

Clinical Performance Guideline
Neonatal Resource Services
Apnea and Bradycardia

**Medical Necessity
Guideline**

Purpose: To provide guidelines for the management and follow-up of neonatal and infantile apnea to determine the optimal course of treatment and subsequent case management of the neonate with neonatal apnea.

Target Client Population: Preterm and full-term neonates with the following diagnosis(es): Apnea: with or without bradycardia, and/or significant hypoxemic desaturations.

<p>Background</p>	<p>For decades investigators have tried to understand the complex developmental neuropathology involved in apnea of prematurity (AOP) in an effort to interrupt or treat apnea. There is lack of consistent definitions and monitoring practices for AOP. This may lead to significant variation in practice. (Eichenwald, 2016)</p> <p>In the preterm infant, an apnea event may include a shorter pause in airflow that may result in bradycardia or hypoxemia. Recurrent events are frequently a manifestation of general problems and may lead to events requiring intervention. The AAP defines infant apnea as cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia (<100 bpm), cyanosis, pallor, and/or marked hypotonia. (Eichenwald, 2016)</p> <p>The clinical goal is establishment of regular breathing patterns in infants to facilitate a safe discharge from the NICU and, in select patients, outpatient follow up until they “outgrow” their respiratory control immaturity.</p> <p>Supportive as well as pharmacological treatments are incorporated into clinical practice to diminish the frequency and severity of central apneas.</p> <p>The challenge with neonates is determining when to safely remove medical treatment and/or monitoring electronically and let the infant mature and self-regulate his or her own breathing.</p> <p>Apnea of infancy, as opposed to AOP, refers to infants > 37 weeks’ gestation at the onset of apnea and is likely to be associated with underlying etiology. In stable term infants, heart rates as low as 70 beats per minute while sleeping are acceptable. (Benitz, 2015) The AAP has made recommendations for older infants readmitted due to brief resolved unexplained events (BRUEs) formerly known as apparent life threatening events (ALTEs).</p>
<p>Treatment Criteria</p>	<p><u>Clinical evidence supports the following:</u></p> <p><u>Diagnostic(s)</u></p> <ul style="list-style-type: none"> • Apnea and bradycardia experienced during feeding is not directly related to AOP. Events are not more prevalent post-feeding. (Slocum, 2009) • Feed-related events that do not cease following interruption of the feeding should prompt for immediate caregiver feeding education, training and review of the discharge plan. • Gastroesophageal Reflux (GER) is rarely associated with apnea. Antireflux

medications (e.g., antacids, prokinetic agents, proton-pump inhibitors) are not recommended in the neonate due to ineffectiveness and potential treatment complications. (Tipnis, 2009; Wheatley, 2009; Eichenwald, 2016; Ho, 2015)

- Apnea and/or bradycardia may be induced by care interventions (e.g., eye examination, suctioning, placement of a gavage tube) and are not necessarily related to immaturity or underlying pathology.
- Term infants should have an appropriate evaluation for the etiology of apnea and hospital stay should be based on the underlying diagnosis and related comorbidities.
- Pneumocardiograms (PCGs) are not recommended in the management of apnea because they have a high false-positive rate, cannot predict with accuracy the occurrence of severe apnea or death, and are not beneficial in identifying which patients should be discharged with a home monitor. (AAP, 2008)

Medication Therapy

- Methylxanthines (caffeine, aminophylline and theophylline) help to reduce the frequency of events in infants with central apnea and are appropriate.
- Caffeine is the only FDA approved treatment for AOP and is the preferred drug of choice for this indication particularly due to its long half-life, wide therapeutic index and lack of need to monitor drug level. Theophylline is not recommended due to its side effects including the increased risk of seizures, tachycardia and feeding intolerance.
- It is recommended to discontinue caffeine once the infant is apnea free for 5-7 days off positive airway pressure (defined by high-flow nasal cannula or CPAP) or by 33-34 weeks, whichever comes sooner. (Eichenwald, 2016) Failure to stop caffeine in a timely manner can lead to an unnecessary delay in discharge.
- Because caffeine has a long half-life it needs to be discontinued before the infant is ready to be discharge. Observation is more important than testing with caffeine levels.
- An observation period of 5-7 days after discontinuing caffeine is a reasonable timeframe to demonstrate cardio-respiratory stability before safe hospital discharge.
- Caffeine is generally considered very safe with a broad therapeutic index. Although caffeine toxicity can occur at higher doses, routine checking of caffeine levels has not been recommended.

Home Monitoring

- Home apnea monitoring might be considered for infants discharged home on caffeine.
- An association between AOP and an increased risk for sudden infant death is not supported in the medical literature. (Eichenwald, 2016) Due to lack of medical evidence, home monitoring to prevent SIDS is not recommended.
- Home respiratory monitoring may be warranted to recognize events in

premature infants who are at high risk of recurrent episodes of apnea, bradycardia, and hypoxemia.

- Home apnea monitors would be appropriate for neonates who have experienced an ALTE and who are technology-dependent (ventilator, tracheostomy with collar, gastrostomy, etc.), have unstable airways, have rare medical conditions affecting regulation of breathing, or have symptomatic chronic lung disease.
- CPR and home monitoring equipment training for parent(s)/caregivers(s) are recommended prior to discharge.
- Caregiver education, training, discharge teaching and rooming-in should be considered concurrently with other aspects of hospital care.
- The use of home cardiorespiratory monitoring up until 43 weeks post menstrual age (PMA) may be considered for infants who continue to have unresolved apneic events. (Eichenwald, 2016)

Apnea Countdown/Discharge

- An apnea/bradycardia “countdown” of up to 5 days for a preterm infant is a reasonable period to demonstrate cardio-respiratory stability before a safe hospital discharge. However, for infants born at ≤ 30 weeks’ gestation up to a 7-day countdown may be appropriate. There may be select infants born at less than 26 weeks’ gestation that warrant a longer observation period prior to discharge based on their individual frequency and severity of events. (Eichenwald, 2016)
- In convalescing preterm infants, brief isolated self-limited bradycardia occurrences and feed-related events that cease with interruption of the feeding are not indications to delay discharge. (Eichenwald, 2016) Extended stay for a brief observation period may be warranted based on the degree and duration of the bradycardia event.
- For infants who have feeding-related events that do not cease with interruption of the feeding, consideration should be given to providing the caregiver feeding education and training with appropriate discharge follow-up. “Full” countdown periods are not indicated.
- Brief self-limited oxygen desaturation events are not an indication to delay discharge. Extended stay for a brief observation period may be warranted based on the degree and duration of the desaturation event.
- Routine screening of infants with PCGs is not appropriate and its use is not an applicable reason to delay discharge from the hospital. (AAP, 2008; Ho, 2015)
- An apnea/bradycardia countdown in a term infant should be based on etiology. Up to 3 days observation may be appropriate in the majority of such cases.
- Since apnea, bradycardia and oxygen desaturation can persist in maturing preterm infants, repeat countdowns, in general, should be reserved for infants with events needing significant intervention. (Ramanathan, 2001)

	<ul style="list-style-type: none"> If an infant fails two apnea countdowns, consideration should be given to discharge on a home monitor, initiation or restart of caffeine, or a search for other etiologies.
Clinical Evidence	<ul style="list-style-type: none"> A clinical practice guideline from the AAP (Tieder et al, 2016) outlines the replacement of the term ALTE (apparent life-threatening events) with BRUE (brief resolved unexplained events) and provides graded recommendations for the evaluation and management of infants at-risk for these events based on current evidence. The goals of this guideline include a reduction in costly and unnecessary medical interventions, promotion of a family- and patient-centered approach to care, and improvement of patient outcomes in infants <1 year of age who have experienced a BRUE. A clinical report from the American Academy of Pediatrics authored by Eichenwald et al (2016) reviewed the evidence on the definition, epidemiology and treatment of AOP. A significant variation in apnea monitoring practices among NICUs has been observed throughout the country. Based on an observational study by Henderson-Smart it was noted that the proportion of infants with apnea decreases significantly with increasing gestational age, particularly beyond 30 weeks' gestation. Implementation of policies and procedures for documenting and monitoring cardiorespiratory events would promote consistency in discharge timing. Discharge readiness would include an event-free period of time which may require individualization based on the infant's gestational age at birth and characteristics of the recorded events. A Cochrane review by Ballout et al (2017) evaluated whether body positioning affected cardiac and respiratory activity in spontaneously breathing preterm infants with clinically significant apnea. Five RCTs of cross-over design with 114 preterm infants <37 weeks' gestation were included for analysis. Comparators included supine vs prone, prone vs right lateral, prone vs left lateral, right lateral vs left lateral, prone horizontal vs prone head elevated, right lateral horizontal vs right lateral head elevated, and left lateral horizontal vs left lateral head elevated. The evidence was of low to very low quality and was identified as insufficient to determine whether body positioning affected oxygen saturation, bradycardia and apnea in this patient population. The authors concluded that it may be reasonable to assume positioning of the spontaneously breathing preterm infant does not affect their cardiorespiratory responses. As part of the "Choosing Wisely" campaign Ho et al (2015) identified five tests and procedures in newborn medicine that contributed to health care waste. Two of these items were focused on preterm infants with apnea. The authors indicated the routine use of pneumograms for evaluation of ongoing and/or prolonged apneic events prior to discharge should be avoided because routine testing has not demonstrated a reduction in acute life-threatening events or mortality. It was also noted that the routine use of GER medications should be avoided. Not only is there a paucity of evidence supporting their efficacy in treating apnea and desaturation, several clinical studies have demonstrated adverse physiological effects in infants. <p><u>SIDS</u></p> <ul style="list-style-type: none"> In 2004, Kiechl-Kohlendorfer, et al performed a prospective study of 164 infants to investigate whether there was an association between SIDS and ALTE. The authors found several substantial differences in SIDS and ALTE epidemiology including age at event, with ALTE manifesting 10 weeks earlier on average. In

addition, smoking in pregnancy was the only prominent SIDS risk condition that emerged as a significant risk predictor of overall ALTE. Of note, none of the ALTE infants experienced SIDS later in life. The authors concluded that although there are some similarities in the clinical presentation and epidemiology between SIDS and ALTE, they should not be considered different manifestations of the same disease.

- In an article by Zhao, et al (2011), the authors stated that the risk factors for SIDS in premature infants were strongly associated with maternal age, tobacco use, meteorologic factors (such as cold and dry weather) and genetics but not AOP.

Diagnostics

- A retrospective study by Reid et al (2017) sought to determine the frequency of cardiorespiratory events in 79 premature infants following routine exams for retinopathy. The authors determined there was an increase in cardiorespiratory events in 19-25% of these infants with the greatest increase identified in those of younger gestational age and lower birthweight. No alteration in medical care, however, was necessary for these infants in the absence of any other clinical signs of sepsis or clinical deterioration during the continuous 24 hour monitoring following the exam.
- In an article by Slocum, et al (2009), the authors conducted a retrospective review of premature infants with a gestational age of 23 to 37 weeks at birth and a post-conceptual age of 34 to 48 weeks to determine if GER and cardiorespiratory events increase after feeding. The authors concluded the common clinical impression that apnea, bradycardia and desaturations are more prevalent after feeding is not supported.
- A 2010 article by Poets indicated that hypoxemia during feeding was most likely related to an immature coordination between sucking, swallowing and breathing and potentially to an immature laryngeal chemoreflex, hypoxemia after feeding may be caused by diaphragmatic fatigue; gastro-esophageal reflux only rarely played a role.
- A 2011 article by Mathew on the pathogenesis and management of AOP stated while both GER and apnea are common in very low birth weight infants, there is no compelling evidence supporting a causal relationship between the two. He noted that there were well designed studies that have shown no temporal relationship between GER and apnea.
- In 2011, the American Academy of Pediatrics reaffirmed a 2008 policy statement on Hospital Discharge of the High Risk Neonate. This policy statement indicated that formal laboratory analyses of breathing patterns (i.e., pneumograms) were of no value in predicting SIDS and were not helpful in identifying patients who should be discharged with home monitors.
- In 2013, Mittal, et al, performed a prospective observational study of 300 infants diagnosed with ALTE to determine if a positive result on pneumography, diagnosis of gastroesophageal reflux disease (GERD), or non-treatment of those diagnosed with GERD with antireflux medications predicted an increased recurrence risk of ALTE over the first 4 weeks of follow-up. The study found that of the 228 admitted patients, 110 had pneumography. Of these, 41 were positive for apnea, GER or both. Six of these 41 infants had a recurrent ALTE during the 4 week follow-up as compared with 8 of 69 infants with normal pneumography. The authors concluded

that an abnormal result on pneumography for apnea/reflux did not predict increase in recurrence rate of ALTE during the subsequent 4 weeks and that a negative pH probe study does not affect the decision to diagnose or treat GERD where clinically indicated thus questioning the justification for doing pneumography or pH probe studies in infants with ALTE.

- A review by Finer et al (2006) discussed AOP and defined “clinically significant apnea” as outlined in the literature. The authors indicated that a breathing pause lasting longer than 20 seconds or a breathing pause lasting longer than 10 seconds that is associated with bradycardia or oxygen desaturation should be considered as a clinically significant apnea in an infant.
- The panel for the Consensus Development Conference on Infantile Apnea and Home Monitoring (NIH 1987) defined AOP as periodic breathing with pathologic apnea in a premature infant that usually ceases by 37 weeks gestation (menstrual dating). Apnea of infancy was a term that pertained to infants who were > 37 weeks gestational age when the pathologic apnea commenced.
- Benitz and the Committee on Fetus and Newborn (2015), developed a policy statement reviewing issues related to the length of initial hospitalization and readmissions in healthy term infants. Recommendations on the minimum discharge criteria for a term infant included stable vital signs for 12 hours preceding discharge. This document noted that a heart rate as low as 70 beats per minute is acceptable for a sleeping infant who is not demonstrating any signs or symptoms of circulatory compromise.

Medication Therapy

- Schmidt et al (2006, 2007) randomly assigned infants with birth weights of 500 to 1250 g during the first 10 days of life to receive either caffeine or placebo, until drug therapy for AOP was no longer needed. Of the infants who were assigned to caffeine and who remained alive at a postmenstrual age of 36 weeks, 36 percent received supplemental oxygen, as did 47 percent assigned to placebo. Positive airway pressure was discontinued one week earlier in the infants assigned to caffeine (median postmenstrual age, 31.0 weeks) than in the infants in the placebo group (median postmenstrual age, 32.0 weeks). The authors concluded that caffeine therapy for AOP reduced the rate of bronchopulmonary dysplasia in infants with very low birth weight. Follow-up assessment of these infants for neurodevelopmental issues was also performed 18-21 months of age. The rates of death, deafness, and blindness and the mean percentiles for height, weight and head circumference at follow-up did not differ significantly between the two groups. However, treatment with caffeine as compared with placebo reduced the incidence of cerebral palsy (4.4% vs. 7.3%) and of cognitive delay (33.8% vs. 38.3%). The authors concluded that caffeine therapy for AOP improved the rate of survival without neurodevelopmental disability at 18 to 21 months in infants with very low birth weight.
- In 2009, Mueni, et al, reviewed the literature regarding current management strategies for infant apnea. The authors concluded that the two most widely used methylxanthines, caffeine and theophylline, were typically prescribed in preterm infants till a gestational age of 34 to 35 weeks. However, caffeine was found to be safer and easier to give and had better therapeutic properties. Caffeine was therefore recommended for the treatment of apnea.
- In 2010, Henderson-Smart, et al, reviewed the results of six trials that reported on

the effects of methylxanthine therapy on apnea. In these studies, caffeine therapy led to a reduction in apnea and use of IPPV in the first two to seven days. The authors concluded that caffeine was effective in reducing the number of apneic attacks and the use of mechanical ventilation in the two to seven days after starting treatment. Caffeine was also associated with better longer term outcomes. In view of its lower toxicity, caffeine was the preferred drug for the treatment of apnea.

- In an article by Picone, et al (2012), the authors concluded that the duration of (caffeine) therapy for treating AOP had not been clearly established. There were no indications on whether therapy should be continued until the end of gestation or whether it should be discontinued at an earlier stage, once an apnea regression of at least one week has been observed and with a possibility of recommencing treatment in the event of recurrence. The authors additionally stated that given that AOP usually spontaneously resolves around 36-40 weeks of gestation, the treatment should be extended to this age.
- In 2013, Francart, et al, reviewed the results of a retrospective trial and concluded that (caffeine) therapy was typically continued until 32 to 34 weeks of age and it was common practice at North Carolina Children's Hospital to allow the patient to outgrow their maintenance dose.
- In 2014, Schoen, et al, reviewed the literature on neonatal methylxanthine therapy and found that methylxanthine therapies, including caffeine and theophylline are a mainstay in the treatment and prevention of AOP, although little is known about the long-term safety and efficacy of these medications. They noted that caffeine was associated with fewer adverse effects and had a wider therapeutic window when compared with theophylline. Caffeine was shown to improve acute neonatal outcomes when used promptly in larger doses.
- Marcus et al (2014) evaluated the long-term effects of caffeine therapy utilized for AOP. The authors sought to examine whether therapeutic neonatal caffeine administration resulted in long-term adverse effects on sleep architecture and ventilatory control. This prospective follow-up study of the Caffeine for Apnea of Prematurity (CAP) trial included 201 subjects aged 5-12 years who had been randomized to receive caffeine versus placebo as preterm neonates. After review of actigraphy, polysomnography and parental sleep questionnaire results no long-term adverse effects on objective or subjective sleep measures at school age were identified. No differences in sleep architecture were apparent between the children who had received caffeine therapy and the placebo group.
- An additional follow-up study of the CAP trial was performed by Doyle et al (2014). The authors evaluated whether caffeine therapy affected rates of developmental coordination disorder (DCD) in prior preterm neonates. After 1,433 five year old children were examined for clinical signs of cerebral palsy and assessed using Full-Scale IQ and the Movement Assessment Battery for children (MABC), the authors concluded that the rate of DCD was lower in children who had been treated with caffeine therapy than the children who had received placebo. No long-term adverse effects of early caffeine therapy were identified in this study.
- Tipnis & Tipnis (2009) discussed GER and GERD as they present in the preterm infant. Studies from Peter et al (2002), DiFiore et al (2005) and Barrington et al (2002) demonstrated the occurrence of both apnea and GER in preterm infants. However, evidence supported these episodes arose as separate events and not as simultaneous events. Evaluation of GER treatment with prokinetic agents has

demonstrated lack of improvement in apnea episodes.

- A cross-over trial by Wheatley & Kennedy (2009) included 18 infants and attempted to ascertain whether antireflux medications could reduce bradycardia events associated with GER. Over time, the occurrence of bradycardia episodes was found to decrease in both the placebo and drug periods. The use of either metoclopramide or ranitidine did not reduce the incidence of bradycardia events and in some preterm infants experienced an increased incidence.

Home Monitoring

- In 2001, Ramanathan, et al, performed a longitudinal cohort study of 1079 infants to determine if preterm infants, siblings of infants who died of SIDS and infants who had experienced an idiopathic, ALTE had a greater risk of cardiorespiratory events than healthy term infants. The authors found that the likelihood of experiencing at least one extreme event decreased as postconceptional age (PCA) increased until about 43 weeks PCA, after which all groups had similarly low rates of having at least one extreme event.
- In 2009, Silvestri performed a review of existing data in order to determine when it was appropriate to discontinue monitoring at hospital discharge versus when it was appropriate to prescribe monitoring in the home. He noted that when maturing cardiorespiratory patterns and resolving AOP had contributed to an apparent life threatening event (ALTE), monitoring through age 43 weeks documenting resolution of apnea and bradycardia was usually sufficient.

Surveillance

- Eichenwald, et al (2001), studied premature infants delivered at 30 to 34 6/7 weeks gestational age (GA), who were free of significant medical or surgical complications and compared postmenstrual age (PMA) at discharge to assess the impact on hospital stay of the recognition and recording of physiologic maturity and the required margin of safety. The authors concluded that NICUs vary widely in length of hospital stay for healthy premature infants. They speculated that this variation resulted in part from differences in monitoring for and documentation of AOP and feeding behavior.
- Lorch, et al (2011) performed a retrospective cohort study of infants born at 34 weeks gestational age or earlier. This study found that there was a 95% success rate reached with a 7 day apnea or bradycardia free interval. Infants with a gestational age of 30 weeks or less had a 5% to 15% lower success rate than infants with a gestational age more than 30 weeks. The authors concluded that the risk of recurrence for apnea or bradycardia differed depending on the gestational age of the infant and the postmenstrual age of the last apnea or bradycardia event.
- Eichenwald, et al (2011) performed a multicenter prospective cohort study of moderately preterm infants to determine whether the variability in length of stay would be affected by the rate of documented apnea. The authors concluded that NICU's vary in the proportion of moderately preterm infants diagnosed with apnea, which significantly affects length of stay.

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Revision History

The following are approved changes incorporated into the revision numbers indicated below.

Revision Date	Description of Change	
V1.0	05/16/2013	New Guideline (MB)
V2.0	05/01/2014	Job aid revised into medical necessity clinical guideline (LK)
V2.0	09/08/2014	Will replace JA2229739 on 01/01/2015. (CE)
V3.0	05/05/2015	Annual review with update by RS. (CE)
V4.0	05/05/2016	Annual review with revisions by RS. Information from the 2016 AAP publication added. (CE)
V5.0	05/05/2017	Annual review with revisions by AJ. Additional criteria on caffeine therapy and observation period after discontinuation included. (CE)
V6.0	05/04/2018	Annual review by AJ. Information regarding routine caffeine levels was revised to “not recommended”, the apnea/bradycardia countdown in a term infant was clarified and the content was reorganized to separate AOP from other forms of apnea. Approved by MTAC 06/07/2018. (CE)