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).

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.

• 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.

• The routine screening of all asymptomatic preterm infants with pneumocardiograms (PCGs) is not appropriate. In addition, pneumocardiograms (PCGs) are not recommended in the management of Apnea of Prematurity 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 discharge with a home monitor, therefore, its use is not appropriate 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.
- Once the baby is off positive pressure and episode free for 5 – 7 days, consideration should be given for discontinuing the caffeine.
- Home apnea monitoring might be considered for infants discharged home on caffeine.

Home Monitoring

- Home monitoring to prevent SIDS is not appropriate.
- Home respiratory monitoring “may be warranted for 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.
- The main caregiver(s) or parent(s) as well as ancillary caregivers must pass CPR training, and should be trained on home monitoring equipment and durable medical equipment (DME) prior to discharge.
- Parents are encouraged to room in overnight x 1 night to familiarize themselves with the baby’s habits on the monitor the evening before discharge home.
- The use of home monitors for up to 44 weeks post menstrual age (PMA) would be appropriate in infants with apnea of prematurity who have experienced an apparent life threatening event (ALTE).
- An apnea “countdown” of 5 days is a reasonable period to demonstrate cardiorespiratory stability before a safe hospital discharge. However, for babies born at < 30 weeks’ gestation a 7-day countdown is more appropriate.
- If an infant fails two apnea countdowns, consideration should be given to discharge on a home monitor, or 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 that 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.

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 at least one week has been observed and with a possibility of recommencing of 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.
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


Revision History

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

<table>
<thead>
<tr>
<th>Revision</th>
<th>Date</th>
<th>Description of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>05/16/2013</td>
<td>New Guideline (MB)</td>
</tr>
<tr>
<td>2.0</td>
<td>01/07/2014</td>
<td>Job aid revised into medical necessity clinical guideline (LK)</td>
</tr>
</tbody>
</table>