Clinical Performance Guideline
Neonatal Resource Services
Apnea and Bradycardia

Purpose/Goal: To provide guidelines to determine the optimal course of treatment and subsequent case management of the neonate with neonatal apnea.

Target Client Population: Neonates with the following diagnosis(es): Apnea: with co-existing bradycardia, and/or significant hypoxemic desaturations.

Background
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 and remove its impact on Apparent Life Threatening Events (ALTE’s), apnea spell sequelae, and death from Sudden Infant Death Syndrome (SIDS).

In convalescing infants, pathologic apnea is commonly defined as lasting for 20 seconds duration or longer or for less than 20 seconds when accompanied by a significant decrease in heart rate <80 beats per minute or oxygen saturation <85% (excluding transient oxygen desaturation <85% without need for supplemental oxygen). (Finer, 2006)

Bradycardia is defined as heart rate <80 beats per minute. In stable term infants, heart rates as low as 70 beats per minute while sleeping are acceptable. (Benitz, 2015)

Apnea of infancy, as opposed to apnea of prematurity, refers to infants with a gestational age of 37 weeks or more at the onset of apnea and is more likely to be associated with an underlying etiology. (NIH, 1987)

Recurrent apnea events are a frequent manifestation of general problems in preterm infants often resulting in loss of effective breathing that can sometimes lead to severe hypoxemia and bradycardia requiring resuscitation.

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.

Supportive as well as pharmacological treatments are incorporated into clinical practice to diminish the frequency and severity of central apneas.

The challenge with neonates is determining when to safely remove treatment medically and/or monitoring electronically and let the infant mature and self-regulate his or her own breathing.

Treatment Criteria
Clinical evidence supports the following:

Diagnostic(s)

- Apnea and bradycardia experienced during feeding is not directly related to apnea of prematurity. Events are not more prevalent post-feeding. (Slocum, 2009)
- Prolonged hospitalization is not appropriate in neonates who have feeding-related events that do not cause significant physiologic changes and that are
easily corrected by feeding interruption. Consideration should be given to providing the caregiver feeding education and training with appropriate discharge follow-up.

- Gastroesophageal Reflux (GER) is rarely associated with apnea. Anti-reflux 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)

- Apnea and/or bradycardia induced by care interventions (e.g., eye examination, suctioning, placement of a gavage tube) are typically not associated with an 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 co-morbidities.

- 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. Thus, the routine screening of infants with PCGs is not appropriate and its use is not an applicable reason to delay discharge from the hospital.

**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. Theophylline is not recommended due to its side effects including the increased risk of seizures, tachycardia and feeding intolerance.

- Caffeine should be discontinued once the infant is off positive pressure or by 32-34 weeks, whichever comes sooner, and apnea free for 5 – 7 days.

- An observation period of 5 days for infants > 30 weeks gestation and 7 days for infants ≤ 30 weeks after discontinuing caffeine is a reasonable time frame to demonstrate cardio-respiratory stability before a safe hospital discharge.

- Home apnea monitoring might be considered for infants discharged home on caffeine.

**Home Monitoring**

- Due to lack of medical evidence, home monitoring to prevent SIDS is not appropriate.

- 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 apparent life threatening event (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.
- Any parent/caregiver rooming-in to familiarize themselves with the infant’s habits on the monitor should occur while the infant requires continued hospitalization prior to meeting discharge criteria.
- The use of home monitors up until 44 weeks post menstrual age (PMA) would be appropriate in infants with apnea of prematurity who have experienced an apparent life threatening event (ALTE).

**Apnea Countdown**

- An apnea/bradycardia “countdown” of 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 a 7-day countdown may be appropriate.
- An isolated self-limited bradycardia episode which can be physiologic in nature may be considered for a shorter countdown period.
- An apnea/bradycardia countdown of up to 3 days following the last event for a term infant is appropriate.
- 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)
- 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**

**SIDS**

- In 2004, Kiechl-Kohlendorfer, et al performed a prospective study of 164 infants to investigate whether there was an association between SIDS and apparent life threatening events (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 Zhoa, et al (2011), the authors stated that the risk factors for sudden infant death syndrome in premature infants were strongly associated with maternal age, tobacco use, meteorologic factors and genetics but not AOP.

**Diagnostics**

- 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-conceptional age of 34 to 48 weeks to determine if gastroesophageal reflux 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 apnea of prematurity stated while both gastroesophageal reflux (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 apparent life-threatening events 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 apparent life-threatening events (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 apnea of prematurity 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 apnea of prematurity 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**

- In 2006, Schmidt, et al, 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 apnea of prematurity 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 apnea of prematurity reduced the rate of bronchopulmonary dysplasia in infants with very low birth weight.

- In 2007, Schmit, et al, 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 apnea of prematurity was no longer needed. 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 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. The authors concluded that caffeine therapy for apnea of prematurity 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 on apnea. In these studies, methylxanthine therapy led to a reduction in apnea and use of IPPV in the first two to seven days. The authors concluded that Methylxanthine 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 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 apnea of prematurity. 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 Caffeine for Apnea of Prematurity (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 anti-reflux 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 demonstrated 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, apparent life-threatening event 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 apnea of prematurity had contributed to an apparent life threatening event (ALTE), monitoring through age 43 weeks documenting resolution of apnea and bradycardia was usually sufficient.

**Surveillance**

- Darnall, et al (1997), performed a retrospective review of 91 infants to determine the length of time one should wait after the cessation of apnea before sending an infant home without a monitor. The authors concluded that otherwise healthy preterm infants continued to have apneas separated by as many as 8 days before the last apnea before discharge.

- 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 apnea of prematurity 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.

**Bibliography**


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Revision History

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

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<thead>
<tr>
<th>Revision</th>
<th>Date</th>
<th>Description of Change</th>
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<td>V1.0</td>
<td>05/16/2013</td>
<td>New Guideline (MB)</td>
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<td>05/01/2014</td>
<td>Job aid revised into medical necessity clinical guideline (LK)</td>
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