially the premature and/or critically ill infant, initially has a decreased glomerular filtration rate and generally has decreased renal function. Prolonged dosing intervals often are used for medications with renal excretion, and serum drug levels often are required.

Quality management program

In addition to patient care issues, a quality management program assesses all aspects of the transport program, including continuous monitoring and assessment of communications, initial and continuing education, ambulance and aircraft maintenance, and operational issues, especially safety.

Quality management should be deeply imbedded into the program by beginning with a program scope of care and mission statement. Hospital administration should guide the process with the involvement of transport staff and the medical director.

Transport programs should have established patient care guidelines that are reviewed on an annual basis by the staff, management, and medical director. There should be prospective agreement on the applicable quality indicators. Industry guidelines for standards of operation and standards of care, such as those issued by the Association of Air Medical Services (AAMS) and the Commission on Accreditation of Medical Transport Systems (CAMTS), are available, and should be used. However, for many other issues the team should decide on the indicators (objective measures that are prospectively delineated and collected for analysis) and the thresholds (statistical measure of compliance on the specific indicator) for acceptable outcome or compliance. Thresholds must be attainable, realistic goals for assessing compliance and quantifying improvement.

Annual review needs to be made of the quality assurance process itself. Involving the staff in a peer review process increases the success of a quality assurance program.

Data collection

Data collection provides important information that is used in quality assurance functions, as described above. The transport team often takes on the task of data collection so that it functions as a component of a larger system of perinatal care.

Transport data are monitored to provide hospital or physician-specific topics for review by perinatal outreach programs. Referring practitioners are interested in hearing discussions on issues they perceive to be timely. Discussing recent cases and situations in their institutions is effective in outreach and continuing education efforts.

Data collection increases the efficiency of a transport service. Monitoring the hour of transport requests, length of transport time, length of time at bedside, incidence of delayed calls, and incidence of overtime is useful in altering schedules or timing of elective reverse transports.

Finally, data collection should be used increasingly for clinical or outcomes research. There is a surprising paucity of published data on neonatal transport issues and outcomes.

REVERSE TRANSPORT OF THE CONVALESCENT NEONATE — Section 9 of 11

Patient Issues

- Does the convalescing newborn's medical condition necessitate care that can be provided at the potential accepting hospital? Is the accepting hospital capable of providing the care required by the recovering neonate?
- Can the predictable future needs of the infant be met by the institution (eg, subspecialty medical or surgical consultations)?
- Have the parent(s) granted permission for the infant to be transported?
- Does the remaining estimated length-of-stay balance the costs and risks of reverse transport?
- Are there social factors that may affect the choice of convalescing hospital?
- Does the third-party payer (eg, insurance company) approve the transfer? Will the costs of the transport and subsequent hospitalization be approved by or be acceptable to the parents?
- Do the physicians and hospitals at both ends agree the transfer is in the baby's best interest?
- Will the ultimate follow-up physician provide care at the receiving hospital, thereby facilitating continuity of care?

Administration issues

- Are there adequate Level I and II nursery personnel who are sufficiently experienced in caring for the infant population?

- Are there enough Level II beds at the tertiary center?

- Is there a well-functioning working relationship between the tertiary and Level I and II hospitals relative to physicians, staff, and administration?

- What would motivate the Level I and II hospitals to participate in the perinatal system as full partners, rather than be resigned to a role such as "patient donors" or competitors to the tertiary hospital?

Team configuration issues

- The triage of personnel for a reverse transport generally is easier because the infant is more stable and his/her medical condition is known. This allows matching the transport team configuration to the infant's medical needs. For example, if the infant has stable respiratory status (ie, no oxygen requirement), then the presence of a physician or respiratory therapist is less important.

- These considerations reduce costs and maintain the availability of the primary team for incoming calls.

Picture 1. Transport of the critically ill newborn. Interior of an ambulance configured for neonatal ground transport. Two incubators are loaded; the transport incubator is in the foreground, and a second incubator is in the background. Two crew members are on board. The vehicle is a Freightliner FL60 chassis (Mt Holly, NC), configured for medical transport by Innovative Coachworks (Birmingham, Ala). Note the excellent patient access and equipment availability.

Picture 2. Transport of the critically ill newborn. Interior of a rotor aircraft (helicopter) configured for neonatal transport. A flight incubator and 2 crew members are on board. The aircraft is an MBB (Messerschmidt-Bolkow Blohn) Model BK-117A4 manufactured by American Eurocopter (Grand Prairie, Tex), reconfigured and operated by Omniflight (Dallas, Tex). Note the limited access to the incubator and equipment that highly restricts crew movements.

Picture 3. Transport of the critically ill newborn. Interior of a fixed-wing aircraft configured for neonatal transport. A flight incubator and 2 crew members are on board. The aircraft is a King Air Model 200 (Raytheon-Beech Aircraft, Witchita, Kan). Note that interior space is adequate.

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Transport of the Critically Ill Newborn excerpt