Consensus Guidelines for Management of Apnea of Prematurity
UCSF NCNC (Northern California Neonatal Consortium)

Executive summary

Definition

- Respiratory pause >20 seconds
- Shorter respiratory pause with bradycardia, desaturation, cyanosis or pallor
- "Significant" events: Require intervention, not related to feeding

Objectives

- Standardize the care of neonates with apnea of prematurity
- Minimize the use of non-evidence based treatment modalities for apnea of prematurity
- Provide guidance for safe discharge of neonates diagnosed with apnea of prematurity

Recommendations

- **How to start caffeine**
  - Load: 20 mg/kg IV
  - Maintenance therapy: 5 mg/kg q24 hours IV or PO
- **When to start caffeine**
  - <30 weeks GA (based on <1250gm in CAP Trial):
    - Start within 2 hours after birth for apnea prophylaxis regardless of level of respiratory support
  - 30-34 weeks GA:
    - Investigate & rule-out other etiologies of apnea
    - Start for repeated, severe apnea of prematurity events: Bradycardia associated with apnea, color change associated with apnea, need for stimulation for recovery, events during sleep
  - >34 weeks GA:
    - Investigate & rule-out other etiologies of apnea
    - Consider for repeated, severe apnea of prematurity events
- **When to consider discontinuation**
  - Infants born <26 weeks GA: discontinue at 36 weeks CGA
    - Consider *early* discontinuation after 35 weeks CGA if infant is apnea-free for 3 days *and* <2 weeks from anticipated discharge
    - Consider extension beyond 36 weeks if infant has persistent significant apnea events
  - Infants born ≥26 weeks GA: discontinue at 33-34 weeks CGA if apnea-free for 3 days *and* <2 weeks from anticipated discharge, unless still having significant events

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- **Discharge planning ("Countdown")**
    - Infants born <30 weeks GA: 7 day event-free observation time
    - Infants born ≥30 weeks GA: 5 day event-free observation time
    - *Note: "*event-free observation" starts 120 hours (5 days) after the last dose of caffeine
        - Evidence: Lorch SA et al: Epidemiology of apnea and bradycardia resolution in premature infants. *Pediatrics.* 2011. Aug; 129(2): e366-73.

Methods

This guideline was developed through local consensus based on published evidence and expert opinion as part of the UCSF Northern California Neonatal Consortium.
Disclaimer: These clinical practice guidelines are based upon the evidence-based consensus opinions of consortium members affiliated with UCSF Benioff Children's Hospitals. They are intended to guide pediatric/neonatal providers, but do not substitute for individual clinical judgment. Evaluation and treatment of specific patients should be adapted based upon the unique conditions of each patient, family and clinical environment.

Metrics Plan

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PART I: Background

- **Definition**
  - Respiratory pause >20 seconds
  - Shorter respiratory pause associated with bradycardia, desaturation, cyanosis or pallor
  - "Significant" events:
    - Require intervention (i.e. stimulation, oxygen, positive pressure)
    - Not related to feeding (i.e. feeding disco-ordination, post-feeding event)
- **Pathophysiology**
  - Classification:
    - Central mechanisms (cessation of respiratory effort):
      - Immaturity of respiratory control:
        - Slowed brainstem conduction time
        - Up-regulated inhibitory neuromodulators (dopamine, GABA, prostaglandins)
        - Functional immaturity
    - Peripheral mechanisms:
      - Exaggerated laryngeal chemoreflex
      - Impaired chemosensitivity in carotid body
        - Decreased response to hypercapnea
        - Biphasic response to hypoxia with resultant inappropriate decrease in minute ventilation
      - Exaggerated bradycardic response to hypoxia
      - High vagal tone
    - Obstructive (usually at pharyngeal level)
    - Mixed (most common)
- **Epidemiology**
  - Incidence inversely proportional to gestational age
    - 100% <= 28wks
    - 85% 30wks
    - 20% 34wks
  - Natural history
    - Severe events resolve first, isolated bradycardia events resolve last
      - 92% resolve by 37wks
      - >98% resolve by 40wks
    - Persistent events beyond full term corrected gestational age (>40wks CGA) are common in infants born @ <28wks GA
      - 6-22% of infants born at 24-28wks GA, proportionate to GA
    - Eventual cessation of events
      - Virtually no extreme events >43wks CGA

- **Outcomes**
    - Negative neurodevelopmental outcomes and retinopathy correlated with apnea of prematurity events / hypoxia and supplemental oxygen administration
    - Severity and duration of apnea of prematurity events *not* correlated with sudden unexplained infant death (SUID) / sudden infant death syndrome (SIDS)

PART II: Management

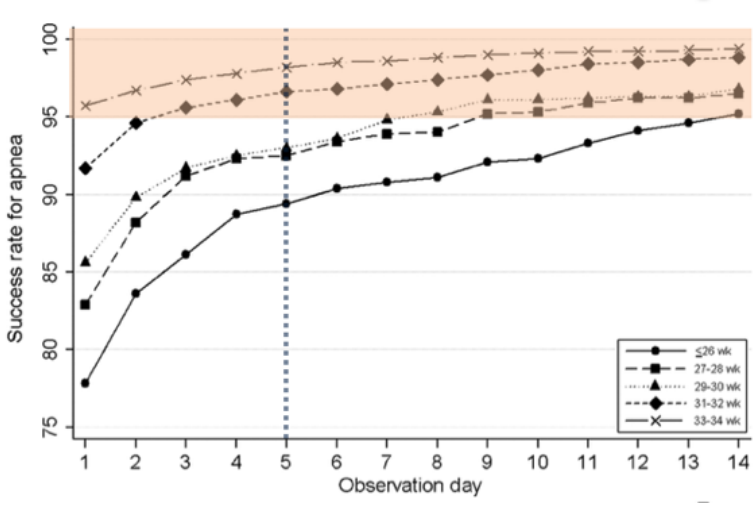
- **Caffeine**
    - **Background Data:**
        - Methylxanthines: caffeine and theophylline
        - Mechanism of action:
            - Decrease inhibition via efferent pathways
            - Decrease laryngeal chemoreflex
        - Outcomes:
            - Cochrane 2010 Review:
                - Short-term benefits
                - >50% reduction in events
                - Decreased positive pressure ventilation
            - CAP Trial ("caffeine for apnea of prematurity"):
                - Decreased time with ETT, positive pressure, supplemental oxygen
                - Decreased BPD
                - Neurodevelopmental outcomes @ 18mo = decreased risk of death or disability
                - Neurodevelopmental outcomes @ 5yrs = no significant differences
        - Timing**:**
            - Prophylactic or early treatment (<3 days old)
                - Mixed data:
                    - CAP Trial (BENEFIT):
                        - Greater reduction in respiratory support duration
                        - Lower incidence BPD
                        - Shorter duration mechanical ventilation
                    - Cochrane Review 2010 (NO DIFFERENCE):
                        - No difference in meta-analysis
            - Prolonged treatment
                - Rhein 2014 (UNCLEAR BENEFIT):
                    - Decreased desaturation episodes of uncertain clinical significance
                        - Lower rate of intermittent mild hypoxemia at 35wks
                        - Lower mean time with SaO2 <90% at 35wks
                        - Episodes were *not* clinically apparent / *not* apnea

- **Indications for Caffeine:**
  - <30 weeks GA (based on <1250gm in CAP Trial):
    - Start within 2 hours after birth for apnea prophylaxis
    - *Note:* regardless of level of respiratory support
    - Goal = maximize minute ventilation, minimize intubation
  - 30-34 weeks GA:
    - Investigate & rule-out other etiologies of apnea
    - Start for repeated, severe apnea of prematurity events:
      - Bradycardia associated with apnea
      - Color change associated with apnea
      - Need for stimulation for recovery
      - Events during sleep
  - >34 weeks GA:
    - Investigate & rule-out other etiologies of apnea
    - Consider for repeated, severe apnea of prematurity events (see above definition)
- **Dosing & Titration of Caffeine:**
  - Load: 20 mg/kg IV
  - Maintenance therapy: 5 mg/kg q24 hours IV or PO
  - Titration:
    - Consider re-loading caffeine for frequent apnea and bradycardia episodes
    - Consider titrating up maintenance dose (max 10 mg/kg q24 hours IV or PO) based on severity and frequency of apnea and bradycardia episodes
- **Duration of therapy:**
  - Infants born <26 weeks GA: discontinue at 36 weeks CGA
    - Consider *early* discontinuation after 35 weeks CGA if infant is apnea-free for 3 days *and* <2 weeks from anticipated discharge
    - Consider extension beyond 36 weeks if infant has persistent significant apnea events
  - Infants born ≥26 weeks GA: discontinue at 33-34 weeks CGA if infant is apnea-free for 3 days *and* <2 weeks from anticipated discharge
    - Consider extension beyond 33-34 weeks CGA if infant is still having significant events
  - *Note*: Neonates with severe neurologic injury may have prolonged apnea
  - *Note:* Consider re-starting caffeine therapy if recurrent apnea of prematurity after caffeine therapy discontinued

- **Respiratory Support**
  - **Background Data:**
    - Modes of support:
      - nCPAP @ 4-6cm H2O
        - Reduces frequency and severity of apnea
          - Mechanism: splints open upper airway, maintains higher end-expiratory lung volume
      - Variable-flow CPAP (bubble CPAP) may be *more* effective than conventional CPAP
        - Decreases work of breathing
        - Infant driven
      - Alternatives to nCPAP = not well studied:
        - Non-synchronized non-invasive positive pressure ventilation (NIPPV)
          - More effective than nCPAP in reducing frequency of events
        - Synchronized NIPPV
          - More effective than CPAP in preventing re-intubation
        - HFNC
          - May be equivalent to nCPAP but limited, non-reproduced data
  - **Indications:**
    - If frequent and/or severe apnea persists after initiation of caffeine, consider addition of non-invasive respiratory support such as nasal cannula or nCPAP.
    - For otherwise well infants born at > 28 weeks who are now >32 weeks CGA with mild to moderate apnea, it may be reasonable to initiate treatment with nasal cannula rather than caffeine given the duration of treatment and subsequent observation required for caffeine. (Please also see "Atypical Cases" section below).

PART III: Monitoring

- **Inpatient Monitoring for Resolution ("countdown")**
  - **Background Data:**
    - No historic evidence-based standard
      - Significant variation between institutions + no empiric data
      - Most observe for ≥ 5 days event-free prior to discharge
    - Evidence:
      - Lorch 2011: 5-7 day observation period successfully predicted resolution of apnea in 94-97% *but* significantly lower for those born at earlier gestational age
        - >=30wks → 1-3 days to achieve 95% resolution
        - 27-28wks → 9 days
        - <26wks → 13 days



Lorch SA et al; Epidemiology of apnea and bradycardia resolution in premature infants. Pediatrics. 2011 Aug;128(2):e366-73

- Darnall 1997
  - "Margin of safety" = 8 days
- Zupancic 2003
  - Cost analysis – incremental decrease in cost effectiveness with increased monitoring days, particularly at increasing gestational age
    - Cost effectiveness threshold of $100k/QALY:
      - 30-34wks ~5 days
      - 24-29wks ~7-8 days

- **Consensus Timing Prior to Discharge** (based on cost effectiveness + prediction of resolution)**:**
  - Infants born <30 weeks GA: 7 day event-free observation time
  - Infants born ≥30 weeks GA: 5 day event-free observation time
  - *Note: "*event-free observation" starts 120 hours (5 days) after the last dose of caffeine
  - Consider discontinuation of the pulse oximeter while continuing the cardiorespiratory monitor for babies with a CGA of 34 0/7 week who have been off supplemental oxygen and off caffeine for >5 days.

- **Home Monitoring**
  - Not routinely recommended
    - May be difficult to obtain
    - May actually increase parental anxiety. Rather than home monitoring, education around safe sleep may be useful.
    - Special cases: May be exception for certain genetic syndromes

PART IV: Atypical Cases

- Late onset: Apnea events with onset after approximately 2 weeks of life
    - Consider other causes/etiology (e.g. chronic lung disease, obstructive physiology, sepsis/infection)
    - Monitoring and treatment for apnea of prematurity as described above might not apply to these events
- Early onset: Apnea within the first 24 hours of life
    - Consider other causes/etiology (e.g. intracranial injury, sepsis/infection)
    - Monitoring and treatment for apnea of prematurity as described above might not apply to these events
- Feeding associated events
    - May still be considered significant especially if frequent, or associated with color change or deep bradycardia, or requiring intervention. If clinically worrisome, helpful to obtain details from nursing about the events.
    - Parents need to be able to safely feed the infant and perform any needed intervention prior to discharge home.
    - If the infant is otherwise stable and approaching discharge, it may be reasonable to feed the infant OFF the monitors for both parents and staff.
- Self-resolving events
    - Generally well-tolerated. Should not typically be used to re-start the countdown. However, may still be considered significant especially if frequent, or associated with color change or deep bradycardia. If clinically worrisome, helpful to obtain details from nursing about the events.

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