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# Apnea of Prematurity

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## abstract

Apnea of prematurity is one of the most common diagnoses in the NICU. Despite the frequency of apnea of prematurity, it is unknown whether recurrent apnea, bradycardia, and hypoxemia in preterm infants are harmful. Research into the development of respiratory control in immature animals and preterm infants has facilitated our understanding of the pathogenesis and treatment of apnea of prematurity. However, the lack of consistent definitions, monitoring practices, and consensus about clinical significance leads to significant variation in practice. The purpose of this clinical report is to review the evidence basis for the definition, epidemiology, and treatment of apnea of prematurity as well as discharge recommendations for preterm infants diagnosed with recurrent apneic events.

## BACKGROUND

Apnea of prematurity is one of the most common diagnoses in the NICU. Despite the frequency of apnea of prematurity, it is unknown whether recurrent apnea, bradycardia, and hypoxemia in preterm infants are harmful. Limited data suggest that the total number of days with apnea and resolution of episodes at more than 36 weeks' postmenstrual age (PMA) are associated with worse neurodevelopmental outcome in preterm infants.[1,2] However, it is difficult to separate any potential adverse effects of apnea from the degree of immaturity at birth, because the incidence of apnea is inversely proportional to gestational age.[3] Research into the development of respiratory control in immature animals and preterm infants has facilitated our understanding of the pathogenesis and treatment of apnea of prematurity (Table 1). However, the lack of consistent definitions, monitoring practices, and consensus about clinical significance leads to significant variation in practice.[4–6] The purpose of this clinical report is to review the evidence basis for the definition, epidemiology, and treatment of apnea of prematurity as well as discharge recommendations for preterm infants diagnosed with recurrent apneic events.



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## DEFINITION AND CLASSIFICATION

An apneic spell is usually defined as a cessation of breathing for 20 seconds or longer or a shorter pause accompanied by bradycardia (<100 beats per minute), cyanosis, or pallor. In practice, many apneic events in preterm infants are shorter than 20 seconds, because briefer pauses in airflow may result in bradycardia or hypoxemia. On the basis of respiratory effort and airflow, apnea may be classified as central (cessation of breathing effort), obstructive (airflow obstruction usually at the pharyngeal level), or mixed. The majority of apneic episodes in preterm infants are mixed events, in which obstructed airflow results in a central apneic pause, or vice versa.

## EPIDEMIOLOGY AND TIME COURSE TO RESOLUTION

In an observational study, Henderson-Smart[3] reported that the incidence of recurrent apnea increased with decreasing gestational age. Essentially, all infants born at ≤28 weeks' gestation were diagnosed with apnea; beyond 28 weeks' gestation, the proportion of infants with apnea decreased, from 85% of infants born at 30 weeks' gestation to 20% of those born at 34 weeks' gestation. This relationship has important implications for NICU policy, because infants born at less than 35 weeks' gestation generally require cardiorespiratory monitoring after birth because of their risk of apnea. As expected with a developmental process, some infants born at 35 to 36 weeks' gestation may have respiratory control instability, especially when placed in a semiupright position.[7]

In Henderson-Smart's study, apneic spells stopped by 37 weeks' PMA in 92% of infants and by 40 weeks' PMA in more than 98% of infants.[3] The proportion of infants with apnea/bradycardia events persisting beyond 38 weeks' PMA is higher in infants who were 24 to 26 weeks' gestational age at birth compared with those born at ≥28 weeks' gestation.[8] Infants with bronchopulmonary dysplasia may have delayed maturation of respiratory control, which can prolong apnea for as long as 2 to 4 weeks beyond term PMA.[8] In most infants, apnea of prematurity follows a common natural history, with more severe events that require intervention resolving first. Last to resolve are isolated, spontaneously resolving bradycardic events of uncertain clinical significance.[8]

Most studies examining the time course to resolution of apnea of prematurity have relied on nurses' recording of events in the medical record; however, several studies have shown a lack of correlation with electronically recorded events.[9,10] Standard NICU monitoring techniques are unable to detect events that are primarily obstructive in nature. With continuous electronic recording, it is evident that some preterm infants continue to have clinically unapparent apnea, bradycardia, and oxygen desaturation events even after discharge. The Collaborative Home Infant Monitoring Evaluation Study examined the occurrence of apnea/bradycardia events in >1000 preterm and healthy term infants monitored at home.[11] "Extreme events" (apnea >30 seconds and/or heart rate <60 beats per minute for >10 seconds) were observed most frequently in former preterm infants, decreasing dramatically until about 43 weeks' PMA. After 43 weeks' PMA, "extreme events" in both preterm and term infants were very rare.

Preterm infants with resolved apnea also may have clinically unapparent intermittent hypoxia events. In a recent study in former preterm infants after discontinuation of medical therapy for apnea, the mean number of seconds/hour of oxygen saturation less than 80% was 20.3 at 35 weeks' PMA, decreasing to 6.8 seconds/hour at 40 weeks' PMA.[12]

## MONITORING FOR APNEA/BRADYCARDIA

Most infants in NICUs are continuously monitored for heart rate, respiratory rate, and oxygen saturation. Cardiac alarms are most commonly set at 100 beats per minute, although lower alarm settings are acceptable in convalescent preterm infants. Apnea alarms are generally set at 20 seconds. However, apnea detection by impedance monitoring is potentially misleading. Impedance monitoring is prone to artifact attributable to body movement or cardiac activity and is unable to detect obstructive apnea. Practices differ as to when continuous oximetry is discontinued. In a study investigating the age at last recorded apnea and age at discharge from the hospital in 15 different NICUs, the duration of use of pulse oximetry was significantly different among hospital sites.[5] Later discontinuation of pulse oximetry was associated with a later PMA at recorded last apnea and longer length of stay, suggesting that oximetry may detect events that cardiorespiratory monitoring does not.

There are no data to suggest that a diagnosis of apnea of prematurity is

**TABLE 1** Factors Implicated in the Pathogenesis of Apnea of Prematurity

| Central Mechanisms | Peripheral Reflex Pathways |
|---|---|
| Decreased central chemosensitivity | Decreased carotid body activity |
| Hypoxic ventilatory depression | Increased carotid body activity |
| Upregulated inhibitory neurotransmitters | Laryngeal chemoreflex |
| Delayed central nervous system development | Excessive bradycardic response |

associated with an increased risk of sudden infant death syndrome (SIDS) or that home monitoring can prevent SIDS in former preterm infants. Although infants born preterm have a higher risk of SIDS, epidemiologic and physiologic data do not support a causal link with apnea of prematurity. The mean PMA for SIDS occurrence for infants born between 24 and 28 weeks' gestation is estimated to be 47.1 weeks, compared with 53.5 weeks for term infants.[13] Apnea of prematurity resolves at a PMA before which most SIDS deaths occur; in the Collaborative Home Infant Monitoring Evaluation Study, extreme events in former preterm infants resolved by 43 weeks' PMA.[11] As such, routine home monitoring for preterm infants with resolved apnea of prematurity is not recommended. Cardiorespiratory monitoring after hospital discharge may be prescribed for some preterm infants with an unusually prolonged course of recurrent, extreme apnea. Current evidence suggests that if such monitoring is elected, it can be discontinued in most infants after 43 weeks' PMA unless indicated by other significant medical conditions.[14]

## TREATMENTS

### Xanthine Therapy

Methylxanthines have been the mainstay of pharmacologic treatment of apnea for decades. Adverse effects include tachycardia, emesis, and jitteriness. Both theophylline and caffeine are used, but caffeine citrate is preferred because of its longer half-life, higher therapeutic index, and lack of need for drug-level monitoring. Xanthines have multiple effects on respiration, including increased minute ventilation, improved carbon dioxide sensitivity, decreased periodic breathing, and decreased hypoxic depression of breathing. Their primary mechanism of action is thought to be blockade of inhibitory adenosine $A_1$ receptors, with resultant excitation of respiratory neural output, as well as blockade of excitatory adenosine $A_{2A}$ receptors located on γ-aminobutyric acidergic neurons. Specific polymorphisms in the $A_1$ and $A_{2A}$ adenosine receptor genes have been associated with a higher risk of apnea of prematurity as well as variability in response to xanthine therapy.[15] These observations may help explain apparent genetic susceptibility to apnea of prematurity, high concordance of its diagnosis in twins, and variability in response to xanthine therapy.[16]

The largest trial of caffeine citrate (Caffeine for Apnea of Prematurity Trial) randomly assigned 2006 infants with birth weights between 500 and 1250 g to caffeine or placebo in the first 10 postnatal days to prevent or treat apnea or to facilitate extubation.[17] Dosing of caffeine citrate in this study included a loading dose of 20 mg/kg followed by maintenance of 5 mg/kg per day, which could be increased to 10 mg/kg per day for persistent apnea. Caffeine-treated infants had a shorter duration of mechanical ventilation, lower incidence of bronchopulmonary dysplasia, and improved neurodevelopmental outcome at 18 months.[18] Differences in neurodevelopmental outcome were less evident at 5 years but favored the caffeine-treated subjects.[19] The study did not collect data on the frequency of apnea and therefore did not directly address the effect of caffeine on apnea; however, the data indicated that caffeine therapy, as used clinically in this trial, is safe and may have additional benefits by yet unknown mechanisms. However, the use of prophylactic caffeine solely for potential neurodevelopmental benefits requires additional study.

The optimal time to start caffeine therapy in infants at risk of apnea is not known. In infants >28 weeks' gestation who do not require positive pressure support, one reasonable approach would be to await the occurrence of apnea before initiating therapy.[20] In the Caffeine for Apnea of Prematurity Trial, earlier treatment with caffeine (<3 days) compared with later (≥3 days) was associated with a shorter duration of mechanical ventilation, although it is not clear whether infants started earlier on caffeine were assessed to be more likely to be extubated soon.[21] In a retrospective cohort study in 62 056 infants with very low birth weight discharged between 1997 and 2010, early caffeine therapy compared with later therapy was associated with a lower incidence of bronchopulmonary dysplasia (23.1% vs 30.7%; odds ratio: 0.68; 95% confidence interval: 0.69–0.80) as well as a shorter duration of mechanical ventilation (mean difference: 6 days; $P < .001$).[22] Further trials are needed to assess the safety and the potential benefits of early prophylactic caffeine in infants who require mechanical ventilation.

No trials have addressed when to discontinue xanthine treatment in preterm infants; however, timely discontinuation is advised to avoid unnecessary delays in discharge. Because of variability in when apnea resolves, the use of any specific gestational age may result in unnecessarily continuing therapy.[4,5,8] One approach might be a trial off therapy after a clinically significant apnea-free period (off positive pressure) of 5 to 7 days or 33 to 34 weeks' PMA, whichever comes first. However, there may be significant effects of caffeine on respiratory control in preterm infants with clinically resolved apnea. A recent study in preterm infants who had been treated with caffeine for apnea showed a decrease in the frequency of intermittent hypoxia episodes in those who received a prolonged course of therapy compared with a

usual-care group.[12] Further study is necessary to determine the implications of this finding.

### Nasal Continuous Positive Airway Pressure

Nasal continuous positive airway pressure (NCPAP) at pressures of 4 to 6 cm $H_2O$, usually in conjunction with treatment with a xanthine, is effective in reducing the frequency and severity of apnea in preterm infants.[23] It appears to work by splinting open the upper airway and decreasing the risk of obstructive apnea.[23] NCPAP may also decrease the depth and duration of oxygen desaturation during central apneas by helping maintain a higher end-expiratory lung volume. Limited evidence suggests that variable-flow continuous positive airway pressure (CPAP) devices may be more effective in the reduction in apnea events than conventional delivery systems for CPAP (ventilator or bubble CPAP).[24]

Humidified high-flow nasal cannula or nasal intermittent positive-pressure ventilation may be acceptable substitutes for NCPAP. However, larger studies that specifically examine the advantages and disadvantages of nasal intermittent positive-pressure ventilation and high-flow nasal cannula versus conventional NCPAP on the incidence and severity of recurrent apnea are needed.

### Blood Transfusion

An increase in respiratory drive resulting from increased oxygen-carrying capacity, total content of oxygen in the blood, and increased tissue oxygenation is the proposed mechanism for red blood cell transfusions to reduce apnea of prematurity. Retrospective and prospective studies of the effects of blood transfusions on the incidence and severity of recurrent apnea in preterm infants are conflicting, perhaps because of a lack of blinding of caregivers.[25,26] A recent study that used a novel computer algorithm to detect apnea, bradycardia, and oxygen desaturation in continuously recorded physiologic data from 67 preterm infants showed decreased apnea for the 3 days after blood transfusions compared with 3 days before.[27] These authors also reported that the probability of an apnea event in a 12-hour epoch was higher with a lower hematocrit, adjusted for PMA. These results suggest that anemia may increase the likelihood of apnea of prematurity and that blood transfusions may result in a short-term reduction in apnea. However, there are no data to indicate that blood transfusion results in any long-term reduction in apnea.

### Gastroesophageal Reflux Treatment

Preterm infants have a hyperreactive laryngeal chemoreflex response that precipitates apnea when stimulated. In addition, almost all preterm infants show some degree of gastroesophageal reflux (GER). These 2 physiologic observations have led to speculation that GER can precipitate apnea in preterm infants and that pharmacologic treatment of GER might decrease the incidence or severity of apnea. Despite the frequent coexistence of apnea and GER in preterm infants, several studies examining the timing of reflux episodes in relation to apneic events indicate that they are rarely temporally related.[28,29] Additional data indicate that GER does not prolong or worsen concurrent apnea.[30] There is no evidence that pharmacologic treatment of GER with agents that decrease gastric acidity or that promote gastrointestinal motility decreases the risk of recurrent apnea in preterm infants.[31,32] Indeed, some studies have shown a coincident increase in recorded events with pharmacologic treatment of GER.[32] In addition, recent data suggest harmful effects (including an increased incidence of necrotizing enterocolitis, late-onset sepsis, and death) of medications to reduce gastric acidity in preterm infants.[33]

## DISCHARGE CONSIDERATIONS

Practice and management surrounding discharge decisions for infants with apnea of prematurity vary widely, but most physicians require infants to be apnea/bradycardia free for a period of time before discharge. In 1 survey, the majority of neonatologists (approximately 75%) required a 5- to 7-day observation period.[4] Common practice is to initiate this countdown period a few days after discontinuation of caffeine therapy (caffeine half-life, approximately 50–100 hours)[34] and to include only spontaneously occurring (ie, not feeding-related) events. Limited information exists about the recurrence of apnea or bradycardia after a specific event-free period. In a retrospective cohort of 1400 infants born at ≤34 weeks' gestation, Lorch et al[35] reported that a 5- to 7-day apnea-free period successfully predicted resolution of apnea in 94% to 96% of cases. However, the success rate was significantly lower for infants born at younger gestational ages. A 95% success rate threshold was 1 to 3 apnea-free days for infants born at ≥30 weeks' gestation, 9 days for those born at 27 to 28 weeks' gestation, and 13 days for infants born at <26 weeks' gestation. Similar gestational age effects were observed in another smaller retrospective study by Zupancic et al.[36] These results suggested that the specified event-free period need not be uniform for all infants, and shorter durations may be considered for older gestational ages. However, such recommendations are based on observed events, which may not be accurate, and the prescribed event-free periods do not

preclude the possibility that a new circumstance (eg, intercurrent illness) may result in the re-emergence of apnea.

Discharge considerations are usually based on nursing observation and recording of apnea or bradycardia events, which may not always correlate with those events that are electronically recorded.[9,10] Preterm infants with a history of apnea who are otherwise deemed ready for discharge may have clinically unsuspected apnea, bradycardia, and/or hypoxemia events if archived continuous electronic recording is interrogated.[37] There is no evidence, however, that such events predict the recurrence of clinically significant events on discharge, SIDS, or the need for readmission to the hospital. As such, more intensive monitoring or pneumogram recordings in convalescent preterm infants approaching discharge may not be useful. However, standardizing the documentation and clinical approach to apnea within individual NICUs may reduce the variation in discharge timing.[38]

Infants born preterm may develop apnea and other signs of respiratory control instability with certain stresses, including general anesthesia and viral illnesses. Additional close monitoring in these situations may be indicated in preterm infants until 44 weeks' PMA, including former preterm infants readmitted for elective surgical procedures, such as hernia repair. In addition, the exacerbation of apnea has been reported in very preterm infants after their initial 2-month immunizations or ophthalmologic examinations, and rarely after the 4-month immunizations, while still in the NICU.[39]

## CLINICAL IMPLICATIONS

1. Apnea of prematurity reflects immaturity of respiratory control. It generally resolves by 36 to 37 weeks' PMA in infants born at ≥28 weeks' gestation.
2. Infants born at <28 weeks' gestation may have apnea that persists to or beyond term gestation.
3. Individual NICUs are encouraged to develop policies for cardiorespiratory monitoring for infants considered at risk of apnea of prematurity.
4. Initial low heart rate alarms are most commonly set at 100 beats per minute. Lower settings for convalescent preterm infants older than 33 to 34 weeks' PMA may be reasonable.
5. Caffeine citrate is a safe and effective treatment of apnea of prematurity when administered at a 20-mg/kg loading dose and 5 to 10 mg/kg per day maintenance. Monitoring routine serum caffeine levels usually is not contributory to management. A trial off caffeine may be considered when an infant has been free of clinically significant apnea/bradycardia events off positive pressure for 5 to 7 days or at 33 to 34 weeks' PMA, whichever comes first.
6. Evidence suggests that GER is not associated with apnea of prematurity, and treatment of presumed or proven GER solely for the reduction in apnea events is not supported by currently available evidence.
7. Brief, isolated bradycardic episodes that spontaneously resolve and feeding-related events that resolve with interruption of feeding are common in convalescent preterm infants and generally need not delay discharge.
8. Individual units are encouraged to develop policies and procedures for caregiver assessment, intervention, and documentation of apnea/bradycardia/desaturation events as well as the duration of the period of observation before discharge.
9. A clinically significant apnea event–free period before discharge of 5 to 7 days is commonly used, although a longer period may be suitable for infants born at less than 26 weeks' gestation. The specific event-free period may need to be individualized for some infants depending on the gestational age at birth and the nature and severity of recorded events.
10. Interrogation of electronically archived monitoring data may reveal clinically unsuspected events of uncertain significance. Such events do not predict subsequent outcomes, including recurrent clinical apnea or SIDS.


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## ABBREVIATIONS

CPAP: continuous positive airway pressure
GER: gastroesophageal reflux
NCPAP: nasal continuous positive airway pressure
PMA: postmenstrual age
SIDS: sudden infant death syndrome

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