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Clinical Associations, Treatment, and Outcome of Apnea of Prematurity

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Objectives After completing this article, readers should be able to:

1. Identify common neonatal problems that may present with apnea.
2. Describe the role of pharmacologic and nonpharmacologic treatment of apnea.
3. Characterize the findings of long-term follow-up of infants who have apnea.

Clinical Associations

Although apnea typically results from immaturity of the respiratory control system (see accompanying article in this issue), it also may be the presenting sign of other diseases or pathophysiologic states that frequently affect preterm infants. A thorough consideration of possible causes is always warranted, especially when there is an unexpected increase in the frequency of episodes of apnea or bradycardia (Fig. 1).

Central nervous system problems, particularly intracranial hemorrhage, can precipitate apnea in the preterm infant. Asphyxia, including transient birth depression, may cause either episodic or prolonged apnea. Malformations of the brain or less likely, the spinal cord, should be considered in an otherwise healthy infant who presents with apnea at birth. Infections (bacteremia possibly accompanied by meningitis) may cause unstable breathing patterns and should prompt the appropriate evaluation and possibly antibiotic therapy. In the older infant, the onset of a viral illness such as respiratory syncytial virus (RSV) infection sometimes is heralded by apnea, although the precise mechanism whereby RSV presents with apnea is unclear. Anemia, another frequent problem in preterm infants, whether iatrogenic or due to bleeding, is a potential precipitating factor. Blood transfusions have been demonstrated to improve irregular breathing patterns in preterm infants, although the risk of blood transfusion has limited its use as treatment for apnea. It has been assumed, although unproven, that enhanced oxygen-carrying capacity, as with red blood cell transfusion, may decrease the likelihood of hypoxia-induced respiratory depression. Other disease states that may precipitate apnea include metabolic disorders such as hypoglycemia or electrolyte imbalance. Temperature instability and metabolic acidosis may be associated with apnea, although there is always the risk that sepsis is the underlying precipitant. Medications that produce sedation, such as the opiates, and drugs that depress muscle function (eg, magnesium) can produce apnea, as can prostaglandin E₁ (alprostadil) infusion used to maintain ductal patency in infants in whom cardiac lesions are suspected.

Gastroesophageal reflux (GER) often is incriminated in causing neonatal apnea, but such an attribution should be made cautiously. Despite the frequent coexistence of apnea and GER in preterm infants, investigations of the timing of reflux in relation to apneic events indicate that they are not commonly related temporally. Monitoring studies demonstrate that when a relationship between reflux and apnea is observed, apnea may precede rather than follow reflux. This suggests that loss of respiratory neural output may be accompanied by a decrease in lower esophageal tone and resultant reflux in some infants. Although physiologic experiments in animal models reveal that reflux of gastric contents to the larynx induces reflex apnea, there is no clear evidence that treatment of reflux will affect the frequency of apnea in most preterm infants. Therefore, pharmacologic management for reflux with agents that decrease gastric acidity or enhance gastrointestinal

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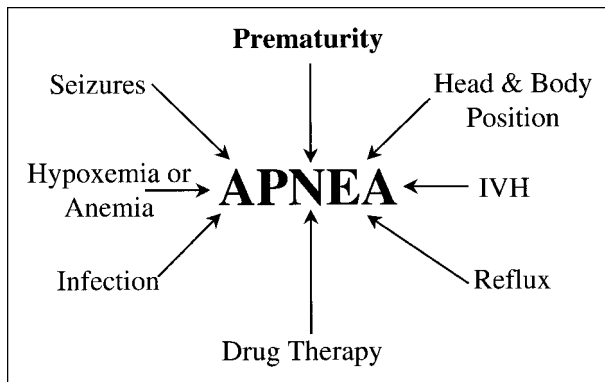


Figure 1. Multiple etiologic factors that may contribute to apnea in preterm infants. IVH=intraventricular hemorrhage

motility generally should be reserved for preterm infants who exhibit signs of emesis or regurgitation of feedings, regardless of whether apnea is present.

Xanthine Therapy

Methylxanthines have been the mainstay of pharmacologic treatment of apnea; there is now a 25-year history of their use in infants. Both theophylline and caffeine are used and have multiple physiologic and pharmacologic mechanisms of action. Xanthine therapy increases minute ventilation, improves CO₂ sensitivity, decreases hypoxic depression of breathing, enhances diaphragmatic activity, and decreases periodic breathing. The precise pharmacologic basis for these actions, which are mediated by an increase in respiratory neural output, is still under investigation. A likely major mechanism of action is through competitive antagonism of adenosine receptors. Adenosine acts as an inhibitory neuroregulator in the central nervous system and is released during hypoxia. Neonates exhibit hypoxic respiratory depression, and the ability of methylxanthines to block this response may contribute to their effect on apnea. Other adenosine-mediated pathways of respiratory neural inhibition also may be blocked by xanthine therapy. Our understanding of the role of xanthines may be enhanced by future studies correlating physiologic observations with labeling and localization of both adenosine and its receptor subtypes in respiratory-related regions of the developing brainstem.

Treatment usually is initiated with a loading dose followed by maintenance therapy. Theophylline is available in oral and intravenous preparations. The intravenous form is aminophylline, a complex of theophylline and ethylenediamine. For oral theophylline, the loading dose is 5 to 6 mg/kg, followed by 1 to 2 mg/kg every

8 to 12 hours. Dosing of intravenous aminophylline is increased by 20% because it is 85% theophylline by weight. Caffeine is similarly available for both oral and intravenous use and has some advantages over theophylline. Because it has a higher therapeutic index, toxicity is less of a concern. Also, once-daily dosing is possible due to its longer half-life. A typical loading dose of 20 mg/kg caffeine citrate is followed in 24 hours by 5 to 8 mg/kg per dose, administered once every 24 hours. A recent Cochrane review of the use of methylxanthines concluded that both theophylline and caffeine are effective in reducing both apnea episodes and the use of mechanical ventilation in preterm infants. In many centers (including ours), xanthine therapy is employed routinely to enhance successful extubation of very low-birthweight infants. The review further concluded that caffeine was the preferable drug and that studies of the long-term effects of methylxanthine treatment on growth and development were needed. These issues are being addressed in an ongoing international trial in which preterm infants are being randomized to caffeine or placebo therapy, with neurodevelopmental outcome as a major endpoint.

Elimination of methylxanthines is prolonged in infants compared with children or adults, and it is especially prolonged in preterm infants. The half-life of caffeine in preterm infants averages 50 hours. The metabolic pathways for the elimination of theophylline are underdeveloped in the preterm infant and include conversion by methylation to caffeine. Overall, disposition can be highly unpredictable. Serum concentrations of methylxanthines may vary considerably among infants and are not entirely predictable based on dosage. Serum concentrations of theophylline should be monitored whenever aminophylline or theophylline is used. Caffeine levels are less critical, but they also may be followed at the beginning of treatment. Xanthine therapy should be discontinued at least 1 to 2 weeks prior to discharge, a guideline that is especially relevant for caffeine because of its longer half-life.

The methylxanthines have some well-documented adverse effects. Toxic levels may produce tachycardia, cardiac dysrhythmias, feeding intolerance, and infrequently seizures, although these effects are seen less commonly with caffeine at the usual therapeutic doses. Mild diuresis is caused by all methylxanthines. Certain drug-drug interactions are relevant to methylxanthines, particularly medications that affect liver function and those whose clearance depends on cytochrome P-450. The half-life of methylxanthines is prolonged in infants who have liver disease. The observation that xanthine

therapy causes an increase in metabolic rate and oxygen consumption of approximately 20% suggests that caloric demands may be increased with this therapy at a time when nutritional intake already is compromised.

Role of Continuous Positive Airway Pressure

Nonpharmacologic strategies also are used widely in the treatment of apnea. Tactile stimulation often terminates a brief episode, and this is a frequent nursing intervention in neonatal intensive care units. Continuous positive airway pressure (CPAP) at 5 to 6 cm H₂O is relatively safe and effective therapy. Because longer episodes of apnea frequently involve an obstructive component, CPAP appears to be effective by splinting the upper airway with positive pressure and decreasing the risk of pharyngeal or laryngeal obstruction. CPAP also probably benefits apnea by increasing functional residual capacity (FRC), thereby improving oxygenation status. It has been shown that at higher FRC, time from cessation of breathing to desaturation and resultant bradycardia is prolonged. High-flow nasal cannula therapy recently was suggested as an equivalent treatment modality that may allow CPAP delivery while enhancing mobility of the infant. For severe or refractory episodes, endotracheal intubation and artificial ventilation may be needed. Minimal ventilator settings should be used to allow for spontaneous ventilatory efforts and to minimize the risk of barotrauma.

Management of Persistent Apnea and Role of Home Monitoring

Apnea of prematurity generally resolves by about 36 to 40 weeks' postconceptional age. However, in the most immature infants (24 to 28 weeks' gestation), apnea frequently persists beyond 36 weeks' postconceptional age and may persist beyond 40 weeks' postconceptional age. Recent findings suggest that cardiorespiratory events in such infants return to the baseline "normal" level at about 43 to 44 weeks' postconceptional age. In other words, beyond 43 to 44 weeks' postconceptional age, the incidence of cardiorespiratory events in preterm infants does not significantly exceed that in term babies (Fig. 2).

Apnea and bradycardia are resolved in many preterm infants by the time they are ready for hospital discharge, as determined by maturation of temperature control and feeding pattern. An apnea-free observation period, usually ranging from 3 to 7 days, is used as a criterion for determining the discharge date. For a subset of infants, however, the persistence of cardiorespiratory events may delay discharge. In these infants, apnea longer than

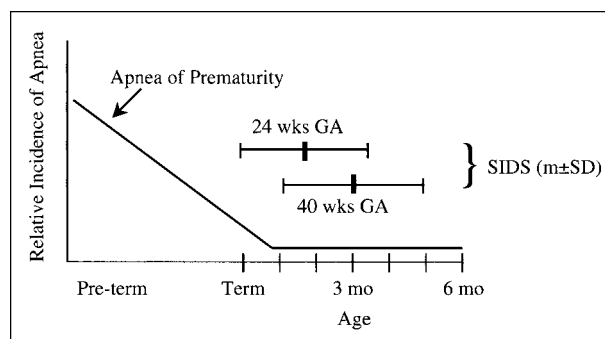


Figure 2. Relative incidence of apnea episodes in preterm infants with advancing postnatal age. The typical ages for sudden infant death syndrome (SIDS) deaths are shown by the horizontal bars (mean±SD) that include most SIDS deaths. The typical age for SIDS deaths in the most immature infants (eg, 24 weeks' gestational age) is shifted to the left, but not into the zone of relatively higher incidence of apnea episodes. GA=gestational age

20 seconds is rare; rather, they exhibit frequent bradycardia to less than 70 or 80 beats/min with short respiratory pauses. The reason why some infants exhibit marked bradycardia with short pauses is unclear. For a few of these infants, home cardiorespiratory monitoring until 43 to 44 weeks' postconceptional age may offer an alternative to a prolonged hospital stay.

Apnea and Sudden Infant Death Syndrome

The apparent lack of a relationship between persistent apnea of prematurity and sudden infant death syndrome (SIDS) has become clearer in recent years. Significant progress in reducing the rate of SIDS was made with the "Back to Sleep" program for term and preterm infants. This effort was based on the observation that decreasing the incidence of prone sleeping (in conjunction with avoidance of cigarette smoke exposure and overheating of an infant) reduced the rate of SIDS. The finding of an intervention that decreased SIDS rates helped remove some of the mystery surrounding these deaths that are by definition unexplained. Apnea and SIDS remain linked epidemiologically because they both occur in certain population groups (eg, preterm infants). Although early case reports seemed to indicate that children who had apnea were at risk of dying of SIDS, careful analysis of a large cohort of infants failed to find any relationship between apnea and later deaths. Currently, no clinical evidence reliably links a ventilatory control abnormality to SIDS.

Long-term Effect of Apnea

Because idiopathic apnea is seen most often in high-risk preterm infants, separating the consequences of preterm birth from the effects of apnea of prematurity has proven difficult. Infants born prematurely often experience multiple problems during their time in the neonatal intensive care unit, and many of these conditions, particularly periventricular leukomalacia and intraventricular hemorrhage, may contribute to poor neurodevelopmental outcome. Additionally, studies that assess improvement in long-term outcome as a result of treating apnea of prematurity are few and confounded by these same issues.

Two recent reports of long-term follow-up of these at-risk infants have addressed this problem. In one cohort of preterm infants followed to early school age, apnea of prematurity was among the factors that predicted poor neurodevelopmental outcomes. The outcomes measured included cognitive function, neuropsychological abilities, academic achievement, and parent and teacher ratings of child behavior and school performance. In another series of very low-birthweight infants followed to 24 months of age, pre-discharge apnea correlated with lower mental and motor neurodevelopmental scores. Other series of case comparisons have reported no difference in the outcome of infants who have had apnea. It is possible that recurrent hypoxia is the detrimental feature of the breathing abnormalities exhibited by preterm infants. Finally, a possible relationship between

apnea of prematurity and sleep-disordered breathing in childhood is being explored.

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NeoReviews Quiz

7. Although immaturity of the mechanisms of respiratory control is the major determinant of apnea in preterm neonates, other causes of apnea warrant investigation, particularly in an infant who has an unexpected increase in the frequency of episodes. Of the following, the *least* confirmed cause of apnea in preterm neonates is:
 - A. Anemia.
 - B. Gastroesophageal reflux.
 - C. Intracranial hemorrhage.
 - D. Perinatal asphyxia.
 - E. Sepsis.
8. Methylxanthines are used frequently in the pharmacologic treatment of apnea in preterm neonates. Of the following, the *most* important mechanism of action of methylxanthines in the treatment of apnea of prematurity is:
 - A. Competitive antagonism of adenosine receptors.
 - B. Enhanced activity of the diaphragm.
 - C. Increased carbon dioxide sensitivity of the neural respiratory center.
 - D. Stimulation of the laryngeal abductor muscle.
 - E. Suppression of the carotid body chemoreceptor.
9. A 6-week-old preterm infant whose estimated gestational age at birth was 26 weeks is being readied for discharge to home. Her mother asks about the need for cardiorespiratory monitoring at home. Of the following, the *most* likely postmenstrual age at which such monitoring would be discontinued in this infant would be:
 - A. 36 weeks.
 - B. 38 weeks.
 - C. 40 weeks.
 - D. 42 weeks.
 - E. 44 weeks.
10. Caffeine has several advantages over theophylline for the treatment of apnea of prematurity, including which of the following?
 - A. Longer half-life, allowing for less frequent dosing.
 - B. No need for a loading dose.
 - C. No associated feeding intolerance.
 - D. Faster onset of action.
 - E. No effect on metabolic rate.
11. Disposition of methylxanthines:
 - A. Is consistent among patients.
 - B. Proceeds by the same metabolic pathways in infants and adults.
 - C. Is enhanced in preterm infants.
 - D. Includes the conversion of theophylline to caffeine.
 - E. Can be predicted based on dosage.
12. Which of the following conditions may cause apnea in a preterm infant?
 - A. Metabolic alkalosis.
 - B. Spina bifida.
 - C. Prostaglandin E₁ administration for a ductal-dependent cardiac lesion.
 - D. Diaphragmatic hernia.
 - E. Meconium aspiration.

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