

Essentials of Neonatology

The Why Behind the What

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Introduction

As a student or resident working in a neonatal intensive care unit, it's easy to feel overwhelmed by data and the multitude of management decisions that must be made for every patient, every day. Most handbooks of neonatology attempt to ease the tasks of data analysis and clinical decision-making by presenting specific management algorithms: "if the abdomen is distended 2 cm above baseline, you should consider ordering an X-ray", or "the umbilical arterial catheter should be positioned with its tip between T6 and T10". Such advice may help you know **what** to do in a specific clinical situation, but it doesn't give you the background information needed to help you understand **why** you are ordering that X-ray or placing that line tip in a certain location.

This handbook is designed differently from most in that it attempts to provide the "why" without offering much detail about the "what". Neonatology is plagued by a relative lack of robust clinical research data that can be used to inform therapeutic decision-making at the point of care. As a consequence, there is seldom one "right" way to approach a clinical problem in neonatology. Knowledge of the underlying pathophysiology and applicable clinical research will help you to decide what way is the "right" way for you to manage a given problem. Providing that knowledge is the goal of this handbook.

The sections of this handbook correspond to various disease processes and management issues in neonatology. No attempt is made to provide a comprehensive overview of neonatal care, but an effort has been made to include the topics that mostly commonly confront the resident or student in the NICU. Each section begins with an outline of key points that provide a convenient summary if you're not inclined to read the entire section. The remainder of the section is divided into specific headings that are pertinent to the topic at hand, generally with an emphasis on newer knowledge and more controversial aspects of the topic. For those interested in further reading, a bibliography is included at the end of each section. The PDF version of this handbook uses bookmarks to flag the start of each section.

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Apnea of Prematurity

Key Points

- Apnea of prematurity is the result of developmental immaturity of respiratory control and resolves by 40-44 weeks' postmenstrual age in all infants
- Apnea of prematurity typically includes both central and obstructive components
- Severe apnea during the neonatal period may be associated with worse neurodevelopmental outcomes
- Caffeine is the preferred pharmacologic therapy for apnea of prematurity
- Nasal CPAP may improve apnea that includes an obstructive component
- Apnea of prematurity is not a risk factor for SIDS

Physiology

Apnea is formally defined as cessation of breathing lasting at least 20 seconds. Clinically, apnea is manifested in the preterm infant by an episode of decreased oxygen saturation and/or bradycardia, and evaluation of the infant during the episode may reveal a complete absence of respiratory effort (central apnea) or the presence of respiratory effort without air movement (obstructive apnea). In fact, most neonatal apnea is mixed, with both central and obstructive components.

Apnea of prematurity results from developmental immaturity of several mechanisms involved in regulating respiratory control and in maintaining patency of the upper airway. These mechanisms include chemoreceptor responses to oxygen and carbon dioxide levels, laryngeal afferent reflexes that affect respiratory drive, and regulation of pharyngeal muscle tone during sleep.

The ventilatory response to CO_2 is mainly mediated by central chemoreceptors located in the medulla and elsewhere. Whereas term neonates and adults have sustained increases in respiratory drive in response to hypercapnia, preterm infants have a blunted or absent hypercapnic respiratory response. This blunted hypercapnic response is probably not responsible for the initiation of apneic episodes but presumably prolongs such episodes by interfering with recovery. In addition, both term and preterm infants have a CO_2 apneic threshold (CO_2 level below which apnea is triggered) that is only slightly below the normal baseline pCO_2 . This finding suggests that brief periods of hyperventilation might trigger apneic episodes.

Peripheral chemoreceptors located in the carotid body are the main regulators of respiratory drive in response to hypoxia. Whereas adults demonstrate a sustained increase in respiratory drive under hypoxic conditions, preterm infants demonstrate only a brief period of hyperventilation followed by sustained respiratory depression in response to hypoxia. Conversely, there is evidence that exposure to

repeated episodes of hypoxia, such as might occur in an infant with chronic lung disease, can upregulate peripheral chemoreceptor sensitivity and result in an apneic response to a brief episode of hyperoxia.

Activation of laryngeal afferent nerve fibers in both term and preterm infants results in apnea and bradycardia. This phenomenon, known as the laryngeal chemoreflex, is exaggerated in preterm infants and may be responsible for the apnea seen in association with feeding or reflux episodes in some infants. However, the relationship of this reflex to apnea of prematurity is less clear; as discussed below, the available evidence argues against a causal role for reflux in the pathogenesis of apnea of prematurity.

Upper airway obstruction plays an important role in apnea of prematurity, and the usual site of obstruction is the pharynx. The pharynx is the most collapsible portion of the upper airway, and central regulation of pharyngeal tone is important for maintaining airway patency. Loss of central regulation of tone is most likely during active sleep states, when most apnea is thought to occur.

Epidemiology, Natural History and Outcomes

Apnea of prematurity occurs in at least 70% of babies born prior to 35 weeks of gestation. Apnea gradually resolves with advancing postnatal age, as respiratory control mechanisms mature. The duration of apnea tends to be inversely related to gestational age at birth; 20-25% of infants born at 24 weeks will continue to have apnea at 40 weeks' postmenstrual age. In all infants, apnea of prematurity resolves by about 44 weeks' postmenstrual age, and persistence of significant apnea past that age should lead to consideration of alternative explanations for the apnea.

As previously noted, apnea of prematurity is a manifestation of immature respiratory control, and there is no evidence of an underlying pathologic disorder of respiratory control in infants with apnea of prematurity. Specifically, there is no evidence of a causal relationship between apnea of prematurity and sudden infant death syndrome (SIDS).

The clinical consequences of apnea of prematurity have long been debated. It is reasonable to suppose that the intermittent episodes of hypoxia and bradycardia that accompany apnea might lead to injury in the developing brain. There is no direct evidence supporting that relationship, but recent studies have suggested that increasing severity and duration of apnea in the neonatal period may be independently associated with worse neurodevelopmental outcomes.

Treatment

Methylxanthines are the mainstay of pharmacologic treatment for apnea of prematurity. Either theophylline or caffeine can be used, but caffeine is generally preferred due to ease of dosing (once per day) and its broad therapeutic range. Adenosine is an inhibitory neuroregulator in the central nervous system, and the main mechanism of methylxanthine action is thought to be antagonism of adenosine receptors in the CNS. Clinically, methylxanthines improve respiratory function by increasing minute

ventilation, increasing CO₂ sensitivity, decreasing hypoxic depression of breathing, and improving diaphragmatic contractility. They are also weak diuretics, an effect that may help to improve lung compliance in infants with chronic lung disease.

A large multicenter trial has demonstrated that caffeine, when given to infants with apnea of prematurity, significantly decreases the duration of respiratory support and decreases the incidence of bronchopulmonary dysplasia, with no evidence of any significant adverse effects. At 18-21 months, the caffeine-treated infants had better neurodevelopmental outcomes, although that effect was no longer evident by 5 years of age.

Apnea of prematurity typically includes a component of dynamic upper airway obstruction. Nasal CPAP may help to relieve that obstruction by splinting the upper airway, and it will also promote alveolar recruitment and stabilization of lung volumes. CPAP can be provided by a number of devices, including high-flow nasal cannula, but traditional nasal CPAP provided via nasal prongs or a nasal mask is the best-studied mode of delivery.

Traditionally, gastroesophageal reflux (GER) has been implicated as an important cause of apnea of prematurity. Episodes of GER and apnea are both common events in preterm infants. However, several studies have documented the lack of an association between episodes of GER and subsequent apnea in preterm infants. Based on these data, GER should not be routinely viewed as a cause of apnea in preterm infants, and regular use of anti-reflux medications in infants with apnea is not indicated.

Most practitioners consider apnea of prematurity to be resolved when there have been no recorded events for at least 5-7 consecutive days. Some preterm infants will continue to have apnea when they are otherwise ready for discharge. Management options for these infants include continued inpatient care until the apnea resolves, discharge on caffeine therapy, discharge with an apnea monitor, or discharge on both caffeine and an apnea monitor. The option chosen will depend on the specific clinical circumstances and preferences of both physician and parent. If an infant is discharged on caffeine, most practitioners would also order an apnea monitor. The caffeine should be continued until at least 40 weeks' postmenstrual age, with continued monitoring for an additional period of time after caffeine is discontinued.

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Bilirubin

Key points

- Increased bilirubin production, decreased hepatic conjugation of bilirubin and increased enterohepatic recirculation all contribute to neonatal hyperbilirubinemia
- Bilirubin is a powerful antioxidant and low levels of bilirubin are likely beneficial
- Bilirubin circulates bound to albumin at up to a 1:1 molar ratio (8.2 mg of bilirubin per gram of albumin)
- Unbound (free) bilirubin is mainly responsible for bilirubin neurotoxicity
- Phototherapy converts unconjugated bilirubin into photoisomers (lumirubins) that can be excreted in urine and bile
- The wavelength of the light source, the distance of the light from the patient, and the surface area of skin exposed all determine the efficacy of phototherapy
- Polymorphisms in the glucuronyltransferase gene and in the organic anion transporter protein that carries bilirubin into the hepatocyte may contribute to the increased incidence of hyperbilirubinemia in certain populations. Combinations of these polymorphisms with other risk factors for jaundice, such as ABO incompatibility, may significantly increase the risk of jaundice.
- There are no clear evidence-based guidelines for the use of phototherapy in preterm infants (< 35 weeks)
- Aggressive use of phototherapy in infants weighing <750 grams at birth may be associated with increased mortality

Physiology

Bilirubin is produced by the catabolism of heme-containing proteins, mainly hemoglobin from senescent red blood cells but also myoglobin and certain enzymes. Heme breakdown takes place in cells of the reticuloendothelial system, where heme oxygenase-1 converts heme into biliverdin, producing one mole of Fe^{2+} and one mole of carbon monoxide per mole of heme metabolized. Conversion of heme into biliverdin is the rate-limiting step in bilirubin production. Biliverdin is then immediately converted by biliverdin reductase to unconjugated bilirubin. Unconjugated bilirubin circulates tightly bound to albumin up to a 1:1 molar ratio, equivalent to 8.2 mg of bilirubin per gram of albumin. Circulating bilirubin is then taken up by hepatocytes in a process mediated by an organic anion transporter protein. In the hepatocyte, a glucuronyltransferase enzyme adds one or two glucuronyl moieties to produce conjugated bilirubin, which is then excreted into bile. In the intestine, conjugated bilirubin may be converted to stercobilin or urobilin by bacterial activity and excreted in the stool. Alternatively, a

glucuronidase enzyme that is active in the brush border of the intestinal epithelial cells in the immediate newborn period may convert conjugated bilirubin back to the unconjugated form, which is then taken up by enterocytes and circulated back to the liver (enterohepatic recirculation).

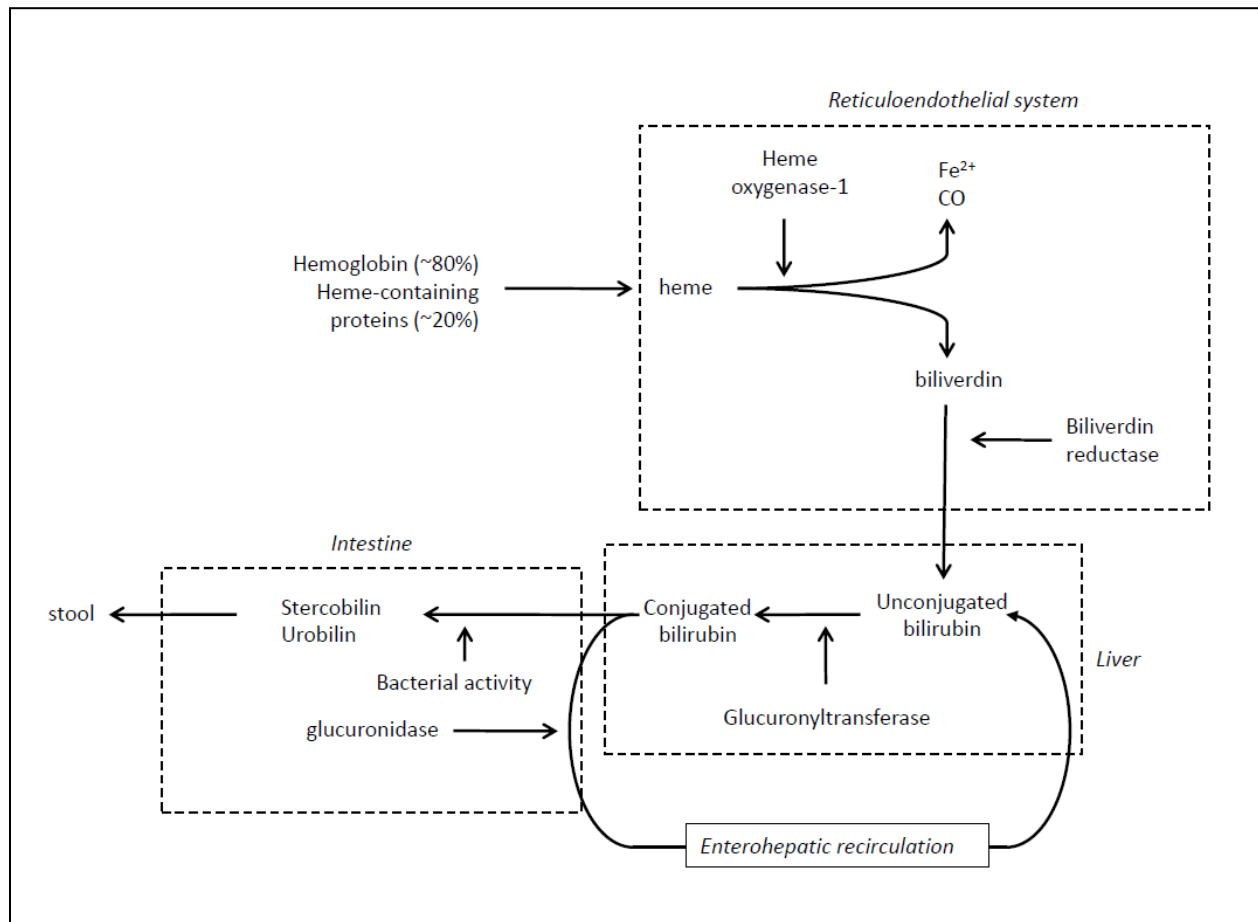


Figure 1. Overview of bilirubin metabolism

Physiologic Basis of Neonatal Hyperbilirubinemia

All neonates experience some degree of unconjugated hyperbilirubinemia during the first days of life. Fundamentally, this physiologic hyperbilirubinemia results from an imbalance between bilirubin production and excretion. Factors contributing to an increased rate of unconjugated bilirubin production in the neonate include a shortened red blood cell life span, a relatively large red blood cell mass per unit of body weight, and enhanced enterohepatic recirculation of bilirubin (see Fig. 1). At birth, the activity of the glucuronyltransferase enzyme in the liver that is responsible for conjugation of bilirubin is only about 1% of adult values and gradually increases toward adult values over the first several weeks of life. Physiologic hyperbilirubinemia is characterized by an average peak bilirubin level of 5-7 mg/dl during the first week of life. Factors such as poor breast feeding and certain genetic polymorphisms (discussed below) may exacerbate physiologic hyperbilirubinemia, but peak bilirubin levels in excess of 15-17 mg/dl usually have an identifiable pathologic cause.

Beneficial Effects of Bilirubin

Bilirubin is a very potent antioxidant and accounts for a significant portion of the antioxidant capacity of neonatal serum. Oxidation of bilirubin converts it back into its precursor molecule, biliverdin, which is then rapidly reduced back to bilirubin by biliverdin reductase. This bilirubin-biliverdin redox cycle allows a very small amount of bilirubin to have a significant amount of antioxidant capacity. Data that directly address the clinical importance of bilirubin as an antioxidant in human neonates are lacking; however, there are data documenting an inverse relationship between serum bilirubin levels and coronary artery disease as well as peripheral atherosclerotic disease in adults.

Neuropathologic Effects of Bilirubin

Both neurons and glial cells are uniquely susceptible to injury induced by unconjugated bilirubin. Unconjugated bilirubin bound to albumin does not cross the blood-brain barrier to any significant degree, but free (unbound) unconjugated bilirubin can cross the blood-brain barrier, and conditions that disrupt the blood-brain barrier, such as sepsis or acidosis, may result in greater exposure of neural cells to bilirubin. For reasons that are not well understood, certain regions of the brain, including the basal ganglia, brainstem nuclei, cerebellum, and hippocampus, are particularly susceptible to the toxic effects of bilirubin.

The cellular and molecular mechanisms of bilirubin-induced neurologic injury are not well understood. Data from animal studies and *in vitro* work have revealed a variety of toxic effects of bilirubin, including: alteration of dendritic development in neurons; alteration of membrane dynamic properties; increase in extracellular levels of glutamate, an excitotoxic neurotransmitter that leads to increased neural apoptosis; activation of inflammatory pathways in glial cells; and toxic effects on oligodendroglial cells, leading to altered myelination. Many of these effects are enhanced in more immature nerve cells, a finding that may explain the neonate's unique susceptibility to bilirubin-induced neurologic injury.

Clinically, the acute effects of bilirubin neurotoxicity include lethargy, hypotonia and poor feeding. Later on, a high-pitched cry may emerge and the infant may become hypertonic, with opisthotonic posturing. Abnormalities of brainstem auditory evoked responses are also seen. There is evidence that many of these acute clinical manifestations, particularly the abnormal auditory responses, are reversible with prompt reduction of the bilirubin level.

The chronic form of bilirubin encephalopathy, or kernicterus, results from irreversible bilirubin-induced neural injury and is characterized by chorioathetoid cerebral palsy, sensorineural hearing loss, paralysis of upward gaze, and sometimes cognitive handicaps. The pathologic correlate of kernicterus is bilirubin staining of the basal ganglia, cerebellum, hippocampus and brainstem nuclei seen on autopsy.

Development of bilirubin neurotoxicity is dependent on the level of bilirubin, particularly the unbound, or free, fraction; permeability of the blood-brain barrier; and the duration of exposure to elevated levels of bilirubin. Although bilirubin neurotoxicity becomes more frequent at total bilirubin levels > 20 in

infants with hemolytic disease, the correlation between peak bilirubin level and neurotoxicity is much weaker for otherwise healthy, full-term infants without hemolysis.

Phototherapy

The concept of phototherapy was initially developed at Rochford General Hospital in Britain in the mid-1950's, when nurses there noted that jaundiced infants appeared less yellow following exposure to sunlight. Subsequently, a variety of clinical trials done mainly in the 1960s and 1970s established the efficacy of phototherapy in reducing the need for exchange transfusion.

Phototherapy works by acting on bilirubin located in the dermal and subdermal tissues. When light at a wavelength of approximately 460 nm (in the blue spectrum) impacts bilirubin, the molecule can undergo one of several photoisomerization or photooxidation reactions. The main photoisomer produced, lumirubin, is relatively water-soluble and can be directly excreted in the urine or bile without conjugation. The photooxidation products are also water-soluble and can be excreted in urine. Lumirubin formation is very rapid and is thought to be mainly responsible for the efficacy of phototherapy.

Factors influencing the efficacy of phototherapy include the spectrum and strength of the light source, the distance of the light source from the skin surface, and the amount of skin surface area exposed to light. The spectral irradiance is a measure of the intensity of light exposure in the 460-490 nm spectrum and is expressed in $\mu\text{W}/\text{cm}^2/\text{nm}$. Spectral irradiance is commonly measured with a hand-held radiometer. Studies have shown that a spectral irradiance of at least 30 is required for optimal efficacy of phototherapy. Spectral power, defined as the spectral irradiance multiplied by the amount of skin surface area exposed, cannot be directly measured but is the ultimate determinant of phototherapy efficacy.

Exchange transfusion

The technique of exchange transfusion was developed in the late 1940s, prior to the advent of phototherapy, as a means of reducing the incidence of kernicterus in infants with hemolytic disease secondary to Rh isoimmunization. Exchange transfusions are uncommonly performed today but remain the ultimate treatment for severe hyperbilirubinemia when phototherapy is not adequately effective or when immediate reduction of the bilirubin level is necessary.

Exchange transfusions are performed mainly in infants with active immune-mediated hemolysis. In those infants, the exchange transfusion removes bilirubin but, more importantly, eliminates sensitized red blood cells that would otherwise be destroyed and also eliminates some of the maternally-acquired antibody that is responsible for the hemolysis.

Exchange transfusions are most commonly performed using a special umbilical venous catheter with multiple side-holes suitable for withdrawing and infusing blood but can also be performed using an

arterial catheter to withdraw blood and a venous catheter to infuse. An amount of blood equal to twice the infant's blood volume, or 160-200 ml/kg, is exchanged in small aliquots, usually of 10 ml for full-term infants. The whole blood used for the exchange is typically O-negative packed red cells reconstituted in AB-positive plasma. Complications of exchange transfusions are uncommon in experienced hands but can include thromboembolic events, air embolism, infection, and electrolyte imbalances. All infants who undergo an exchange transfusion are thrombocytopenic following the procedure, due to removal of platelets, but this is not typically of clinical significance.

Management Guidelines

The AAP has published a comprehensive set of guidelines for the management of hyperbilirubinemia in neonates > 34 weeks of gestation. Highlights of these guidelines include:

- The risk for significant hyperbilirubinemia should be assessed prior to discharge for all infants, either using clinical risk factors or by measuring the transcutaneous or serum bilirubin level. Bilirubin levels can be plotted on the Bhutani nomogram to assess subsequent risk for developing significant hyperbilirubinemia.
- A nomogram based on postnatal age, total serum bilirubin level, and risk category defines thresholds for initiating phototherapy. After 4 days of age, term infants who do not have hemolytic disease and are otherwise well do not require phototherapy until their bilirubin level exceeds 20; that threshold becomes progressively lower for infants with risk factors and who are younger.
- Phototherapy should always be intensive, defined as a spectral irradiance of at least 30 $\mu\text{W}/\text{cm}^2/\text{nm}$.
- A separate nomogram, based on postnatal age, bilirubin level and risk category defines thresholds for performing an exchange transfusion. The exchange transfusion level for term infants without hemolysis or other risk factors who are at least 4 days of age is 25 mg/dl.
- An initial trial of intensive phototherapy is recommended for infants who present with bilirubin levels at or near the exchange transfusion level. Exceptions include infants with signs of acute bilirubin encephalopathy and infants with bilirubin levels > 5 mg/dl above the exchange threshold; those infants should have immediate exchange transfusion.

An online tool available at www.bilitool.org uses the nomograms contained in these guidelines to provide specific management recommendations based on the bilirubin level, patient age and risk category.

Appropriate thresholds for the initiation of phototherapy and performance of exchange transfusions are not well defined for premature infants < 35 weeks of gestation. Some practitioners begin phototherapy when the bilirubin level (mg/dl) is greater than the weight in kilograms multiplied by 5. While this rule of thumb is a fair approximation of various published expert opinions, it is not supported by any clinical evidence. Phototherapy is probably not effective or necessary when the serum bilirubin level is < 5, regardless of weight or gestational age. In a recent randomized trial of phototherapy in extremely low

birthweight infants, aggressive phototherapy, defined as phototherapy started whenever the bilirubin level was > 5 -7, was compared to conservative phototherapy, started at a bilirubin level of 8-10. Aggressive phototherapy did reduce rates of neurodevelopmental impairment but was associated with a higher mortality rate in the smallest infants (those weighing 501-750 grams at birth). Given these results, the optimal use of phototherapy in extremely low birthweight infants remains uncertain, but aggressive phototherapy should be used with caution in the smallest infants.

Genetics of Hyperbilirubinemia

Family studies have suggested that genetic effects are responsible for many cases of hyperbilirubinemia that occur in the absence of apparent risk factors such as hemolysis or prematurity. Polymorphisms or gene mutations in the glucuronyltransferase gene promoter, in the gene itself, and in an organic anion transporter protein involved in bringing unconjugated bilirubin into the hepatocyte have all been described as potential causes of hyperbilirubinemia.

Gilbert syndrome is a well-known condition associated with mild jaundice in adults at times of physiologic stress. Gilbert syndrome is caused by a polymorphism in the glucuronyltransferase gene promoter. Normally, the promoter contains a region with 6 TA repeats, but in Gilbert syndrome, there are one or two extra TA repeats. These extra repeats reduce gene expression by about 70% in homozygous individuals. The Gilbert genotype does not seem to increase the risk of neonatal jaundice by itself, but infants with the Gilbert genotype who also have other risk factors, including G6PD deficiency and ABO incompatibility, are at higher risk for significant hyperbilirubinemia.

Crigler-Najjar syndrome, types I and II, are rare but well-described conditions resulting in significant and prolonged neonatal hyperbilirubinemia. CN-I, inherited in an autosomal recessive fashion, results from a nonsense mutation in the glucuronyltransferase gene that leads to production of an inactive enzyme. More than 30 different mutations have been identified in CN-I. CN-II, a milder form of the disease, results mainly from missense mutations in the glucuronyltransferase gene that lead to production of partially active enzyme.

Several polymorphisms in the coding region of the glucuronyltransferase gene that increase the risk of neonatal hyperbilirubinemia have also been described. Many of these polymorphisms are more common in Asian populations and may combine with other risk factors to further increase the risk of jaundice.

An organic anion transporter protein, SLCO1B1, is thought to play a role in uptake of unconjugated bilirubin by hepatocytes. A variant allele of this gene has been described as a cause of increased hyperbilirubinemia risk in Taiwanese newborns, but not in other populations.

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Hypotension

Key Points

- There is no generally accepted numeric definition of hypotension in term or preterm infants
- Systemic perfusion (capillary refill, urine output, acid-base status) should be carefully assessed before undertaking treatment of hypotension
- Treatment of hypotension has not been shown to improve any neonatal outcome
- Volume expansion is not helpful except in cases of documented blood loss
- In neonates, inotropes mainly act by increasing vascular resistance (afterload)
- Steroids increase blood pressure largely by increasing adrenergic receptor expression

Physiology and Definitions of Hypotension

Blood pressure is affected by cardiac output and systemic vascular resistance, or afterload. Cardiac output in turn is affected by intravascular volume status, or preload, and myocardial contractility. Animal data suggest that the baseline cardiac contractility in the newborn is already at near-maximal levels and, except in specific pathologic states, is unlikely to respond to cardiac inotropes or to volume loading. Increases in afterload may cause some increase systemic blood pressure, but excessive increases in afterload may worsen systemic perfusion given the infant's inability to further increase cardiac contractility.

Well-defined and robust normative data for blood pressures in newborn infants, and particularly in premature newborns, do not exist, although several studies have attempted to define such norms. One commonly used rule of thumb is that the mean blood pressure should be equal to or greater than the gestational age in weeks, but that guideline is not supported by any data. Blood pressures do tend to vary directly with gestational age, and blood pressures spontaneously increase through the first hours and days of life. There are also no reliable data that establish a relationship between a specific minimum blood pressure and subsequent neonatal morbidity or mortality. In light of these considerations, most experts would suggest that a single number not be used to define hypotension in the neonate. Rather, in the infant with suspected hypotension, systemic perfusion should be assessed, and if systemic perfusion is felt to be adequate, then the infant can be managed expectantly. Clinical tools for assessing systemic perfusion include capillary refill, urine output, acid-base status, and lactate levels.

Treatment Options

Treatments aimed at increasing the blood pressure are generally indicated in hypotensive infants with evidence of impaired systemic perfusion, although there is no evidence that such treatment improves outcome. Treatments used include volume expansion, inotropic support, corticosteroids, and vasopressin.

Volume expansion is appropriate in the rare infant with clinically apparent blood loss, such as might occur in a twin-twin transfusion or perinatal hemorrhage secondary to placenta previa, abruption or vasa previa. Otherwise, however, volume depletion is unlikely to play a significant role in most cases of neonatal hypotension. Furthermore, there is evidence that aggressive volume expansion in the preterm infant may be associated with an increased risk of neurologic morbidity, bronchopulmonary dysplasia and even mortality. Therefore, the routine use of fluid boluses to treat hypotension in neonates is not recommended except in cases of documented hypovolemia.

Inotropic support may be provided by dopamine, dobutamine, or epinephrine infusion. These catecholamines all act on the α and β -adrenergic receptors in the cardiovascular system. Adrenergic receptors are present in the myocardium, with β receptors being quite plentiful in the term infant, but stimulation of these receptors has little effect on myocardial contractility, inasmuch as contractility is already near maximum at baseline. Stimulation of peripheral α -1 receptors causes vasoconstriction that is mainly responsible for the increase in blood pressure seen with catecholamine infusion. Among these three agents, epinephrine causes the most widespread adrenergic receptor activation and may have the greatest effect on blood pressure. Dobutamine may have a positive inotropic effect but does not typically raise the blood pressure due to its vasodilatory effect resulting from β -2 receptor activation. Dopamine can cause effective vasoconstriction and blood pressure elevation; however, it also acts on dopaminergic receptors in parts of the hypothalamus and pituitary and can disrupt production of various hormones, including thyrotropin-releasing hormone. It should also be noted that the renal vasodilatory effect of low-dose dopamine that occurs in adults is probably not present in newborns.

Corticosteroids clearly cause blood pressure elevation in neonates; the two most widely studied are dexamethasone and hydrocortisone. Hydrocortisone is generally preferred for blood pressure management due to a perceived lack of side effects. Many premature neonates, particularly those who are sick or stressed, are thought to have relative adrenal insufficiency, and steroid treatment directly addresses this. Steroids up-regulate adrenergic receptor expression, an effect thought to be mainly responsible for their cardiovascular effects. Steroids are frequently prescribed for treatment of neonatal hypotension refractory to catecholamine therapy and are sometimes used as a primary treatment.

Vasopressin, an endogenously released peptide hormone, has been used to treat refractory septic shock in adults. Limited case reports and case series in neonates suggest that low-dose vasopressin is also effective in infants with refractory hypotension, but the very limited published experience in neonates precludes any recommendation for routine use of vasopressin in this population. Potential side effects include hyponatremia and decreased splanchnic organ perfusion.

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Patent Ductus Arteriosus (PDA)

Key Points

- Prostaglandins play a key role in maintaining ductal patency *in utero*
- Oxygen is a potent constrictor of the ductus, and rising blood oxygen levels play an important role in bringing about initial constriction of the ductus following delivery
- There are two phases of ductal closure: an initial muscular constriction followed by vascular remodeling that produces final anatomic closure
- Increased sensitivity to prostaglandins and decreased sensitivity to the constrictor effects of oxygen help to explain the prevalence of PDA in premature infants
- The natural history of the PDA in premature infants has not been studied, and information about the causal role of the PDA in neonatal morbidity is lacking
- There is no gold standard for the diagnosis of a clinically significant PDA
- Treatment decisions are controversial and vary widely among individuals and institutions
- Surgical ligation of the PDA may increase the risk of neurodevelopmental delay independent of other factors

Physiology

The ductus arteriosus connects the descending aorta and the main pulmonary artery, allowing most of the fetal right ventricular output to bypass the high-resistance pulmonary circulation during intrauterine life. A PDA is an essential component of the fetal circulation; premature closure of the PDA *in utero* may result in fetal demise or the development of severe pulmonary artery hypertension.

Several factors contribute to ductal patency in the fetus. Vasodilatory prostaglandins, mainly PGE₂ and PGI₂, are produced by the placenta and help to maintain ductal relaxation. Ductal smooth muscle is oxygen-sensitive, and the low oxygen tensions seen in the fetus limit the potential for oxygen-induced ductal constriction. The high pulmonary arterial pressures in the fetus may also help to stent open the ductus.

At birth, both expansion of the lungs with air and exposure to oxygen lower pulmonary vascular resistance, and the intraluminal distending pressure in the ductus is reduced. Rising oxygen levels are sensed by ductal smooth muscle cells, triggering calcium influx and muscle contraction. Loss of placentally derived prostaglandins and an increase in prostaglandin clearance by the lungs decrease circulating prostaglandin levels, further contributing to ductal constriction. The net effect of all these mechanisms is a physiologic constriction of the ductus that, in the healthy term infant, produces local hypoxia of the ductal smooth muscle. Subsequent cell death and production of hypoxia-inducible

growth factors, such as transforming growth factor β and vascular endothelial growth factor, result in vascular remodeling and final anatomic closure of the ductus.

Persistence of Ductal Patency in Preterm Infants

In healthy full-term infants, functional closure of the ductus arteriosus takes place over the first 2-3 days of life, and only about 1/2000 full-term infants will have a persistent PDA. In contrast, failure of ductal closure is frequent in preterm infants; about 1/3 of very low birthweight infants (<1500 grams) will have a persistent PDA.

Several factors are responsible for the frequent failure of ductal closure in preterm infants. Compared to the term infant, the ductus in the preterm infant is less sensitive to the constrictor effect of oxygen and is more sensitive to the dilatory effect of prostaglandins and of nitric oxide. In addition, the ductal musculature is less developed in the preterm infant, and when initial ductal constriction does take place, it may not be forceful enough to produce local hypoxia of the ductal smooth muscle, thereby hindering the process of subsequent anatomic closure. The frequent presence of lung disease in preterm infants may also result in persistent elevation of pulmonary vascular pressures, increasing the intraluminal distending pressure in the ductus.

Consequences of a PDA In Preterm Infants

When pulmonary vascular resistance falls in the postnatal period, left to right shunting of blood across the PDA will result in increased pulmonary blood flow that in turn may result in pulmonary edema and decreased lung compliance. Increased pulmonary venous return can lead to left ventricular volume overload and myocardial dysfunction. A large left to right shunt across the PDA will also limit gut and renal perfusion. These potential pathophysiologic effects suggest that infants with a PDA might be at higher risk of various morbidities, including chronic lung disease and necrotizing enterocolitis.

Epidemiologic studies suggest that the presence of a PDA is associated with development of chronic lung disease. Studies done in prematurely delivered baboons have shown that the presence of a PDA is associated with decreased alveolar development similar to that seen in very premature infants with chronic lung disease. However, there is no evidence that closure of the PDA is associated with a reduced incidence of chronic lung disease. Therefore, although there is clearly an association between the PDA and chronic lung disease, a direct causal relationship has not been proven.

The presence of a PDA is known to decrease mesenteric perfusion in animal models and in human infants. However, there is no compelling evidence for a causal relationship between the presence of a PDA and development of necrotizing enterocolitis.

Determining the contribution of a PDA to neonatal morbidities requires knowledge of the natural history of an untreated PDA in preterm infants. Unfortunately, closure of the PDA has always been assumed to be desirable, and virtually all PDA treatment trials have specified surgical closure of the PDA

as a backup therapy if the PDA persisted. As a result, we know little about the natural history of the PDA and its consequences in preterm infants.

Assessing the Clinical Significance of a PDA

As noted above, a PDA can lead to significant hemodynamic compromise. There is no gold standard for determining the clinical impact of a PDA, but physical exam, echocardiography, and measurement of brain natriuretic peptide (BNP) all may play a role in assessment.

Typical physical exam findings in an infant with a PDA include a harsh, holosystolic murmur, an active precordium, bounding pulses, and a widened pulse pressure. While the physical exam has been shown to be poorly predictive of the presence or absence of a PDA, the presence of findings suggesting a significant degree of ductal-level shunting (bounding pulses, widened pulse pressure) may be of value in individual cases.

Echocardiography is the most commonly used tool for diagnosis and assessment of the PDA. There is no agreed-upon set of echocardiographic criteria used to define a clinically significant PDA. Commonly used markers include a left atrial-to-aortic root diameter ratio of > 1.4 , ductal diameter > 1.4 mm/kg body weight, left ventricular enlargement, and diastolic flow reversal in the descending aorta.

BNP is a peptide produced in the cardiac ventricles in response to pressure or volume loading. BNP levels are commonly used in the assessment of congestive heart failure in adults. Several studies have documented elevation of BNP levels in infants with a significant PDA, and those levels reliably fall following closure of the PDA. However, a wide range of optimal cut-points for a BNP level that is diagnostic of a significant PDA have been reported in the literature, and at this time, there is no single BNP value that is clearly diagnostic of a clinically important PDA. Trending of BNP levels in an individual patient may provide some information about the relative status of the PDA, although a recent study suggests that such an approach is of limited value.

Pharmacologic Treatment of the PDA

As discussed above, prostaglandins play a significant role in maintaining ductal patency in the immediate postnatal period. Treatment with intravenous indomethacin, a cyclooxygenase inhibitor, will cause ductal closure in about 75% of infants who have not been previously treated. Repeat courses of indomethacin are generally ineffective if the ductus remains patent as documented by echocardiography following the initial course of therapy. Intravenous ibuprofen is equally effective in bringing about ductal closure and may have less impact on renal function, but it is presently unavailable in the US.

Treatment Controversies

Our lack of knowledge concerning the natural history of the PDA in the preterm infant and the lack of evidence supporting a causal relationship between the PDA and any neonatal morbidity mean that treatment decisions are often difficult, and the approach to treatment of the PDA varies widely between individuals and institutions. Within that framework of uncertainty, most neonatologists would probably advise pharmacologic treatment of the PDA in an infant with clear evidence of hemodynamic compromise who is requiring mechanical ventilation.

Surgical ligation of the PDA is the remaining option for treatment in an infant who has failed indomethacin. Ligation of the PDA is associated with several potential morbidities, including hemorrhage, infection, chylothorax, damage to the recurrent laryngeal nerve resulting in vocal cord paresis, and, rarely, inadvertent injury of the pulmonary artery or descending aorta. In addition, recent evidence suggests that surgical ligation of the PDA is associated with an increased risk of neurodevelopmental delay, even after controlling for confounding factors. Inasmuch as there are few clear indications for any treatment of the PDA, the risks of surgical ligation may often exceed the perceived benefits.

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Principles of Respiratory Support

Key Points

- Ventilation/perfusion mismatch is the underlying cause of hypoxia and hypercarbia in neonatal lung disease
- The goal of neonatal respiratory support is the recruitment and stabilization of underventilated lung regions while avoiding overdistention of already well ventilated areas of lung
- CPAP helps to recruit and stabilize alveoli while avoiding overdistention of areas of lung that are already well ventilated
- The high flow nasal cannula provides effective CPAP, although the pressure levels cannot be measured and are somewhat unpredictable
- The mean airway pressure is the main determinant of oxygenation in both conventional and high frequency ventilation
- Minute ventilation is the main determinant of CO₂ removal in conventional ventilation
- In high frequency ventilation, CO₂ removal is directly related to the amplitude of the pressure wave and is inversely related to ventilator frequency

Physiology of Neonatal Lung Disease

Most cases of acute neonatal lung disease result from lung immaturity, infection or aspiration. All of these disease processes are characterized by a variable degree of alveolar collapse that is inhomogeneously distributed throughout the lung parenchyma.

Normal pulmonary gas exchange is dependent on an appropriate balance between ventilation and perfusion in the gas-exchanging unit. The driving force for oxygen and carbon dioxide exchange is the gradient between the partial pressure of those gases in the pulmonary capillary and in the alveolar space. If the alveolar space is poorly ventilated, the gas contained within it will never fully equilibrate with the inspired gas, and the pO₂ in the alveolus will be relatively low, limiting the transfer of oxygen into the pulmonary blood perfusing that area. The pCO₂ will also be relatively high in the underventilated alveolus, limiting the passage of CO₂ from the pulmonary blood into the airspace. This condition is known as ventilation-perfusion (V/Q) mismatch. The severity and extent of V/Q mismatch is the primary determinant of oxygenation and ventilation impairment in neonatal lung disease. Note that in areas of complete alveolar collapse, there will be no gas exchange in the affected area, and an intrapulmonary right to left shunt will exist. Figure 1 provides an example of the impact of V/Q mismatch on blood oxygen and carbon dioxide content.

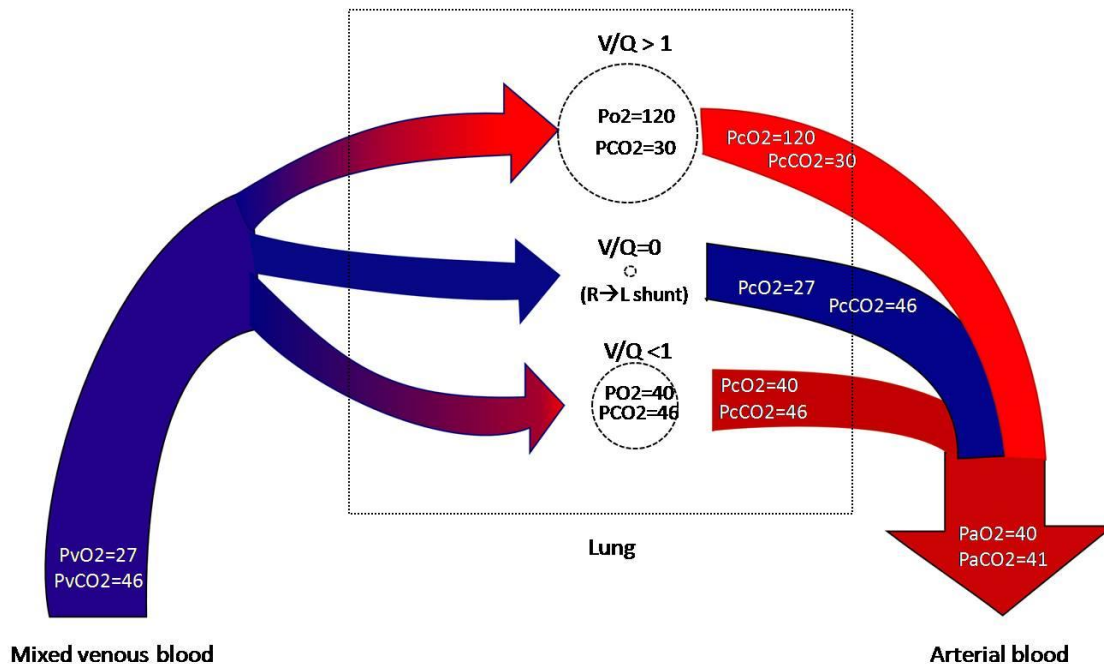


Figure 2. Illustration of the effect of V/Q mismatch in a hypothetical three-compartment lung. In the top compartment, the alveoli are well ventilated ($V/Q > 1$), the intraalveolar gas is completely equilibrated with the inspired gas, and blood oxygenation and CO₂ removal are optimal. In the middle compartment, the alveoli are completely collapsed ($V/Q=0$) and no gas exchange takes place. In the bottom compartment, there is partial alveolar collapse ($0 < V/Q < 1$), the intraalveolar gas is incompletely equilibrated with the inspired gas, and blood oxygenation and CO₂ removal are suboptimal. The relative blood flow to each of these compartments will determine the degree of hypoxia and hypercarbia in mixed systemic arterial blood.

From a physiologic standpoint, the goal of neonatal respiratory support, regardless of the modality, is to minimize the degree of V/Q mismatch by opening and stabilizing collapsed and underventilated areas of the lung while avoiding overinflation and hyperventilation of those areas of lung that are already open and well ventilated. Recruitment and stabilization of lung volumes is accomplished by applying distending pressure to the lung in a manner specific to each support modality, as discussed below.

High-flow nasal cannula

Traditionally, the nasal cannula has been used in the NICU to deliver a blended mixture of oxygen and air at flow rates of ≤ 2 lpm. At those flow rates, a clinically insignificant degree of distending airway

pressure is generated, and the nasal cannula mainly serves as an oxygen delivery device. More recently, nasal cannula flow rates of > 2 lpm (high-flow nasal cannula, or HFNC) have been used to generate positive airway pressure. At flow rates of > 2 lpm, the inspired gas must be humidified to avoid the drying effect of the gas flow on the nasal mucosa.

The available data suggest that HFNC flow rates of 2 to 6 lpm do deliver a clinically significant amount of continuous positive airway pressure (CPAP), and particularly at the higher flow rates, the pharyngeal pressures generated are likely comparable to those achieved with traditional nasal CPAP (see below). However, the pressures generated cannot be directly measured or controlled and vary considerably depending on several factors, including flow rate, size of the cannula relative to the nares, and patient weight. The variability in generated pressures has raised concerns about inadvertent barotrauma and air leak complications with HFNC, particularly at higher flow rates, but the available data and clinical experience to date do not support those concerns.

At this time, HFNC appears to be a reasonable alternative to nasal CPAP devices as a means of delivering CPAP, with the caveat that the pressures delivered will be variable and cannot be directly measured. The main advantage of HFNC is that it is less cumbersome and easier to place and maintain on the infant. The physiologic effects of CPAP devices are discussed below.

Nasal CPAP

The use of continuous positive airway pressure (CPAP) as a mode of neonatal respiratory support was first reported in the early 1970s. Since that time, various methods of delivering CPAP noninvasively through nasal prongs or a tight-fitting nasal mask have been developed. These methods differ according to whether the gas flow through the system is continuous or variable.

In continuous flow CPAP, heated, humidified gas is delivered to the infant at a constant flow rate through nasal prongs. Pressure is generated by resistance to flow in the expiratory limb of the CPAP circuit. In the most widely used form of continuous flow CPAP, the flow resistance is provided by immersing the expiratory tubing in a sterile water chamber to a depth corresponding to the amount of CPAP desired. This system is commonly known as “bubble” CPAP. Some clinicians feel that the bubbling of gas in the water chamber creates oscillating pressure waves in the CPAP circuit that might augment ventilation, but there is no direct proof that this phenomenon occurs.

Variable flow CPAP is delivered via either nasal prongs or nasal mask using a dedicated device that diverts gas flow away from the patient during exhalation, so that the patient is not exhaling against positive pressure. There is evidence that work of breathing is reduced with variable flow CPAP as compared with continuous flow, and a more uniform pressure may be maintained as well.

In all forms of CPAP, the continuous positive pressure helps to recruit and stabilize underventilated or collapsed gas-exchanging units, thereby decreasing V/Q mismatch. Areas of lung that are already well ventilated do not tend to become overexpanded, inasmuch as tidal volume breaths are not being

delivered under pressure. The optimal level of CPAP can really only be determined by the infant's clinical response; experience suggests that pressures of 5-6 cm H₂O are generally adequate.

There is evidence that early nasal CPAP is a reasonable alternative to intubation and surfactant treatment for infants at risk for respiratory distress syndrome (see section on RDS). Nasal CPAP is also commonly used to prevent respiratory failure in recently extubated VLBW infants.

Nasal positive-pressure ventilation

Nasal positive pressure ventilation (NPV) refers to the practice of providing positive pressure breaths noninvasively through nasal prongs or a nasopharyngeal tube. In theory, NPV may aid alveolar recruitment by providing a “sigh” breath that does not overdistend alveoli and cause barotrauma. In practice, a variety of devices and protocols have been used to provide NPV in different studies, making it difficult to draw firm conclusions about the efficacy of this modality. The available evidence suggests that NPV may offer some advantage over nasal CPAP in the treatment of apnea of prematurity and respiratory distress syndrome, and in the prevention of post-extubation respiratory failure.

There are a variety of approaches to the provision of NPV. Most published studies evaluating NPV used nasal prongs attached to a conventional ventilator that delivered breaths in a synchronized manner, using a sensor to detect thoracoabdominal motion. However, that technology is not currently available in the US. Currently, the two NPV delivery systems that are perhaps the most widely used are the SiPAP device and the RAM cannula. SiPAP is essentially bilevel nasal CPAP delivered using a variable flow device. As the device cycles between the higher and lower pressures, a “sigh” breath is effectively delivered. The RAM cannula is a modified nasal cannula that can be attached to a conventional ventilator, allowing ventilator “breaths” to be delivered through the cannula. Although both are FDA-approved devices, neither SiPAP nor the RAM cannula have been evaluated in clinical trials comparing them to standard nasal CPAP.

Conventional ventilation: basic principles

Mechanical ventilation was first used to treat newborns with respiratory failure in the 1960s, and the equipment and techniques used have been progressively refined since that time. Conventional mechanical ventilation delivers positive pressure breaths at a physiologic rate and volume through an endotracheal tube, and it has traditionally been the mainstay of respiratory support for infants with respiratory failure.

At the most basic level, all conventional ventilators work in the same way. There is a constant flow of gas through the ventilator circuit, and the baby can breathe from that gas flow between ventilator breaths. At baseline, a resistance valve in the circuit maintains a set level of pressure, known as the positive end-expiratory pressure, or PEEP. When the ventilator delivers a breath, the exhalation valve in the circuit closes, allowing pressure to build up in the circuit above the PEEP and forcing gas into the patient's lungs. Pressure increases over a very short time until the set peak inspiratory pressure, or PIP,

is reached. The pressure is maintained at the set PIP until the set inspiratory time has expired, at which time the exhalation valve opens and the patient passively exhales until the circuit pressure again reaches the set PEEP. These basic elements of the ventilator cycle are depicted in the graph below:

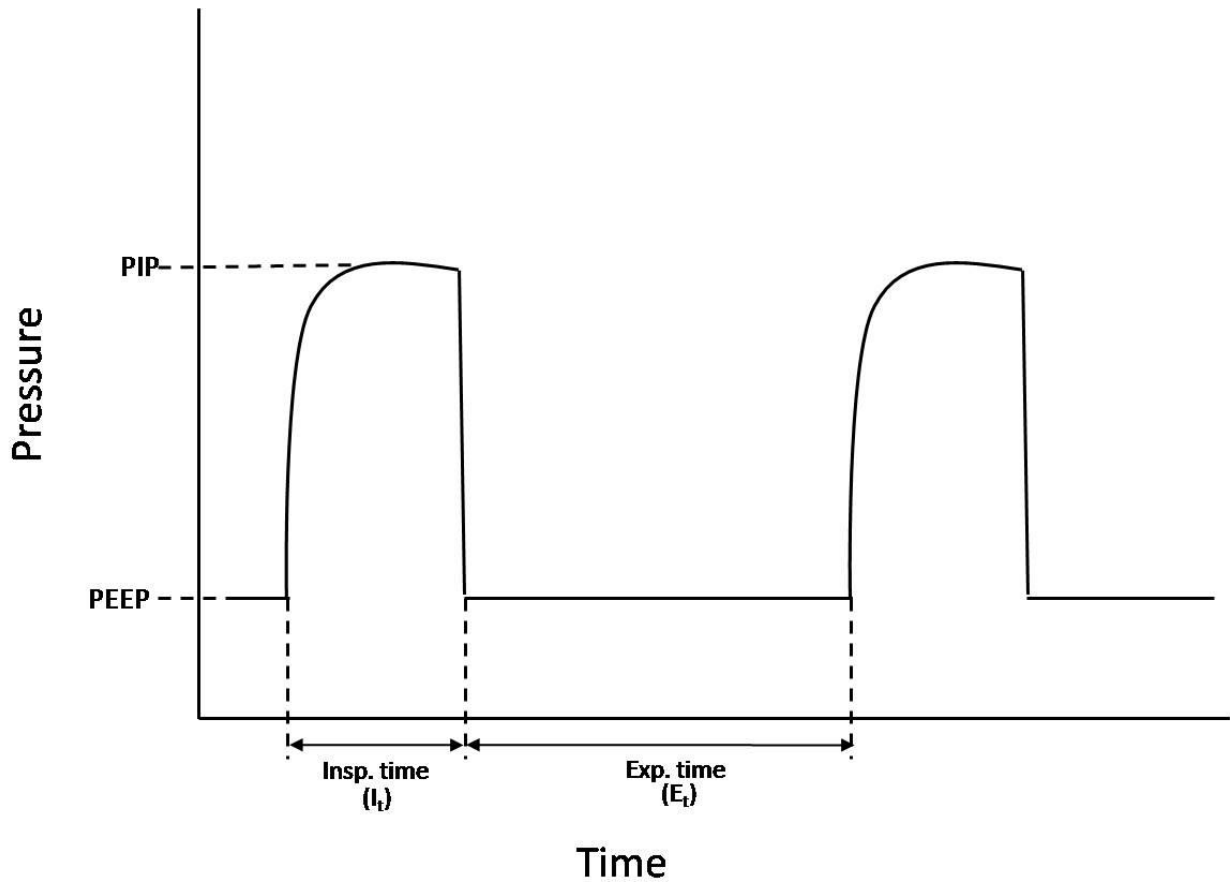


Figure 3. Pressure waveform during the ventilator cycle. Note that $(I_t + E_t)$ is the duration of the respiratory cycle, and the ventilator rate in breaths per minute is given by $60 / (I_t + E_t)$. PIP is set by the operator in pressure-limited ventilation and is set by the ventilator software in volume-targeted ventilation.

Oxygenation is mainly influenced by the mean airway pressure in all ventilated infants. For infants receiving conventional ventilation, the mean airway pressure (MAP) can be calculated from the equation:

$$MAP = \frac{I_t}{I_t + E_t} (PIP - PEEP) + PEEP$$

This equation is valid assuming that the pressure waveform is essentially square as shown in Fig. 2.

From this equation, MAP, and hence oxygenation, can be theoretically improved by either increasing PIP, increasing PEEP, increasing I_t while keeping the rate constant, or increasing the rate while keeping I_t constant. In practice, increasing I_t is not usually helpful inasmuch as a longer I_t tends to allow more gas to flow to ventilated areas of lung without promoting alveolar recruitment and stabilization. Similarly, increasing PIP may tend to overdistend already ventilated lung regions, although increasing PIP may be

necessary if tidal volumes are inadequate (see below). In practice, increasing PEEP is likely to be most helpful in alveolar recruitment and stabilization provided that tidal volumes are adequate.

Ventilation (carbon dioxide removal) is determined by the minute ventilation ($\dot{V}$), which is the amount of gas moved in and out of the lung per unit time and is given by the equation:

$$\dot{V} = R[C(PIP - PEEP) - V_D]$$

Where R = ventilator rate, C = lung compliance and V_D = dead space in the ventilator circuit. Compliance is the change in lung volume produced by a given change in pressure. Note that the quantity $C(PIP - PEEP)$ is the tidal volume of each breath.

From this equation, minute ventilation, and hence carbon dioxide removal, can be theoretically improved by increasing the ventilator rate, increasing lung compliance, increasing PIP, decreasing PEEP, or decreasing V_D . In practice, V_D is always minimized by trimming the endotracheal tube to length. Decreasing PEEP will theoretically increase the tidal volume but will tend to impair oxygenation by decreasing MAP (see above). Compliance cannot be readily changed in any given infant, although an acute improvement in compliance does occur following surfactant treatment (see section on RDS). Increasing PIP beyond levels needed to maintain a physiologic tidal volume may overdistend some areas of lung and worsen V/Q mismatch. Therefore, the best option for increasing minute ventilation and CO_2 removal is usually to increase the ventilator rate.

Conventional ventilation: triggering and breath size determination

Modern conventional ventilators offer a variety of triggering modes (ways to determine when a breath should be given) and allow breath size to be governed either by setting a pressure limit or by setting a desired tidal volume. The most basic form of conventional ventilation is time-cycled, pressure-limited ventilation, in which ventilator breaths are delivered at the set rate, with a constant between-breath interval, and the breath size is determined by the set PIP and PEEP. This most basic mode does not require monitoring of patient effort or delivered gas volumes.

All modern ventilators allow for monitoring of inspiratory effort and measurement of delivered gas volumes using a gas flow sensor. In synchronized ventilation (SIMV), the number of breaths delivered per minute is set by the operator, but those breaths are delivered in synchrony with the patient's inspiratory efforts, implying that the between-breath interval is not necessarily constant. In assist-control ventilation (A/C), a ventilator breath is delivered each time that a sufficient inspiratory effort is sensed, essentially allowing the patient to set the effective ventilator rate (a backup rate is specified in case of apnea). Both of these modes help to decrease work of breathing. A/C ventilation may be especially helpful for infants with severe chronic lung disease when full ventilator support is desired and significant respiratory improvement is not anticipated in the near future.

Lung resistance and compliance can change substantially from breath to breath in neonates, meaning that the delivered gas volume will vary substantially when pressure-limited ventilation is used. Volume-

controlled ventilation allows the operator to set a desired tidal volume, typically 4-5 ml/kg, and the ventilator software then adjusts the PIP as needed to achieve the desired tidal volume, factoring in the measured lung resistance and compliance. Neonatal ventilators do not typically offer true volume-limited ventilation, inasmuch as the breath volume is not identical from breath to breath. Rather, volume targeting is employed, wherein the ventilator software adjusts the PIP over the course of several breaths to “target” the set tidal volume. This approach avoids excessive swings in airway pressure that might occur if the ventilator were attempting to deliver exactly the same volume with every breath in the face of changing lung mechanics. There is evidence that volume-targeted ventilation achieves more homogeneous lung recruitment than does pressure-limited ventilation. Volume-targeted ventilation may be difficult to use in the face of an excessive air leak around the endotracheal tube, although newer ventilators use leak compensation algorithms to overcome this limitation.

In general, all modern neonatal ventilators allow the triggering modes described to be used with either pressure-limited or volume-targeted ventilation. Some ventilators also offer hybrid modes. The most common is pressure support ventilation (PS) used in conjunction with SIMV. PS allows a separate level of pressure support to be provided for patient-triggered breaths that are in excess of the set ventilator rate. PS can be a useful weaning tool, particularly for infants with more severe lung disease.

Conventional ventilation: practical application

There are several different neonatal ventilators on the market, and there is a relative paucity of data concerning the comparative efficacy of the various ventilator modes described above. For these reasons, approaches to ventilator management may vary significantly between units. However, some common principles can be applied:

- There is no role for nonsynchronized (IMV) ventilation in modern neonatal care. SIMV tends to decrease work of breathing compared with IMV, has no disadvantages, and is the default triggering mode used in most units. Some neonatologists prefer to use A/C ventilation, but weaning infants may be more difficult in A/C ventilation inasmuch as the infant receives a full ventilator breath with each inspiratory effort.
- Volume-targeted ventilation, using a physiologic tidal volume of 4-5 ml/kg, is preferable in most circumstances. Compared with pressure-limited ventilation, it promotes more uniform lung recruitment and avoids the barotrauma that could occur with changing lung compliance. Set tidal volumes should be kept in the physiologic range to avoid diffuse microatelectasis or lung overexpansion.
- Infants who are not oxygenating well may benefit from an increase in PEEP. However, physiologic tidal volumes should be maintained, and if pressure-limited ventilation is being used, then the PIP and PEEP should be increased concomitantly to maintain tidal volumes.

High frequency ventilation

High frequency ventilation (HFV) refers to a group of technologies that deliver subphysiologic tidal volumes at supraphysiologic rates in order to avoid barotrauma, promote lung recruitment and stabilization, and improve oxygenation and ventilation. There are three main HFV technologies: high-frequency positive pressure ventilation; high-frequency jet ventilation; and high frequency oscillatory ventilation (HFOV). Of these, HFOV is the most widely used and will be discussed below.

HFOV uses a relatively rigid ventilator circuit that incorporates a variable resistance valve. The circuit is attached to an oscillating diaphragm that is driven by an electronically controlled piston. Gas flows through the circuit at a high rate, and adjustment of the variable resistance valve allows the mean airway pressure (MAP) in the circuit to be set directly. The oscillations of the diaphragm produce a pressure wave in the circuit that oscillates above and below the mean airway pressure. The volume of the resulting “breaths” is quite small, probably near that of the anatomic dead space. The frequency of the pressure wave can be adjusted between 3-15 Hz (180-900 “breaths”/min), and the amplitude of the pressure wave can also be adjusted. The pressure wave is illustrated in Fig. 3 below:

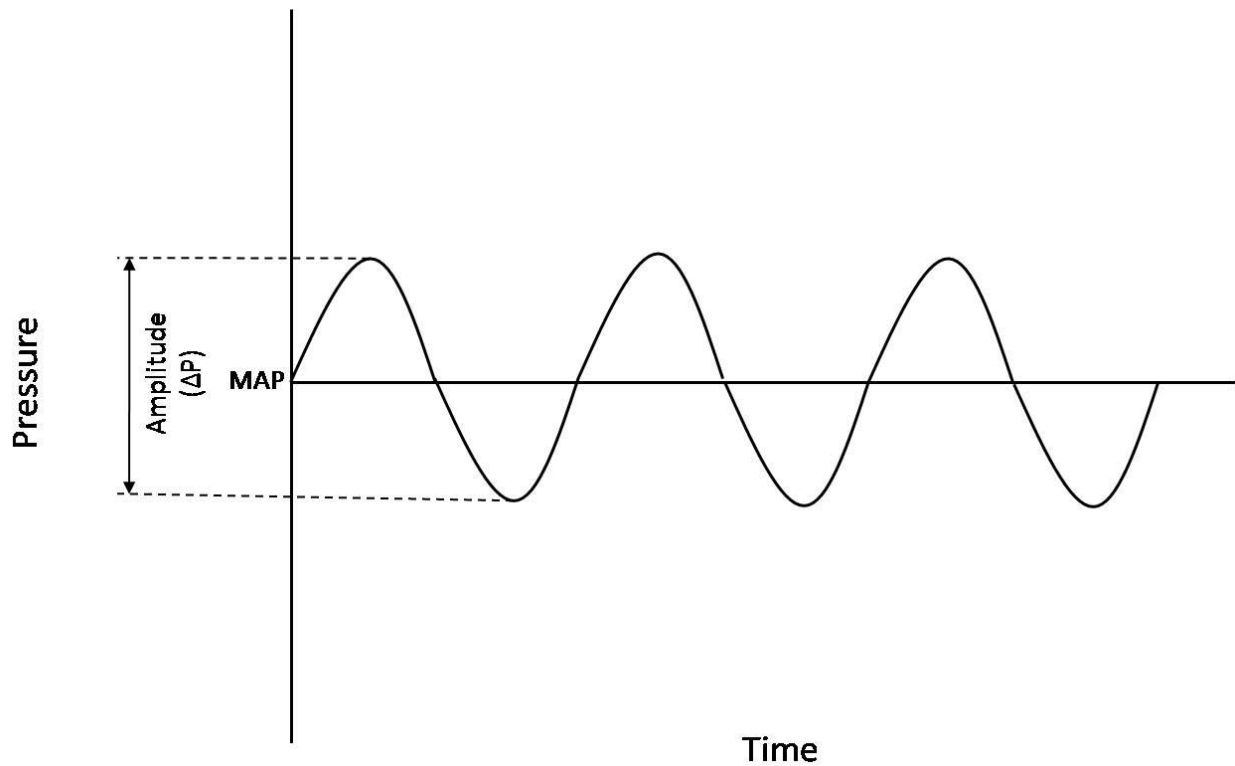


Figure 4 Pressure wave in HFOV. Pressure oscillates above and below the MAP, resulting in an active exhalation phase.

As in conventional ventilation, oxygenation in HFOV is governed by MAP. Unlike conventional ventilation, the MAP is set directly in HFOV. The ability to maintain a constant MAP without tidal volume breathing allows for very effective lung volume recruitment and stabilization.

Ventilation in HFOV is a complex process and relies mainly on enhanced dispersion of gas out of the alveolar spaces rather than on bulk convective flow. Ventilation is directly proportional to the

amplitude but is inversely proportional to the frequency. The inverse relationship between ventilation and frequency may be understood by noting that at lower frequencies, the inspiratory phase is longer, allowing more time for gas penetration into the lung. At first glance, one might question the effectiveness of ventilation in HFOV, inasmuch as physiologic tidal volumes are not being delivered. In practice, ventilation is very effective in HFOV, far exceeding what can be achieved with any form of conventional ventilation.

Available data suggest that HFOV helps to aid resolution of air leak syndromes in ventilated infants with acute lung disease, presumably by reducing barotrauma. HFOV, as compared with conventional ventilation, is also effective as a rescue strategy in term and near-term infants with severe respiratory failure, particularly those with pulmonary hypertension who require inhaled nitric oxide. The role of HFOV as a primary therapy for infants with respiratory distress is less clear, although some centers do use HFOV as a primary mode of ventilation.

The optimal application of HFOV requires an effective lung recruitment strategy. In such a strategy, the MAP is increased until oxygenation improves or until lung overexpansion is seen on CXR. As the infant recovers and oxygen requirements decrease, the MAP can be gradually decreased. Throughout this process, the amplitude and, if necessary, the frequency can be adjusted to optimize ventilation.

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Respiratory Distress Syndrome (RDS)

Key Points

- Anatomic and biochemical lung immaturity both play a role in the pathogenesis of RDS
- Surfactant production begins at about 24 weeks' gestation
- Surfactant is mainly composed of lipids but also contains proteins (surfactant proteins B and C) that are essential for surfactant function
- The physiologic function of surfactant is to lower surface tension at the air-liquid interface in the gas-exchanging unit of the lung, thereby promoting airspace recruitment and improving lung compliance
- Maternal steroid treatment reduces the risk of RDS and mortality in preterm infants
- Surfactant replacement therapy reduces mortality and the incidence of air leak complications in premature infants who have, or are at risk for, RDS but does not reduce the incidence of chronic lung disease
- Early nasal CPAP is a viable alternative to intubation and prophylactic surfactant therapy in spontaneously breathing premature infants at risk for RDS

Developmental physiology of the lung and surfactant production

Respiratory distress syndrome (RDS) is a disease resulting from both anatomic and biochemical immaturity of the lung. Anatomically, true alveoli do not begin to form in the lung until about 32-34 weeks of gestation, and the distal air saccules present before that time are poorly vascularized and offer a limited surface area for gas exchange. Biochemically, the immature lung does not produce an adequate amount of surfactant, a deficiency that fundamentally alters lung mechanics by causing widespread airspace collapse in an anatomically immature lung.

Anatomic development of the fetal lung proceeds through several fairly distinct phases. During the embryonic (3-7 weeks) and pseudoglandular (5-17 weeks) phases, the lung primordium emerges and the main airways and pulmonary vessels develop. The lung is anatomically incapable of gas exchange until late in the canalicular phase of development (16-24 weeks), when the lung has developed to the level of acinar tubule and bud formation in the peripheral lung and the pulmonary capillary network has begun to form. During the saccular phase, from 24-38 weeks, there is continued development of the distal airspaces with formation of air saccules. However, lung surface area does not greatly increase before about 30 weeks of gestation, and true alveoli do not begin to form until the alveolar phase, which begins at 32-34 weeks' gestation.

Surfactant production has the potential to begin early in the saccular phase of lung development, when the pulmonary alveolar epithelium begins to differentiate into type I and type II cells. Surfactant is

secreted by type II cells in the form of lamellar bodies. Biochemically, surfactant is made up of 80-90% phospholipids, mainly dipalmitoylphosphatidylcholine (DPPC), and 10-20% proteins. Surfactant proteins B and C play important roles in the physiologic function of surfactant, while surfactant proteins A and D participate in host defense and also help to regulate surfactant metabolism.

The essential physiologic function of surfactant is to lower surface tension at the air-liquid interface in the gas-exchanging unit of the lung. High surface tension at the air-liquid interface favors collapse of the air sacculi or alveoli according to Laplace's Law:

$$P = 2T/r$$

where P is the pressure required to keep the airspace open, T is the surface tension, and r is the radius of the airspace. For a given airway pressure, lower surface tension means that the distal airspaces are more likely to remain open, thereby decreasing the degree of ventilation-perfusion mismatch and improving lung compliance. Surfactant lowers surface tension in the lung by spreading out into a lipid bilayer or multilayer following secretion by the type II cell. Surfactant proteins B and C help to promote formation of the surfactant film at the air-liquid interface.

Clinical manifestations and differential diagnosis

The clinical signs of RDS typically develop over the first several hours of life but may be present very soon after birth in extremely premature infants. These signs include increased work of breathing, tachypnea, an oxygen requirement, CO₂ retention, and a characteristic 'ground-glass' appearance of the lungs on X-ray. The natural history of RDS is that of a worsening clinical course over the first 2-3 days of life; the treatment strategies discussed below will ameliorate disease severity during this time but will not necessarily be curative. Once the lung begins to make significant amounts of surfactant, at a few days of life, clinical improvement will be seen provided that lung injury has not been too severe. Moderately premature infants with uncomplicated RDS do not usually require respiratory support after about a week of life, although some may have an oxygen requirement past that time. The main acute clinical complication in infants with RDS is air leak, either pneumothorax, pulmonary interstitial emphysema or pneumomediastinum. Air leak complications result from the need for high intrapulmonary pressures to maintain lung expansion. Some degree of lung inflammation always occurs in infants with RDS and is related both to airspace collapse and to ventilator-induced barotrauma. Such inflammation can contribute to the development of chronic lung disease that may require ongoing ventilatory support after the acute phase of RDS is over.

The differential diagnosis for any newborn presenting with the clinical findings of RDS includes sepsis with pneumonia and transient tachypnea of the newborn (TTN). These diagnostic possibilities are not always readily distinguishable at the outset, and evaluation for infection and empiric antibiotic treatment are usually part of the initial management of an infant with RDS. TTN can eventually be distinguished from RDS by its more benign clinical course; infants with TTN do not typically require aggressive respiratory support with CPAP or mechanical ventilation, and their symptoms usually resolve within 24-48 hours.

Maternal steroids for prevention of RDS

In 1972, Liggins and Howie published a landmark study demonstrating that maternal treatment with two doses of betamethasone given 24 hours apart significantly reduced mortality and the incidence of RDS in premature infants. Their study was based on earlier observations in a sheep model wherein maternal glucocorticoid administration was associated with accelerated lung maturation and surfactant production.

Despite the unequivocal results of the Liggins and Howie study, as well as other studies showing similar results, administration of antenatal glucocorticoids to accelerate lung maturation did not become standard of care until the mid-1990s. In 1994, an NIH Consensus Conference released a report that wholeheartedly endorsed the use of antenatal glucocorticoids in mothers at risk for preterm delivery, noting that such treatment “will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs.” Currently, about 80% of very low birthweight infants born in the US receive antenatal glucocorticoids.

Antenatal glucocorticoid treatment is currently indicated in women at risk for preterm delivery between 24 and 34 weeks’ gestation, even in the face of ruptured membranes. There are few data regarding the efficacy of antenatal steroids outside of this age range, although some perinatologists will administer steroids at 23 weeks, and a multicenter trial of antenatal steroid treatment at 34-36 weeks is ongoing. Antenatal steroids are most effective when given at least 24 hours prior to delivery, although there is some evidence of efficacy if they are given as early as 12 hours prior to delivery. The effects of antenatal steroids seem to wane after 7 days. However, concerns about the impact of repeated courses of steroids on fetal growth and brain development have led most perinatologists to abandon the practice of repeating a course of steroids every 7 days if the pregnancy is ongoing.

Surfactant Therapy

The essential role of surfactant deficiency in the pathogenesis of RDS was recognized in the late 1950s. In 1980, Fujiwara published the first report of the successful treatment of infants with RDS via intratracheal instillation of a liquid surfactant preparation. That surfactant preparation, surfactant TA, was obtained by organic solvent extraction from bovine lung. Throughout the 1980s and early 1990s, a multitude of randomized controlled studies examined the effect of surfactant on the incidence of RDS and its complications. Both artificial and natural, animal-derived surfactants were studied in prophylaxis and treatment trials. The main conclusions from these trials can be summarized as follows:

- Surfactant replacement therapy consistently decreases mortality rates and rates of air leak complications in premature infants
- There is no consistent effect on the incidence of other morbidities, including bronchopulmonary dysplasia (BPD)
- There is no evidence that surfactant therapy results in an increase in the rate of neurodevelopmental disability among surviving infants, although there are few long-term followup studies

- Prophylactic surfactant decreases the incidence and severity of RDS, decreases air leak complications, and decreases the incidence of the combined outcome of BPD or death in infants born at ≤ 30 weeks' gestation
- Presently available animal-derived surfactants, including Infasurf (calf lung extract), Surfactant (bovine lung extract) and Curosurf (porcine lung extract) are of essentially equal efficacy but may differ somewhat in rapidity of action and in dosing requirements
- Animal-derived surfactants have been proven generally superior to first-generation artificial surfactants, which are no longer available, although newer artificial surfactants are under development

When evaluating the results of the original surfactant trials, one must remember that those trials were virtually all conducted in an era of infrequent maternal steroid treatment. As discussed above, maternal steroids have a clear impact on fetal lung development, and the effects of maternal steroids and surfactant appear to be additive. It is quite possible that the beneficial effects of surfactant therapy might be less pronounced in the current era of widespread maternal steroid treatment.

Early nasal CPAP for the prevention of RDS

Nasal CPAP has been used to provide respiratory support to infants with RDS since the 1970s, and certain centers have long advocated the early use of nasal CPAP as an alternative to endotracheal intubation and surfactant administration. CPAP promotes alveolar recruitment and stabilization and may be most effective if begun early in infants at risk for RDS, before extensive airspace collapse and lung inflammation have occurred.

Early nasal CPAP has been compared with intubation and prophylactic surfactant administration in several recent trials. The results suggest that short-term outcomes are at least as good in infants treated with CPAP, and early CPAP reduces the number of infants who go on to require ventilation. The long-term followup data that are available to date suggest that rates of neurodevelopmental disability are similar between infants treated with early CPAP and those intubated and given prophylactic surfactant. In summary, early nasal CPAP appears to be a viable alternative to intubation and prophylactic surfactant therapy in infants at risk for RDS.

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Retinopathy of Prematurity (ROP)

Key Points

- Retinal vascularization begins at the optic disk, proceeds toward the peripheral retina and is not complete until about 40 weeks of gestation
- ROP begins when oxygen radical-mediated injury interrupts normal blood vessel growth, creating conditions of relative hypoxia in the avascular retina
- ROP progresses when vascular growth factors, notably VEGF, that are produced by the hypoxic avascular retina cause neovascularization and aberrant blood vessel growth into the vitreous
- Targeting of lower oxygen saturation levels decreases the incidence of ROP but is associated with increased mortality; the optimal oxygen saturation range for premature infants remains unknown
- Screening exams to detect ROP are indicated in all infants with birth weight less than 1500 grams or less than 32 weeks gestation at birth, and in other high-risk infants
- Ablation of the peripheral avascular retina with laser is effective in treating ROP
- Intravitreal injection of bevacizumab, an anti-VEGF antibody, is also effective in treating severe ROP but some questions remain about its use

Pathophysiology of ROP

Development of the retinal blood vessels begins at about 16 weeks of gestation and is complete by 40 weeks. Blood vessel development begins at the optic disc and proceeds outward toward the peripheral retina. ROP results when this normal pattern of blood vessel growth is disrupted.

Following delivery, preterm infants, particularly those with lung disease, are exposed to oxygen levels greatly in excess of those in the intrauterine environment. In adults, retinal blood flow is autoregulated over a wide range of perfusion pressures, whereas in the preterm infant, such autoregulation is absent. In addition, the choroidal blood vessels, which supply the outer layers of the retina, do not constrict under hyperoxic conditions in the newborn. This lack of autoregulation means that the premature retina may be exposed to large excesses of oxygen, resulting in oxygen radical-mediated injury to the retina and its developing blood vessels. The premature retina is largely deficient in antioxidant defense mechanisms, making it particularly susceptible to oxygen radical injury. Hyperoxia will also suppress production of oxygen-regulated vascular growth factors, particularly vascular endothelial growth factor (VEGF), that drive blood vessel development in the retina. The net result is an interruption of normal retinal blood vessel development, termed the vaso-obliterative phase of ROP.

The initial disruption of blood vessel growth during the vaso-obliterative phase results in hypoxia of the avascular portion of the retina. Under hypoxic conditions, the production of vascular growth factors,

including VEGF, is greatly upregulated to levels far exceeding those in the normally developing retina. The result is exuberant neovascularization, with blood vessels growing out into the vitreous. This is the vasoproliferative phase of ROP. If the vasoproliferative phase continues unchecked, the aberrantly growing blood vessels will hemorrhage, resulting in scarring that produces retinal traction and eventually retinal detachment.

The role of oxygen

As noted above, hyperoxia plays a major role in the initiation of ROP, and there is abundant evidence that limiting oxygen exposure in preterm infants will decrease the incidence of ROP. However, restricting oxygen exposure may have unintended consequences. In a large multicenter trial that compared two oxygen saturation ranges in a population of extremely premature infants, the investigators found that targeting a lower oxygen saturation range (85-89% vs 91-95%) lowered the incidence of severe retinopathy by almost 50% but was associated with a significantly higher mortality rate. While there is general agreement that very high saturations (>95%) should be avoided in premature infants who are at risk for ROP, the optimal oxygen saturation range for these infants remains undetermined.

Infants with established ROP, i.e., those who are entering the vasoproliferative phase of the disease, will theoretically benefit from an increased blood oxygen level that will tend to suppress vascular growth factor production, thereby limiting neovascularization. In a large multicenter randomized trial, the administration of supplemental oxygen to infants with established ROP did not demonstrate an overall benefit, but there was some evidence of benefit in certain subgroups. Importantly, there was no evidence that supplemental oxygen exacerbated ROP in infants with established disease. Supplemental oxygen is not presently standard care for infants with established ROP but may be considered in individual cases.

Classification of ROP

ROP is described using the terminology of the International Classification of Retinopathy of Prematurity (ICROP), which allows quantification of the severity and extent of disease in each eye. Disease severity is rated according to stage. Stage 0 corresponds to an immature retina with no evidence of active disease. Stage 1 ROP exists when there is a clear line of demarcation where blood vessel growth has been interrupted, without any evidence of neovascularization; this stage essentially corresponds to the vaso-obliterative phase of the disease. Stage 2 is characterized by the presence of a ridge along the line of demarcation. This finding marks the beginnings of neovascularization. In stage 3, there is evidence of extraretinal blood vessel growth extending from the ridge into the vitreous. Stage 4 refers to the presence of partial retinal detachment and is subdivided into 4A (extrafoveal detachment) and 4B (foveal involvement). Stage 5 is total retinal detachment. In addition to staging, ROP severity can be characterized by the presence or absence of “plus” disease, a term that refers to evidence of

inflammation including dilated, tortuous retinal vessels, vitreous haze, and inflammation of the iris. The presence of plus disease suggests a more aggressive disease process.

The extent of ROP is described according to the zone of the retina in which disease is present (see Figure 1 below), and by the number of clock hours of involvement.

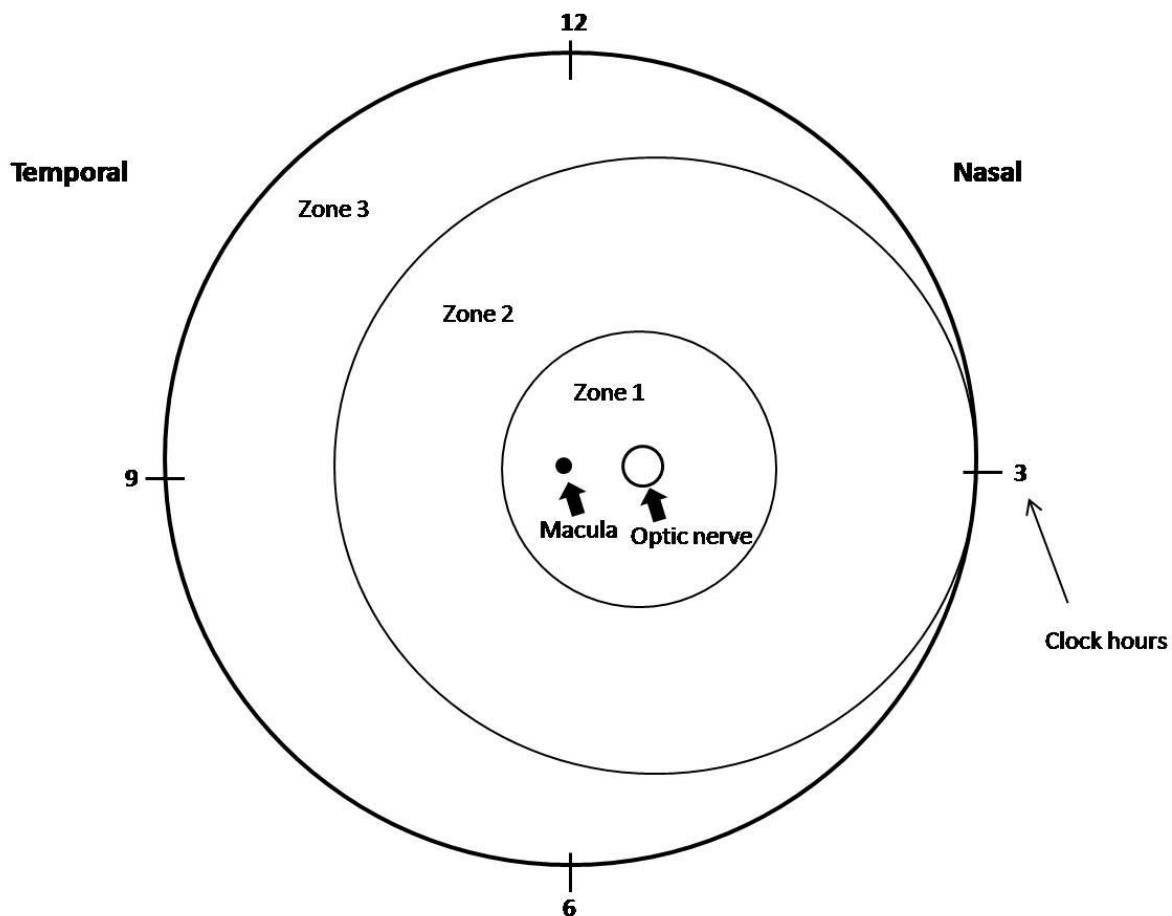


Figure 5. Schematic for describing ROP extent. Zone 1 is defined by a circle centered on the optic nerve with radius equal to twice the distance between the optic nerve and the macula. Zone 2 is defined by a circle centered on the optic nerve with radius equal to the distance between the optic nerve and the nasal edge of the retina. Zone 3 is the peripheral retina.

Screening for ROP

The American Academy of Ophthalmology and the American Academy of Pediatrics have established recommendations for ROP screening, including target populations, timing of the initial exam, and scheduling of followup exams. Infants at risk for ROP include those with birthweight < 1500 grams and gestational age of 32 weeks or less. Less premature infants may also qualify for screening if they have had an unstable clinical course and are felt to be at risk.

ROP gradually evolves following delivery, and its evolution correlates better with postmenstrual age than with postnatal age. Data from natural history studies and early treatment trials indicate that significant ROP is not seen before about 30 weeks postmenstrual age, and disease severity usually peaks as infants near 36-37 weeks postmenstrual age. Based on these observations, the initial screening retinal exam should be performed at 31 weeks postmenstrual age in infants with gestational ages of 27 weeks and less, and at 4 weeks postnatal age for more mature infants. Followup exams are performed according to the severity and location of disease: followup in one week or less is recommended for any disease in zone 1 and for stage 3 disease in zone 2; 1-2 week followup is recommended for immature retinopathy in zone 1 and for stage 2 disease in zone 2; and 2-week followup is recommended for stage 1 disease in zone 2. Infants with less severe disease should be examined every 2-3 weeks until retinal maturation is essentially complete and any ROP has regressed.

Treatment of ROP

The traditional treatment of ROP is aimed at destroying the peripheral avascular retina where vascular growth factors are being produced that drive retinal neovascularization. Cryotherapy was the first such therapy with proven efficacy, but it has been largely supplanted by laser ablation, which is at least as effective and easier to perform. More recently, intravitreal injection of bevacizumab, a monoclonal antibody directed against VEGF, has also shown efficacy in the treatment of ROP.

Optimal criteria for treatment have been developed based on the results of large multicenter intervention trials. Ablative therapy is indicated for any ROP in zone 1 with plus disease, stage 3 ROP in zone 1 without plus disease, and for stage 2 or 3 ROP in zone 2 with plus disease.

The role of bevacizumab in the treatment of ROP is evolving. A large multicenter randomized trial demonstrated that intravitreal injection of bevacizumab, as compared with traditional laser ablation, results in a lower rate of ROP recurrence in infants with zone 1 stage 3+ disease. Bevacizumab treatment is also attractive because it does not require destruction of the peripheral retina, and followup examinations demonstrate full retinal vascularization in treated infants. However, questions remain concerning the safety of bevacizumab. Available data also suggest that ROP can recur long after bevacizumab treatment, requiring prolonged followup of treated infants.

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Principles of Nutritional Support

Key Points

- The goal of postnatal nutritional support of the preterm infant is to achieve growth that approximates fetal growth rates, which are 15-20 g/kg/day during the third trimester
- Postnatal growth failure is very common in premature infants
- Most infants require an enteral energy intake of about 120 cal/kg/day to achieve adequate growth
- The need to excrete excess body water and the potential for excessive transepidermal water loss both complicate initial fluid management of the very preterm infant and necessitate close monitoring of fluid and electrolyte status during the first days of life
- Early parenteral administration of amino acids, beginning on the first day of life, promotes better long-term growth and may also improve glucose tolerance and decrease the incidence of hyperkalemia in extremely premature infants
- Premature infants require more protein, calcium, phosphorus and certain other minerals and vitamins as compared to term infants, and this requirement is reflected in the composition of preterm infant formulas and human milk fortifiers
- Trophic feedings (5-20 ml/kg/day) started early in postnatal life are generally well-tolerated, do not increase the risk of necrotizing enterocolitis, and result in improved subsequent weight gain and feeding tolerance
- Feedings are usually advanced at a rate of about 20 ml/kg/day in significantly preterm infants, but the optimal rate of feeding advancement is unclear

Growth patterns and caloric requirements

The idealized goal of nutritional support in the preterm infant is achievement of extrauterine growth that matches intrauterine growth rates while avoiding complications associated with overly aggressive fluid and nutritional support. In practice, achieving this goal is often difficult.

Fetal growth velocity during the third trimester is generally between 15-20 g/kg/day, with rates being highest early in the third trimester and falling off as the fetus nears full-term. Following delivery, preterm infants undergo an expected weight loss during the first several days of life that may be as great as 10-15% of their birth weight. This initial weight loss largely represents contraction of extracellular fluid volume and is necessary for successful adaptation to extrauterine life. Once preterm infants have regained their birth weight, large cohort studies have indicated that they do generally achieve growth rates that approximate those seen *in utero*. Despite that, postnatal growth failure remains very common among preterm infants, and the vast majority of extremely low birth weight infants are discharged at a weight percentile lower than at birth. Persistent postnatal growth failure has been

associated with worse neurodevelopmental outcomes, while rapid catchup growth following a period of growth failure may increase the risk of developing metabolic syndrome later in life. Optimal postnatal nutritional support, then, should be aimed at achieving growth rates that avoid overt growth retardation while also avoiding excessive rates of weight gain.

Preterm infants in a thermoneutral environment have a resting metabolic rate of 40-50 cal/kg/day. Achieving weight gain of 15 g/kg/day requires another 45-65 cal/kg/day, for a total theoretical energy requirement of 90-120 cal/kg/day in a growing preterm infant. However, calorie requirements may be considerably increased in those infants who are growth-restricted, are ill, or have difficulty with temperature regulation. In practice, most preterm infants are able to grow well with enteral energy intakes of about 120 cal/kg/day or parenteral intakes of about 100 cal/kg/day.

Initial fluid and nutritional management

Fluid requirements of preterm infants during the first days of life are influenced by two main factors: the need to mobilize and excrete excess extracellular fluid volume, and the potential for enhanced free water losses through immature skin. The first requires relative fluid restriction in order to permit appropriate loss of excess body water, while the second may require aggressive fluid support in order to avoid hypernatremic dehydration. The relative importance of these two factors may differ even in babies born at the same gestational age and birth weight, and for that reason, exact fluid requirements for a given infant can be determined only by closely monitoring the infant's fluid and electrolyte status over time. As a rough rule of thumb, term infants have an initial daily fluid requirement of about 60 ml/kg/day, while extremely premature infants with high rates of transepidermal water loss may require as much as 150 ml/kg/day or more. Skin maturation is greatly accelerated following preterm delivery, and in even the most premature infants, transepidermal water losses are fairly insignificant by about two weeks of age.

Assuming normal maternal electrolyte status, all infants will be born with normal serum electrolyte values and do not immediately require provision of electrolytes in intravenous solutions. However, high transepidermal water losses may quickly lead to hypernatremia in extremely premature infants. These infants also tend to excrete potassium poorly, leading to non-oliguric hyperkalemia. For these reasons, close monitoring of fluid status and serum electrolytes is required, with empiric adjustment of intravenous fluid rates and composition as needed. Most practitioners avoid giving electrolytes until urine output is well established and serum electrolytes are within the normal range.

Extremely low birth weight infants who are not receiving protein lose approximately 1-2% of their endogenous protein stores daily and quickly enter a state of negative nitrogen balance following delivery. There is abundant evidence that early provision of parenteral amino acids, beginning within several hours of birth, ameliorates these protein losses and results in improved long-term growth, including head growth. Provision of as much as 3 g/kg/day of amino acids, beginning on the day of birth, appears to be safe and well-tolerated. Administration of amino acids may also help to improve insulin secretion, thereby decreasing the incidence of hyperglycemia and non-oliguric hyperkalemia in these

infants. Early amino acid administration is most easily accomplished through use of a standard hyperalimentation solution containing 10% dextrose and 3% amino acids. Such a solution will give 3 g/kg/day of amino acids and 7 mg/kg/min of dextrose if given at a rate of 100 ml/kg/day.

Calcium and phosphorus

Both calcium and phosphorus are actively transported across the placenta to the fetus, with transport rates peaking during the third trimester. Premature infants are therefore relatively deficient in calcium and phosphorus at birth. Delays in establishing enteral feeds and use of diuretics in infants with chronic lung disease are examples of postnatal factors that may further exacerbate calcium and phosphorus depletion. Significant calcium and phosphorus depletion may impact bone mineralization, leading to osteopenia of prematurity, also known as metabolic bone disease of prematurity. Modern premature infant formulas and human milk fortifiers contain relatively large amounts of calcium, phosphorus and vitamin D that help to replete calcium and phosphorus stores.

Following delivery, serum calcium levels fall in all infants with cessation of active placental transport of calcium. In both term and preterm infants, there is a resulting increase in PTH activity that helps to restore calcium homeostasis, but this PTH response is blunted in significantly premature infants. For this reason, many practitioners empirically provide parenteral calcium supplementation to infants born at less than 30 to 32 weeks of gestation until feedings are established. Alternatively, serum ionized calcium levels can be monitored, and supplementation provided only to those with documented hypocalcemia.

Enteral protein, carbohydrate and fat requirements

Full-term infants generally require protein intake of 3-3.5 g/kg/day to achieve optimal growth, while premature infants require 3.5-4 g/kg/day of enteral protein intake. Premature infant formulas and human milk fortifiers are formulated to provide this higher amount of protein intake. Suboptimal protein intake may account for poor growth in a premature infant who appears to have adequate overall caloric intake.

Nonprotein calories should be divided roughly equally between carbohydrates and fats for optimal growth and body composition. The growing premature infant requires enteral intake of 5-7 g/kg/day of fat and 10-14 g/kg/day of carbohydrate.

Preterm infants are able to readily absorb the saturated fats in human milk due to the composition of human milk fat and the presence of bile salt-activated lipases in human milk. Preterm infant formulas contain a mixture of medium chain triglycerides and polyunsaturated long-chain triglycerides that are well absorbed by premature infants. Modern infant formulas are also supplemented with docosahexaenoic acid (DHA) and arachidonic acid (ARA), two polyunsaturated fatty acids that are thought to be important in neurodevelopment and perhaps in immune function.

Carbohydrate is provided in the form of lactose in human milk and as a mixture of glucose polymers and lactose in premature infant formulas. At birth, premature infants are deficient in intestinal lactase activity compared with full term infants, but lactase activity appears to increase at an accelerated rate following delivery, such that lactose intolerance is not an issue in premature infants.

Parenteral nutrition

Methods of providing total parenteral nutrition (TPN) to premature neonates were established in the 1970s and represent one of the central advances in modern neonatal care. TPN is used for supplemental nutritional support for preterm infants who are gradually being advanced on enteral feeds, and it is used for full nutritional support in infants with intestinal failure due to conditions such as necrotizing enterocolitis, gastroschisis or omphalocele.

As discussed above, preterm infants quickly enter a state of negative nitrogen balance unless exogenous protein is provided, and these infants should be given a standard solution containing dextrose and amino acids beginning on the first day of life. Initially, extremely preterm infants may not tolerate glucose infusion rates of more than 5-6 mg/kg/min, but glucose tolerance typically improves over the first several days of life, and the glucose infusion rate can usually be gradually advanced to 10-11 mcg/kg/min, corresponding to about 125 ml/kg/day of a 13% dextrose solution. Amino acid infusions are well tolerated at all gestational ages and can be started at 3 g/kg/day even on the first day of life. Parenteral amino acid intake of 3-3.5 g/kg/day generally allows for protein accretion to occur at the fetal rate.

After urine output is well established, electrolytes are added to the parenteral nutrition solution. Typical requirements include a sodium intake of 3-4 mEq/kg/day and potassium intake of 2-3 mEq/kg/day, both given as a combination of chloride and acetate salts. Calcium and phosphorus are also given, with typical calcium requirements ranging between 60-80 mg/kg/day of elemental calcium. Inasmuch as renal excretion of electrolytes may vary significantly, and concomitant medical issues may also affect electrolyte balance, close monitoring of electrolytes in premature infants receiving TPN is essential, with empiric adjustment of the electrolyte content depending on laboratory results.

Optimal growth of infants receiving TPN also requires fat intake, with nonprotein calories divided about equally between fats and carbohydrates. Parenteral fat is provided in the form of a 20% lipid emulsion. In the US, available parenteral lipid preparations are derived from vegetable sources and do not contain DHA or ARA. Parenteral lipids are usually started at 1-2 days of life at an initial dose of 0.5-1 g/kg/day and advanced to a maximum dose of 3 g/kg/day. Lipid tolerance should be periodically assessed by checking triglyceride levels, which should be kept below 200 mg/dl.

Approaches to the initiation and advancement of feedings

Intestinal immaturity and concomitant illness are challenges to the provision of enteral feedings to extremely premature infants. In the 1970s, prolonged delays in the initiation of enteral feedings were

common, largely due to concerns that feeding might contribute to the development of necrotizing enterocolitis. Since that time, a number of studies have demonstrated that “trophic” feeds, started in the first few days of life, are well tolerated and do not increase the risk of necrotizing enterocolitis. Trophic feeds have been shown to decrease the incidence of cholestatic jaundice, improve subsequent feeding tolerance, and result in better weight gain. Approaches vary, but trophic feeds are typically started at a volume of 5-20 ml/kg/day and continued at that volume for 3-5 days before the volume is advanced. Very low birth weight infants, or those with gestational age < 29 weeks, are generally appropriate candidates for trophic feedings; more mature infants do not require this approach.

A coordinated suck and swallow mechanism is not present before 32 to 34 weeks of gestation, and preterm infants therefore require feeding via a nasogastric or orogastric tube. Feedings can be given as a continuous infusion or as a bolus, generally every 2 to 3 hours. The available evidence does not prove the superiority of either method, but bolus feeding is generally thought to be more physiologic, and there is some evidence that bolus feeds are better tolerated and result in better weight gain. Continuous feeds may be necessary for some infants with especially poor GI motility.

Feedings should be full-strength human milk or preterm infant formula; there is no role for the provision of diluted milk or formula when initiating feedings. If preterm formula is used, most practitioners begin with the 24 cal/oz preparation, inasmuch as the osmolality is virtually identical to that of 20 cal/oz formula and the nutrient content is higher.

Most infants achieve adequate weight gain with a caloric intake of about 120 cal/kg/day, corresponding to a feeding volume of 150 ml/kg/day of 24 cal/oz formula or fortified breast milk. Full feeding volume is reached by gradually advancing daily intake, and supplemental TPN is given to provide full nutritional support while feedings are advanced. Most practitioners feel that advancing feeding volume too rapidly increases the risk of necrotizing enterocolitis, but the evidence on this issue is not conclusive. Similarly, there is not a well defined optimal rate of advancement, but most practitioners do not advance feeds more quickly than 20-30 ml/kg/day.

Breast milk and breast milk fortification

Breast milk contains a variety of immunoprotective factors, hormones and enzymes and is well tolerated by premature infants. It is the feeding of choice for premature infants, but preterm breast milk does not contain sufficient amounts of protein, calcium, phosphorus and certain trace elements and vitamins to optimally support growth of the preterm infant. For that reason, breast milk requires fortification with a commercially available fortifier that provides additional protein, minerals and vitamins.

The nominal caloric content of breast milk is 20 cal/oz, and standard fortification with a human milk fortifier increases caloric content to 24 cal/oz. However, caloric content of breast milk may vary substantially between individuals and is partially dependent on maternal diet. In addition, milk expressed toward the end of a pumping session (hind milk) contains more fat and hence has a higher caloric content. These factors may need to be considered in an infant who is not growing well on breast

milk feedings despite what initially appears to be an adequate caloric intake. Such infants may require further fortification of breast milk to achieve a caloric content that permits adequate growth.

Formulas

As mentioned above, preterm infant formulas contain additional protein, calcium, phosphorus and certain other minerals and vitamins to support optimal growth. Carbohydrate is provided as a mixture of lactose and glucose polymers and a portion of the fat content is provided as medium-chain triglycerides for ease of absorption. These formulas are provided as prepackaged sterile liquids and are available in a variety of caloric densities.

Following discharge, premature infants may continue to need additional protein and minerals beyond what is contained in term infant formula to achieve optimal growth. “Transitional” formulas have been developed to meet this need. These formulas have nutrient densities that are intermediate between those of preterm and term infant formula. Transitional formulas are typically used for premature infants who are approaching discharge or who weigh about 2 kg. Formula manufacturers recommend that these formulas be continued for at least 6 months following discharge, but the available data suggest that the benefits of these formulas are limited.

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Necrotizing Enterocolitis

Key Points

- Infants with NEC commonly present with signs and symptoms of sepsis, combined with abdominal findings of tenderness and distention
- Pneumatosis intestinalis is the radiologic hallmark of NEC and is thought to represent gas generated by bacterial metabolic activity within the bowel wall
- Infants with NEC often have marked thrombocytopenia and metabolic acidosis, and may develop multi-organ failure in severe cases
- Infants with NEC typically have extensive capillary leak and require aggressive fluid support
- Surgery is not curative in cases of NEC
- The pathogenesis of NEC is multifactorial and involves immature GI host defenses, aberrant bacterial colonization of the gut, and an abnormal inflammatory response to intraluminal bacteria
- Breast milk feeding helps to prevent NEC
- Probiotics show promise for prevention of NEC, but a pharmaceutical grade preparation is not yet available and further studies are needed

Overview and epidemiology

Necrotizing enterocolitis (NEC) is characterized by bowel inflammation and necrosis that is usually of rapid onset and, if severe, can result in bowel perforation, sepsis, and peritonitis. The systemic inflammatory response that is triggered by the disease can result in multiorgan failure and injury to the developing brain. Mortality rates in infants with full-blown NEC are between 20 and 30%. NEC has been recognized as a major cause of morbidity and mortality in preterm infants since the mid-1960s, but despite decades of research, its pathogenesis remains incompletely understood, there is no curative treatment, and preventive strategies thus far have not had a significant impact on disease incidence.

NEC is mainly a disease of preterm infants but does rarely occur in term infants with certain risk factors as discussed below. The average incidence of NEC is 6-7% in very low birth weight infants, but incidence rates may vary substantially between units and in the same unit over time. The age of disease onset is inversely related to gestational age, such that NEC may not occur until 6-8 weeks of age in the most premature infants. This delayed onset makes NEC a particularly devastating disease, inasmuch as it often occurs in a baby whose initial medical problems have largely resolved and who is doing relatively well on full enteral feeds. In fulminant cases, affected infants may go from appearing essentially well to being critically ill in a matter of hours.

Clinical presentation, initial evaluation and diagnosis

The clinical presentation of NEC is that of neonatal sepsis combined with abdominal signs and symptoms. Lethargy, apnea and temperature instability are common, as are abdominal tenderness and distention, absent bowel sounds, and bloody stools. In advanced cases, abdominal wall erythema may be seen.

Feeding intolerance is often the first sign of NEC. Feeding intolerance is fairly common among preterm infants and is therefore not a specific indicator of disease, and it is difficult to objectively define. Signs of significant feeding intolerance usually include increased gastric residuals, with more than 1/3 to 1/2 of the preceding feeding remaining in the stomach when the next feeding is due; the presence of bilious gastric aspirates; and abdominal distention resulting in an abdominal girth that is more than 2 cm above the baseline.

If feeding intolerance is noted, the baby should be assessed clinically. If the infant is essentially well-appearing, has no abdominal tenderness and minimal distention, further evaluation may not be needed. On the other hand, if the infant appears ill, has abdominal tenderness or has significant distention, then an abdominal X-ray is warranted.

NEC is diagnosed if either pneumatosis intestinalis or portal venous gas is seen on X-ray. Pneumatosis intestinalis is manifested by linear streaks or bubbles of gas seen within the bowel wall and is thought to result from metabolic activity of bacteria that have invaded the intestinal tissue. Portal venous gas presumably represents dissection of pneumatosis intestinalis into the portal venous system. In the absence of either pneumatosis intestinalis or portal venous gas, NEC cannot be definitively diagnosed, although a diagnosis of “presumed” NEC may still be made if the clinical picture is overwhelmingly consistent with the diagnosis. In the case of intestinal perforation, intraperitoneal free air may be seen, but free air is not diagnostic of NEC inasmuch as it is also seen in the setting of spontaneous intestinal perforation, a separate disease entity. Infants with NEC also typically have dilated loops of bowel secondary to ileus, but this is not a specific finding.

If NEC is diagnosed or strongly suspected, further evaluation with a CBC, blood culture and blood gas is warranted. Marked thrombocytopenia is common in infants with NEC, and either leukocytosis or leukopenia may also be seen. NEC does not result from systemic infection, as discussed below, but blood cultures are positive in a significant proportion of infants with NEC due to translocation of enteric bacteria across injured gut mucosa. Blood gases often demonstrate significant metabolic acidosis, particularly if the disease is severe.

Medical management

By the time NEC is diagnosed, irreversible bowel injury has already occurred, and medical treatment is limited to the provision of supportive care. The infant is placed on complete bowel rest and a large-bore nasogastric or orogastric tube is placed for GI tract decompression. Nutritional support is provided with hyperalimentation. Broad-spectrum antibiotics are given empirically and are directed against

bowel flora that might seed the bloodstream across injured gut mucosa. Infants with NEC often have marked capillary leak and are prone to large fluid shifts, and close attention must be paid to fluid status, urine output and blood pressure. With severe disease, multiorgan failure may develop, and the infant may require ventilatory support and blood pressure support with pressors.

Serial abdominal X-rays are usually obtained early in the course of the disease, when there is risk of intestinal perforation. The time at which findings of pneumatosis intestinalis and portal venous gas resolve after diagnosis is variable and is not helpful in determining prognosis or directing ongoing therapy.

In uncomplicated cases, gradual clinical improvement is usually seen after the first few days. Infants are usually kept *npo* and maintained on hyperalimentation for 10 days to allow for intestinal mucosal healing. Empiric antibiotics are also continued throughout this time.

Surgical management

The intestinal injury seen in NEC is almost always multifocal, with areas of injured bowel interspersed with segments of bowel that appear healthy. In addition, it is often difficult to determine the ultimate viability of bowel that appears compromised at the time of surgery but is not frankly necrotic. For these reasons, NEC is not a disease that can be cured surgically, except perhaps for the rare case in which there is a single continuous segment of necrotic bowel that can be resected, with the rest of the bowel remaining healthy.

The only absolute indication for surgery in a patient with NEC is intestinal perforation, when there is a need to decompress the abdomen and allow for drainage or removal of intraperitoneal stool and pus. In extremely low birthweight infants with perforation, placement of a peritoneal drain has been shown to result in short-term outcomes that are comparable to those achieved with open laparotomy, although between 25% and 75% of infants initially treated with a peritoneal drain will go on to require laparotomy.

Relative indications for surgery include worsening peritonitis, the presence of a fixed dilated loop of bowel on X-ray, and general failure to respond to supportive care and medical management. In infants who have severe and extensive disease, laparotomy may confirm the absence of any viable bowel, leading to a decision to discontinue support.

Pathogenesis

The pathologic findings in the intestine of infants with NEC are essentially those of ischemic bowel necrosis, and antecedent bowel ischemia was thought to play a key role in the pathogenesis of NEC when the disease was first described in the modern era. The rare cases of NEC that occur in term and late preterm infants are, in fact, often associated with factors predisposing to bowel ischemia, such as cyanotic congenital heart disease or birth asphyxia. However, case-control studies have long since

proven that the only consistent risk factor for the development of NEC in premature infants is prematurity itself.

After decades of research, the pathogenesis of NEC in premature infants remains incompletely understood, but several factors related to intestinal immaturity and aberrant bacterial colonization of the GI tract are thought to be important. Intestinal barrier function and host defenses are impaired at various levels in the preterm gut. For example, gastric acid secretion is limited in premature infants, and a relatively high stomach pH may allow abnormal bacterial colonization of the upper GI tract. The premature intestinal mucosa is also relatively permeable to bacterial toxins and even intact bacteria.

A variety of basic laboratory studies have shown that the immature intestine has an excessive inflammatory response to microbial stimulation. In full term infants, this inflammatory response is moderated by downregulation of different components of the epithelial innate immune response. Current evidence suggests that this developmental regulation does not occur in premature infants, predisposing them to bowel inflammation when intraluminal bacterial colonization occurs.

While NEC is not caused by infection or colonization with a specific microbe, bacterial colonization of the intestine is clearly a prerequisite for the development of NEC. Recent studies have suggested that infants with NEC tend to have abnormal bacterial colonization patterns, with reduced bacterial diversity and a predominance of unusual organisms. These abnormal colonization patterns may result from prior antibiotic use as well as failure to establish initial colonization with beneficial commensal bacteria such as lactobacillus.

NEC is thought to be initiated when abnormal bacterial colonization results in an excessive, poorly modulated inflammatory response in the immature intestine. As this inflammatory response progresses, downstream mediators trigger local vasoconstriction, leading to secondary hypoxic-ischemic injury. Intestinal mucosal integrity is thus further compromised, allowing additional bacterial invasion of intestinal tissue and further amplification of the inflammatory response. By the time the disease is diagnosed clinically, bowel inflammation is already well advanced and cannot be reversed by any currently available therapeutic intervention.

Preventive strategies

A number of strategies aimed at preventing NEC have been proposed over the past few decades. These strategies have included limiting enteral feeds; breast milk feedings; both prenatal and postnatal steroid treatment; and probiotic administration.

Enteral feeding is generally thought to be a prerequisite for the development of NEC. In the 1970s, this observation led to the practice of delaying the introduction of enteral feeds for prolonged periods of time and advancing feedings very slowly once they were begun. This practice clearly has many adverse nutritional consequences and has since fallen out of favor. Several randomized studies have demonstrated that beginning small-volume enteral feeds at 10-20 ml/kg/day within the first few days of life is well tolerated, results in better nutritional outcomes, and does not increase the risk of NEC. These

trophic feedings are usually continued for a period of 3-5 days before the feeding volume is advanced. Most practitioners limit feeding volume increases to no more than 20-30 ml/kg/day, inasmuch as some studies suggest that more rapid feeding advancement does increase the risk of NEC.

Breast milk contains a variety of immunologic factors that may bolster intestinal host defenses, promote colonization with beneficial commensal bacteria, and limit intestinal inflammation. There is evidence that feeding either mother's own breast milk or donor breast milk may decrease the risk of NEC as compared with formula feeding. Feeding mother's own breast milk is encouraged for all premature infants. The use of donor breast milk to feed those infants whose mothers are not supplying milk has been endorsed by the American Academy of Pediatrics, but use of donor milk poses significant issues of cost and logistics that may limit its widespread use.

Both prenatal and early postnatal glucocorticoid treatment have been reported to decrease the incidence of NEC. Prenatal steroids are regularly given to accelerate lung maturity when preterm delivery is anticipated. However, early postnatal steroid treatment has been associated with worse neurodevelopmental outcomes, and postnatal steroids are not commonly used at present.

Probiotics are a group of bacterial organisms, including *Lactobacillus* and *Bifidobacteria* species, that are found in large quantities in the intestinal tract of healthy individuals and are thought to play an important role in modulating intestinal inflammation and in promoting colonization with diverse bacterial species. Several randomized trials have evaluated the effect of probiotic treatment on the incidence of NEC. Taken together, these trials suggest that probiotics do lower the incidence of NEC. However, these trials used various probiotic preparations, enrolled infants were not stratified according to breast milk use, and the effect was not entirely consistent across trials. Most importantly, there are lingering safety concerns, and there is no pharmaceutical grade probiotic preparation available in the US. At this point, probiotics, although promising, cannot be considered standard of care for the prevention of NEC. A large, multicenter, randomized controlled trial using a pharmaceutical grade probiotic preparation will help to define the role of probiotics for NEC prevention.

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Hemorrhagic and Ischemic Brain Injury in the Preterm Infant

Key Points

- Periventricular leukomalacia (PVL) is a form of ischemic brain injury unique to preterm infants that occurs in arterial watershed zones where arterial ingrowth is incomplete
- Intraventricular hemorrhage (IVH) originates in the germinal matrix, a subependymal region containing very fragile blood vessels
- Antenatal steroids and postnatal indomethacin prophylaxis help to prevent IVH
- Post-hemorrhagic hydrocephalus occurs in 60-75% of infants with severe IVH
- About two-thirds of infants with severe IVH or cystic PVL have major neurodevelopmental handicaps at 18-24 months of age

Overview

The vascular development of the human brain is not complete until the fetus is nearly full term. Both anatomic and physiologic immaturities of the cerebral vasculature are mainly responsible for the unique types of hemorrhagic and ischemic cerebral injury that can occur in preterm infants. Hemorrhagic lesions can occur in various areas of the preterm brain, but the most common is germinal matrix hemorrhage that may extend into the ventricular system (IVH). The classic ischemic brain lesion in premature infants, and one which is unique to this population, is periventricular leukomalacia (PVL). Cranial ultrasound is commonly used to detect these forms of brain injury. While absence of overt brain injury does not guarantee normal neurodevelopment, severe IVH and cystic PVL are significantly correlated with future neurodevelopmental impairment and are not uncommon despite modern advances in neonatal care.

Cerebrovascular autoregulation in preterm infants

Adults are able to autoregulate cerebrovascular tone over a wide range of perfusion pressures in order to maintain constant cerebral blood flow despite fluctuations in systemic blood pressure. The autoregulatory range becomes progressively lower and narrower with decreasing age, and in preterm infants, the lower limit of the autoregulatory range is thought to be close to the normal mean arterial blood pressure. When perfusion pressures are outside the autoregulatory range, the cerebral circulation becomes pressure-passive. The extent to which the cerebral circulation is pressure-passive in preterm infants is debated, but there is general agreement that pressure passivity of the cerebral circulation is a real phenomenon in preterm infants. In the pressure-passive circulation, systemic hypotension may result in cerebral hypoperfusion and ischemia, and systemic hypertension may result in excessive regional cerebral blood flow, potentially resulting in hemorrhagic injury.

The cerebral vasculature is also responsive to changes in arterial CO₂ content, with a low CO₂ level causing cerebral vasoconstriction and a high CO₂ level causing cerebral vasodilation. CO₂ sensitivity is preserved even in significantly preterm infants. There is experimental evidence that marked hypocapnea can limit cerebral oxygen delivery. Hypocapnea, particularly when sustained, has also been associated with an increased risk of cystic PVL. Conversely, hypercapnea during the first few days of life has been associated with a higher risk of germinal matrix hemorrhage.

Development of the cerebral vasculature

The blood supply to the brain parenchyma develops through ingrowth of arteries from the pial surface of the brain. Long penetrating arteries supply the deep periventricular white matter, and short penetrating arteries supply the more superficial areas of white matter. Development of these penetrating arteries is not complete in preterm infants, and connections between vessels are sparse. As a result, the periventricular white matter in preterm infants contains a number of arterial watershed zones where relatively mild degrees of hypoxemia or hypoperfusion may result in ischemic injury.

Another notable area of vascular immaturity is the germinal matrix, a region of highly cellular neuroepithelial tissue located in the subependymal region around the lateral ventricles. The germinal matrix is the birthplace of neuronal and glial cells that migrate outward toward the cortex, and as such, it is highly metabolically active and has abundant blood flow supplied by a very fragile network of blood vessels. The germinal matrix gradually involutes during the third trimester and is no longer present by about 34 weeks of gestation. Infants born earlier in the third trimester still have residual germinal matrix tissue, mainly located in the caudothalamic groove. This tissue lies in an arterial watershed area and is prone to injury during periods of hypoperfusion, and the fragile blood vessels contained within it are prone to rupture with fluctuations in perfusion pressure.

Germinal matrix / intraventricular hemorrhage (GM-IVH)

Hemorrhage originating in the germinal matrix is relatively common, occurring in about 25% of all VLBW infants. As noted above, the germinal matrix contains very fragile blood vessels that are thought to be vulnerable to injury from both ischemia and alterations in cerebral perfusion pressure. Most GM-IVH occurs in the first week of life and is readily detected by cranial ultrasound examination.

GM-IVH is commonly described using the Papile grading system. In this system, a grade I hemorrhage is one which is confined to the germinal matrix with no little or no intraventricular extension. A grade II hemorrhage is a germinal matrix hemorrhage that has ruptured through the ependymal lining of the ventricle, resulting in intraventricular blood but without ventricular dilation. A grade III hemorrhage is one in which the lateral ventricle is filled and distended with blood. A grade IV hemorrhage describes the presence of blood in the brain parenchyma adjacent to the original area of germinal matrix hemorrhage. This type of hemorrhage, also referred to as periventricular hemorrhagic infarction, is thought to result from compression of subependymal draining veins by the germinal matrix

hemorrhage, causing a secondary venous infarction. Among VLBW infants, the incidence of grade I/II IVH is about 18% and the incidence of severe (grade III/IV IVH) is about 8% (data from the Vermont Oxford Network).

Periventricular leukomalacia (PVL)

As noted above, the anatomic and physiologic immaturity of the cerebral vasculature renders preterm infants uniquely vulnerable to ischemic injury of the periventricular white matter. PVL is initially seen as periventricular echodensities on cranial ultrasound. If a significant amount of focal necrosis has occurred, small cysts will form as the necrotic neuronal tissue undergoes liquefaction over a period of weeks. In cases where a significant intrauterine insult has occurred remote from delivery, PVL may be evident on cranial ultrasound within the first week of life, but more commonly, PVL results from postnatal injury and may not be evident on ultrasound until several weeks after birth.

The incidence of cystic PVL as detected by cranial ultrasound is about 3% among VLBW infants. However, MRI studies have shown that diffuse, noncystic white matter abnormalities can be detected in the majority of significantly preterm infants when studied at term equivalent age. These more subtle abnormalities may represent one end of a spectrum of white matter injury, with cystic PVL representing the severe end of that spectrum.

Strategies for the prevention of GM-IVH and PVL

A number of strategies for the prevention of GM-IVH have been evaluated in clinical trials, including prenatal and postnatal phenobarbital prophylaxis, postnatal vitamin E, prophylactic pharmacologic paralysis to reduce blood pressure fluctuations, antenatal steroids, and prophylactic postnatal indomethacin. Of these strategies, only antenatal steroids and indomethacin prophylaxis have proven to be effective. Antenatal steroids clearly decrease the risk of IVH. Large trials have shown that prophylactic indomethacin does have a statistically significant impact on the incidence of severe IVH, but the impact on developmental outcome is modest at best.

At present, there are no specific therapies aimed at prevention of PVL, aside from good overall supportive care and maintenance of hemodynamic stability. Abundant data confirm that sustained hypocarbia resulting from overly aggressive mechanical ventilation does increase the risk of PVL, and care should be taken to avoid hypocarbia in ventilated preterm infants.

Post-hemorrhagic hydrocephalus

Infants with IVH are at risk for development of hydrocephalus. In infants with cystic encephalomalacia associated with prior ischemic injury, ventricular dilatation may represent hydrocephalus *ex vacuo*, in which the ventricular space expands due to poor growth or atrophy of brain tissue. In contrast, post-hemorrhagic hydrocephalus (PHH) is a direct result of hemorrhage into the ventricular space. The most

common form of PHH is communicating hydrocephalus, in which intraventricular blood causes inflammation and fibrosis of the arachnoid granulations, impairing CSF resorption. Less commonly, infants with large amounts of intraventricular blood may develop acute non-communicating hydrocephalus due to obstruction of ventricular outflow by blood clots or fibrosis.

Some degree of PHH occurs in about 25% of all preterm infants with IVH and in 60-75% of those infants with severe IVH. Progression of PHH to the point where surgical intervention is required is uncommon in infants with mild IVH but occurs in about 20% of infants with severe IVH. The incidence of PHH is somewhat variable between institutions and across studies, at least in part because there is not a universal objective standard for the radiologic diagnosis of PHH; the diagnosis is often made qualitatively in individual institutions, and various criteria, such as the width of the anterior horn of the lateral ventricle, have been used in published studies.

An initial finding of post-hemorrhagic ventricular dilatation on cranial US warrants serial followup ultrasounds as well as monitoring of the head circumference and physical examination. If evidence of progressive PHH emerges, nonsurgical management may be initially attempted. Oral medications such as carbonic anhydrase inhibitors and other diuretics are not effective in the management of neonatal PHH. Drainage of CSF by performing serial lumbar punctures can be successful in arresting the progression of PHH and is commonly done in some centers, but the optimal timing of this intervention is not clear and is currently under study.

Indications for surgical drainage of CSF in infants with progressive PHH are not widely standardized, but common indications include rapidly increasing head circumference (> 2 cm per week), progressive splaying of the cranial sutures, a full, tense anterior fontanelle, and symptoms including worsening apnea and bradycardia, lethargy and poor feeding. The initial drainage technique of choice is usually placement of a ventricular reservoir (ventricular access device) that can be percutaneously tapped to drain CSF when necessary. Outcomes of infants treated with ventricular access devices have not been well studied, but many of these infants will not go on to require a permanent ventricular shunt. If a permanent ventriculoperitoneal shunt is required, placement is usually deferred, if possible, until the infant is about 2.5 kg due to high rates of skin breakdown and infection seen with shunt insertion in smaller, less mature infants.

Neurodevelopmental outcomes

The presence or absence of hemorrhagic or ischemic brain injury is by no means the only determinant of neurodevelopmental outcome in preterm infants. About 25-30% of VLBW infants with normal cranial ultrasounds throughout their NICU course have evidence of neurodevelopmental delay at 18-24 months, although many of those infants demonstrate significant improvement by school age. Nonetheless, the presence of significant brain injury, particularly cystic PVL and periventricular hemorrhagic infarction (grade 4 IVH), is associated with worse neurodevelopmental outcome. Current data suggest that about two-thirds of surviving infants with periventricular hemorrhagic infarction will have significant cognitive or motor handicaps, and 60-70% of infants with cystic PVL will also have significant handicaps,

particularly cerebral palsy. On the other hand, the presence of mild (grade 1-2) IVH, in the absence of other abnormalities, does not seem to significantly increase the risk of adverse neurodevelopmental outcome.

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