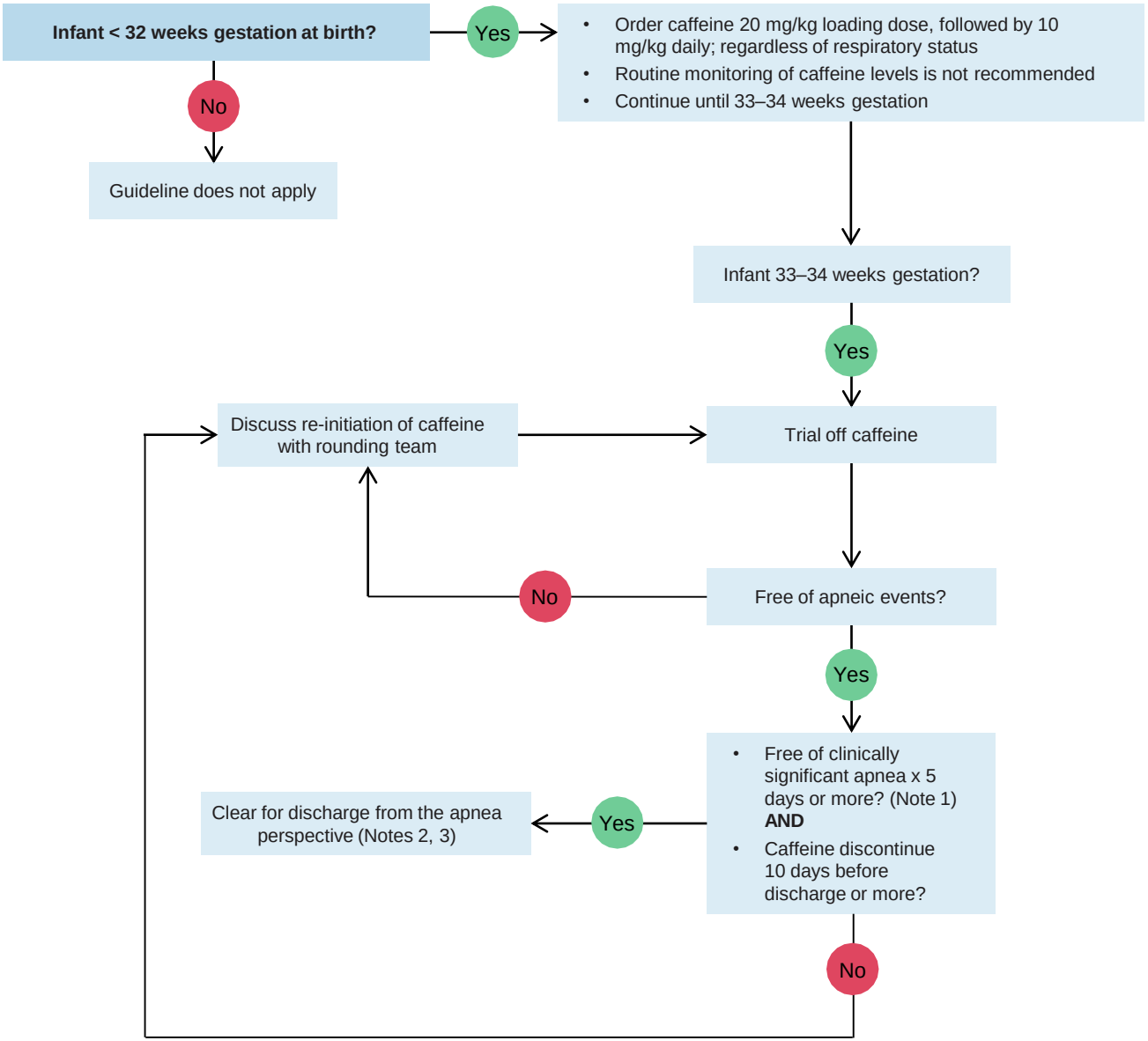
CLINICAL GUIDELINE

APNEA OF PREMATURITY

Children's MINNESOTA

Aim: To standardize discharge management of infants with apnea of prematurity.



NOTE 1

Clinically significant apnea

- Spontaneously occurring event that requires intervention to resolve; with apnea > 20 seconds; OR apnea with associated bradycardia, cyanosis or pallor

NOTE 2

Feeding-related/care-related spells

- Events occurring during feeing or active nursing cares need not delay discharge unless they are very frequent and/or severe (vigorous stimulation or PPV required)
- Parents must demonstrate ability to manage feeding related spells prior to discharge

NOTE 3

Use of archived monitor event recordings (MMUs/CR Scans)

- MMUs/CR scans are not recommended before discharge to screen for clinically unapparent apnea, bradycardia, or desaturation events. They do not predict subsequent outcomes, including recurrent clinical apnea or SIDS.
- MMUs/CR scans may be ordered:
  - To determine if apneic events are central or obstructive in nature
  - To document adequate oxygen baseline saturations for infants being discharged on oxygen or recently weaned off oxygen prior to discharge

Title: Apnea of Prematurity: Treatment, Monitoring, and Discontinuation of Therapy for Discharge

Scope: This Clinical Practice Guideline (CPG) applies to the neonatal units of Children's Minnesota (Neonatal Intensive Care Units of Minneapolis, St. Paul, and Mercy; Infant Care Center of Minneapolis; Special Care Nurseries of Minneapolis)

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Executive Summary: Apnea of prematurity (AOP) is one of the most common diagnoses seen in the neonatal unit. An apneic "spell" is generally defined as a cessation of breathing for 20 seconds or longer or a shorter cessation with accompanying bradycardia, cyanosis, or pallor. Frequency of apnea is inversely related to gestational age with studies showing that essentially all infants born at ≤ 28 weeks gestation will be diagnosed with apnea. As infants advance in gestational age, frequency and severity of spells diminish, being largely resolved by 43 weeks corrected gestational age (CGA).

Xanthene therapy with agents such as caffeine is considered standard of care in the treatment of AOP. While there are no known trials that have determined the optimal approach for discontinuation of this therapy once started, there is general acceptance in the neonatal literature that a demonstrated "apnea-free" period after the discontinuation of xanthene therapy is prudent before discharge.

The intent of this guideline is to standardize the treatment of apnea of prematurity, the monitoring of xanthene therapy, and the discontinuation of therapy at discharge for infants with apnea of prematurity admitted in the one of the neonatal units of Children's Minnesota.

Published Data (see references for full citations)

1. Butler, T.J. et al. (2014). Standardizing Documentation and the Clinical Approach to Apnea of Prematurity Reduces Length of Stay, Improves Staff Satisfaction, and Decreases Hospital Cost.
   A. A prospective, single-center, comparison before and after standardizing the definition of AOP, treatment, and documentation of apneic events. Summary:
      1. Discontinuation of caffeine occurred after 5-7 days of being event-free or at 33 weeks CGA.
      2. Discharge considerations
         a) For infants not started on caffeine, no significant event within 5 days prior to discharge.
         b) For infants recently taken off caffeine, no significant within 7 days of drug discontinuation.
      3. Stimulation definition and criteria were defined for staff to standardize approach and documentation of events
      4. A standard approach reduced length of stay, improved staff satisfaction, and decreased hospital cost.
2. Darnall, R. et al. (1997). Margin of Safety for Discharge After Apnea in Preterm Infants.
   A. Attempt to define a minimal and safe observation period between the time of the last apnea episode and discharge. Summary:
      1. Maintaining preterm infants with a history of AOP in the hospital until they are apnea free for a specific period of time is reasonable.
      2. Infants who have been apnea free for 8 or more days are unlikely to have another apnea, unless they have some other risk factor known to cause apnea (e.g. surgery, infection, receiving FiO2).
      3. Attempts to reduce length of stay by decreasing the number of apnea-free days before discharge are not likely to be successful and could result in a significant event at home.
3. Gannon, B. (2000). Theophylline or Caffeine: Which is the Best for Apnea of Prematurity?
   A. Review comparing theophylline to caffeine.
      1. Both theophylline and caffeine are successful at reducing apneic episodes.
      2. Caffeine rarely has side effects and has a wide therapeutic range.
      3. Caffeine has an earlier onset of action.
      4. Caffeine is the preferred drug of choice for apnea of prematurity.
4. Eichenwald, E. et al. (2001). Inter-Neonatal Intensive Care Unit Variation in Discharge Timing: Influence of Apnea and Feeding management.
   A. Comparison of postmenstrual age at discharge, with impact on hospital stay, in 15 NICUs. Summary:
      i. Length of stay varies widely among NICUs and authors speculate the variation results partly due to differences in monitoring for, and documentation of, apnea of prematurity and feeding behavior.

Published Data (see references for full citations)

5. Eichenwald, E., & Committee on Fetus and Newborn (2016).Apnea of Prematurity
   A. Clinical report reviewing definition, epidemiology, and treatment for apnea of prematurity, as well as discharge recommendations. Summary:
      i. A trial off caffeine may be considered when an infant has been free of clinically significant spells off positive-pressure ventilation for 5-7 days or at 33-34 weeks CGA, whichever comes first.
      ii. Brief isolated bradycardic events and feeding-related events that resolve with interruption of feeding need not delay discharge.
      iii. Individual units should develop policies and procedures for assessment, documentation and duration of observation period before discharge.
      iv. An apnea spell free period of 5-7 days is commonly used, although a longer period of time may need to be individualized based on the gestational age at birth and/or the nature/severity of recorded events.
      v. Electronically archived monitoring data may reveal clinically unsuspected events of uncertain significance, but do not predict outcomes such as clinically significant apnea or SIDS.
6. Khurana et al. (2017). Long-term Neurodevelopment Outcome of Caffeine versus Aminophylline Therapy for Apnea of Prematurity.
   A. Randomized trial to compare mortality and survival with normal neurodevelopment outcome at 24 months corrected age, in infants treated with either caffeine or aminophylline.
      i. Caffeine treated infants showed an 83% less risk of getting cognitive impairment, a 50%less risk of developing motor deficits, and a 24% less risk of developing language problems, although these reductions were not statistically significant.
      ii. Risk of mortality was 9% less in the caffeine treated group.
      iii. Growth parameters were similar between groups.
7. Kumar & Lipshultz (2019). Caffeine and Clinical Outcomes in Premature Neonates.
   A. A review of the pharmacology, safety, and clinical outcomes of caffeine use for apnea of prematurity.
      i. Caffeine facilitates extubation, and decreases extubation failure by stimulating respiratory drive.
      ii. Infants who receive caffeine have lower rates of developmental disability at 18-24 months of age.
8. Moschino et al. (2020). Caffeine in Preterm Infants: Where are we in 2020?
   A. Review summarizing the current knowledge of caffeine therapy and unresolved questions of apnea of prematurity.
      i. Caffeine is effective in reducing frequency of apnea, the need for positive pressure ventilation, and mechanical ventilation.
      ii. Caffeine is effective in enhancing extubation success.
      iii. Caffeine treated infants have lower rates of bronchopulmonary dysplasia, intraventricular hemorrhage, and patent ductus arteriosus.
      iv. Outstanding questions continue about optimal timing and dosing.
      v. Caffeine has a wide therapeutic range with some therapeutic drug monitoring studies showing patients in the therapeutic range almost 95% of the time, arguing against routine monitoring of caffeine levels.

Published Data (see references for full citations)

9. Rostas & McPherson (2019). Caffeine Therapy in Preterm Infants: The Dose (and Timing) Make the Medicine
    A. Literature review of caffeine efficacy and safety as a treatment for apnea of prematurity.
        i. The standard approach to administration (20 mg/kg loading dose of caffeine, followed by 5-10 mg/kg daily) has clear short-term and long-term respiratory benefits.
        ii. The standard approach to administration of caffeine demonstrates an improvement in neurodevelopmental impairment at 18-24 months.
        iii. Data has shown a decreased incidence of severe retinopathy of prematurity in infants receiving caffeine.
        iv. Data has shown a decrease in need for either pharmacologic or surgical closure of patent ductus arteriosus in patients who received caffeine therapy.
        v. Caffeine has a wide therapeutic index and favorable safety profile.
10. Rhein et al. (2014). Effects of Caffeine on Intermittent Hypoxia in Infants Born Prematurely: A Randomized Clinical Trial.
    A. Trial to determine the frequency of intermittent hypoxia in premature infants after discontinuation of routine caffeine treatment and whether extending caffeine treatment to 40 weeks postmenstrual age reduces intermittent hypoxia. Summary:
        i. Clinically unapparent episodes of intermittent hypoxia in premature infants continue after caffeine is discontinued.
        ii. Extending caffeine treatment beyond current clinical recommendations significantly reduces intermittent hypoxia at 35 and 36 weeks postmenstrual age
        iii. Further studies are needed to determine dosing regiments that minimize intermittent hypoxic episodes, if sustained reduction in intermittent hypoxia can be achieved at more than 36 weeks postmenstrual age, and risk and benefit of extended caffeine treatment in very low birth weight infants.
        iv. The clinical importance of intermittent hypoxia observed in the study is unknown and should not provide the bases for a change in current practice.

Clinical Practice Guideline Notes:

1. Initiation of caffeine therapy
   a. When/who
      i. On admission in all infants < 32 weeks gestation regardless of respiratory status
   b. Dose
      i. 20 mg/kg loading dose, followed by 10 mg/kg daily
2. Monitoring of caffeine levels
   a. Routine caffeine levels are not recommended.
3. Discontinuation of caffeine therapy
   a. Trial off caffeine at 33-34 weeks gestation.
   b. Caffeine to be discontinued at least 10 days before discharge.
   c. All infants ≤ 34 weeks at birth, or with a history of documented clinically significant apnea, must be free of significant apnea for at least 5 days before discharge.
4. Re-initiation of therapy after discontinuation
   a. Clinical team will determine if re-initiation is required
   b. If required, re-initiate with caffeine
5. Archived monitor event recordings (MMUs/PCGs)
   a. Not recommended before discharge to screen for clinically unapparent apnea, bradycardia, or desaturations events.
   b. May be ordered to determine if apneic events are central or obstructive in nature.
   c. PCGs may be considered to document adequate baseline oxygen saturations in an infant being discharged in oxygen or recently weaned off oxygen.
6. Additional discharge considerations
   a. Spells occurring during feeding or active nursing cares need not delay discharge unless they are very frequent and/or severe (requiring vigorous stimulation or positive-pressure ventilation).
   b. Parents must demonstrate ability to manage feeding related spells.

Glossary:

1. Clinically significant apnea
   a) A spontaneously occurring event that requires intervention to resolve
   b) Apnea > 20 seconds or apnea with associated bradycardia, cyanosis, or pallor
2. Memory Monitor Unit (MMU) – Three channel recording device measuring heart rate, respiratory impedance waveforms, and saturation. Monitors all three parameters for the duration of the testing but only records an event outside the preset alarm parameters should an alarm condition occur (30 seconds prior to the event, the event itself, and the recovery period).
3. Pneumocardiogram (PCG) – Four channel device measuring heart rate, respiratory impedance waveform, saturation, and air flow (via the use of a nasal/oral airflow thermistor). Continuously records all four parameters for the duration of the testing.

Appendix: Appendix A: Apnea of Prematurity at Discharge
Related References/Resources: Responding to an Apnea or Bradycardia Alarm

References:

1. Butler, T.J., Firestone, K., Grow, J., & Kantak, A. (2014). Standardizing documentation and clinical approach to apnea of prematurity reduces length of stay, improves staff satisfaction, and decrease hospital cost. The Joint Commission Journal on Quality and Patient Safety, 40(6), 263-269. doi:10.1016/s1553-7250(14)40035-7
2. Darnall, R., Kattwinkel, J., Nattie, C., & Robinson, M. (1997). Margin of safety for discharge after apnea in preterm infants. Pediatrics, 100(5), 795-801. doi:10.1542/peds.100.5.795
3. Gannon, B. A. (2000). Theophylline or caffeine: Which is best for apnea of prematurity? Neonatal Network, 19(8), 33-36. Doi:10.191/0730-0832.19.8.33
4. Eichenwald, E., Blackwell, M., Lloyd, J., Tran, T., Wilker, R., & Richardson, D. (2001). Inter-neonatal intensive care unit variation in discharge timing: Influence of apnea and feeding management. Pediatrics, 108(4), 928-933. doi:10.1542/peds.108.4.928
5. Eichenwald, E., & Committee on Fetus and Newborn (2016). Apnea of prematurity. Pediatrics, 137(1), 1-7. doi:10.1542/peds.2015-3757
6. Khurana, S., Shivankumar, M., Sujith Kumar Reddy, G. V., Jayashree, P., Ramesh Bhat, Y., Lewis, L. E. S., & Shashikala (2017). Long-term neurodevelopment outcome of caffeine versus aminophylline therapy for apnea of prematurity. Journal of Neonatal-Perinatal Medicine, 10(4), 355-362. doi:10.3233/NPM-16147
7. Kumar, V. H. S. & Lipshultz, S. E. (2019). Caffeine and clinical outcomes in premature neonates. Children, 6(11), 1-17. doi:10.3390/children6110118
8. Moschino, L., Zivanovic, S. Hartley, C., Trevisanuto, D., Baraldi, E., & Roehr, C. C. (2020). Caffeine in preterm infants: Where are we in 2020? ERJ Open Research, 6(1), 1-19. doi:10.1183/23120541.00330-2019
9. Rostas, S. & McPherson, C. (2019). Caffeine therapy in preterm infants: The dose (and timing) make the medicine. Neonatal Network, 38(6), 365-374. doi:10.1891/0730-0832.38.6.365
10. Rhein, L., Dobson, N., Darnall, R., Corwin, M., Heeren, T., Poets, C., et al. The Caffeine Pilot Study Group (2014). JAMA Pediatrics, 168(3), 250-257. doi:10.1001/jamapediatrics.2013.4271

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