Summary Proceedings From the Apnea-of-Prematurity Group

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

Apnea of prematurity (AOP) is found in >50% of premature infants and is almost universal in infants who are <1000 g at birth. The literature clearly defines clinically significant apnea in infants (breathing pauses that last for >20 seconds or for >10 seconds if associated with bradycardia or oxygen desaturation), but there is no consensus about the duration of apnea, the degree of change in oxygen saturation, or severity of bradycardia that should be considered pathologic. Although caregivers are able to respond successfully to apnea events with drugs (as well as physical and mechanical interventions) in the NICU, it remains unproven whether such interventions have any long-term effects. One of the most effective drugs, caffeine citrate, is currently labeled for short-term use only and within a limited gestational-age population. Clinicians often use off-label drugs that have been approved for gastroesophageal reflux disease, which is common in premature infants, with the belief that such treatments also have an impact on AOP, although this link has never been demonstrated. Key treatment issues include (1) lack of standardization for definition, diagnosis, and treatment of AOP, (2) unproven benefit of intervention, (3) lack of real-time data documenting AOP events, (4) unevaluated sustained treatment improvement at 7 days or later, (5) failure to address confounding conditions, (6) unsubstantiated AOP-gastroesophageal reflux disease relationship, and (7) undetermined role of AOP affecting long-term neurodevelopmental outcomes. In addressing study-design issues, the pulmonary group identified (1) key questions about neonatal apnea, (2) methodologic requirements for study, (3) appropriate outcome measures, and (4) ethical considerations for future studies. This article describes a sample framework for the study of apnea in neonates and identifies future research needs. Plenary-session discussion points are also listed.
Apnea of Prematurity (AOP) is the most common and frequently recurring problem in very low birth weight infants. AOP is found in >50% of premature infants and is almost universal in infants who are <1000 g at birth.1-3 The literature defines clinically significant apnea in infants as breathing pauses that last for >20 seconds or for >10 seconds if associated with bradycardia (eg, <80 beats per minute) or oxygen desaturation (eg, O2 saturation of <80–85%).4,5 This definition may vary depending on geographic location or the infant’s symptomatology. Moreover, there is no consensus about the duration of apnea that should be considered pathologic, and there is no agreement regarding the degree of change in oxygen saturation or severity of bradycardia that constitutes an important apnea event.

Although scientists cannot yet say whether AOP causes a clinically important effect on outcome and is harmful, providing no treatment when an infant stops breathing in the NICU is not an option. The immediate and irresistible urge to respond to apnea is based partly on the uncertainty about exactly what causes the apneic episode and whether the unknown causative factor might also harm the brain or other systems and produce a long-term effect on neurodevelopment.6 Although caregivers are able to respond successfully to apnea events with drugs (as well as physical and mechanical interventions) in the NICU, it remains unproven whether such interventions have any long-term effects, good or bad. One of the most effective drugs, caffeine citrate, is currently labeled for short-term use only and within a limited gestational-age population. Moreover, most premature infants also suffer from gastroesophageal reflux disease (GERD), and many clinicians use off-label drugs that have been approved for GERD in the belief that such treatments also have an impact on AOP, although this link has never been demonstrated.7-9

TREATMENT ISSUES
The pulmonary group identified the following treatment issues.

- The definition, diagnosis, and treatment of the condition have not been standardized.
- The benefit of intervention, apart from a reduction in apnea itself, remains largely unproven.
- Most studies of apnea have not collected real-time data to document the actual event and the preceding baseline, including physiologic parameters such as oxygen saturation.
- Few studies have evaluated sustained treatment improvement at 7 days or later after the initiation of therapy, and the improvements noted 1 to 3 days after therapy usually are not sustained at 1 week.
- Most studies are small in number and thus are not stratified by birth weight, gestation, postconceptional age, or disease processes that have occurred in individual infants.
- Previous studies have not addressed confounding conditions such as hypoxemia, the requirement for oxygen therapy, pharmacologic sedation, glucocorticoid therapy, acute or chronic lung disease, patent ductus arteriosus, intraventricular hemorrhage, sepsis, or other treatments such as dopamine.
- No good evidence exists to support the view that apnea and reflux are temporally or causally related or that the use of antireflux medications (eg, cisapride, metoclopramide) decreases the frequency of apnea.
- The most important issue to be determined is the role of apnea in affecting an infant’s long-term neurodevelopmental outcomes.

STUDY-DESIGN ISSUES
The pulmonary group identified the following study-design issues, which have been divided into 4 basic categories.

Important Questions About Neonatal Apnea
The pulmonary group agreed that the following key questions need to be addressed as a priority.

- Does neonatal apnea affect long-term neurodevelopmental outcome, or is it merely a marker of other complications of prematurity?
- Are xanthines (the primary drug group currently used to treat apnea) associated with improved outcome, both short- and long-term?
- Will future drug therapy for AOP be associated with improved outcome, both short- and long-term?
- Does esophageal reflux cause apnea? If so, are pharmacologic therapies directed at treating GERD likely to be effective for either the reflux or the apnea?

Secondary questions about apnea include the following.

- What is the effect of xanthines on GERD (eg, potentiation)?
- What is the most effective way to intervene for apnea (ie, pharmacologic versus mechanical intervention)?
- Does the etiology of apnea affect response to therapy?
- What are the responses and the associated risks as a function of gestational age and weight?
- What is the appropriate threshold for treatment?
- Is xanthine use outside the hospital setting for post-neonatal infants safe and effective?
- Are other agents (eg, other adenosine inhibitors, progestins) effective and safe in treating AOP?
• What is the effect of baseline oxygenation on the incidence and severity of apnea?
• Are there legitimate uses of xanthines for apnea disorders other than AOP (eg, to counteract apnea associated with prostaglandin administration, for an apparent life-threatening event, for postanesthesia apnea)?
• Is there a relationship between body and head position and apnea?
• What is the appropriate dosing regimen for pharmacologic agents that are commonly used to treat AOP (eg, caffeine, doxapram)?
• Is prophylactic use of xanthines for AOP safe and effective?

Methodologic Requirements for Study
The pulmonary group identified the following important methodologic requirements for studies.

• Studies should include simultaneous assessment of multiple relevant variables. At a minimum, chest-wall movement, heart rate, and oximetry should be included.
• A portion of the study population or study time should include an assessment of nasal airflow to distinguish between central and obstructive apnea.
• AOP must be defined uniformly (eg, apnea duration of 20 seconds or 10–20 seconds if accompanied by bradycardia [<80 beats per minute] or desaturation [SpO₂ < 80%]). The pulmonary group was unable to resolve a concern about failing to account for apnea events <10 seconds in duration that are associated with significant bradycardia/desaturation. However, recording of multiple parameters as just noted would allow an evaluation of such events.
• Studies should examine treatment duration over the long-term (eg, several weeks) and over a wider range of gestational ages. The pulmonary group noted that current approved labeling for caffeine is for short-term use and for those of 28 to 32 weeks’ gestational age.
• Studies must control for conditions that are believed to both cause apnea and independently influence outcome (eg, intraventricular hemorrhage, periventricular leukomalacia, respiratory distress syndrome, bronchopulmonary dysplasia, reflux).
• Studies must be randomized and blinded.
• It is appropriate to conduct studies by examining reflux treatment and its effect on apnea without necessarily including measurement of reflux. The pulmonary group acknowledged that no good evidence is available to support the relationship; nevertheless, clinicians continue to use antireflux medications to treat apnea. Although apnea and GERD occur in nearly all premature infants, they may be unrelated. The pulmonary group agreed that it was important to bridge the investigation of this issue between the gastrointestinal community and neonatologists, because both groups are examining it independently.

Appropriate Outcome Measures
Studies need to include and be powered for short-, intermediate-, and long-term outcomes (see Table 1 for details on the proposed clinical-trial framework).

Ethical Considerations for Future Studies
The following determinations about ethical considerations were made.

• It is ethical to perform randomized, placebo-controlled trials for apnea in preterm infants. The pulmonary group recognized that placebo does not mean that there is no treatment for apnea. The availability of rescue treatments for apnea such as continuous positive airway pressure and mechanical ventilation makes a placebo-controlled trial ethical. It is ethical to perform randomized, placebo-controlled trials for reflux (not involving apnea) in preterm infants.
• It is ethical to perform randomized, placebo-controlled trials for reflux and apnea, with apnea being the outcome, in preterm infants.

### TABLE 1 Framework for a Study of Apnea in Neonates

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Drug priorities</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no difference in neurodevelopmental outcome between patients managed with drug X for apnea vs placebo (or active comparator if labeled for the indication); secondary hypotheses would include the following</td>
<td>The following drugs should be used in studies of apnea (in order of priority)</td>
<td>The study should be powered for neurodevelopmental outcome at 18 mo</td>
</tr>
<tr>
<td>There is no difference in apnea (frequency and severity) at predetermined times sequentially measured between drug X and placebo (or active comparator if labeled for the indication)</td>
<td>Caffeine (dose-ranging studies will need to be performed for a variety of gestational ages for which information is not currently available)</td>
<td>Number of days hospitalized for apnea only</td>
</tr>
<tr>
<td>There is no correlation between apnea (frequency and severity) and neurodevelopmental outcome</td>
<td>GERD agents for treatment of apnea</td>
<td>Frequency and severity of apnea events (measured 2 d after initiation of therapy and weekly until discharge)</td>
</tr>
<tr>
<td>Proposed secondary outcomes include</td>
<td>Drugs for future consideration include specific adenosine receptor subtype antagonists, doxapram, and progesterone</td>
<td>Duration of assisted ventilation/continuous positive airway pressure</td>
</tr>
<tr>
<td>Length of hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of days hospitalized for apnea only</td>
<td></td>
<td></td>
</tr>
</tbody>
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PROPOSED CLINICAL-TRIAL FRAMEWORK
A sample framework for the study of apnea in neonates was proposed (see Table 1), and the characteristics of the clinical study design were identified (see Table 2).

FUTURE RESEARCH NEEDS
The following future research needs were identified.

- A large prospective study is needed to distinguish the role of apnea from the many confounding conditions and other predictors of neurodevelopmental outcome, including gestational age, neuroanatomic abnormalities, exposure to mechanical ventilation, sepsis, postnatal steroid treatment, and occurrence of bronchopulmonary dysplasia.
- Studies and their analyses should include rigorous control of potentially confounding variables.
- Ideally, randomized trials should have a primary hypothesis or coprimary hypotheses powered to assess long-term follow-up.

PLENARY DISCUSSION
During the plenary session, the pulmonary group and other workshop participants made the following points about the study of apnea in neonates.

- The issue of confounding therapies and morbidities when examining long-term outcomes is an important one that will need to be addressed, perhaps with statistical techniques. The group considered excluding the smallest infants, who were likely to have comorbidities, but the pulmonary group believed that the smallest infants were the ones most in need of intervention for apnea and were receiving prophylactic therapy. Multiple variables should fall out if the randomized clinical trial is large enough.
- Although maturation is more relevant than size to respiratory drive, the pulmonary group chose to categorize infants by birth weight because it is more precise than gestational age.
- The pulmonary group may need to analyze available pharmacokinetic data to address the issue of whether to adjust drug doses to maintain the same serum levels as the infant grows.
- Many monitoring systems that record retrievable data on heart rate, respiratory rate, and oxygen saturation offer opportunities for documenting apnea and related physiologic events. Nurse observations have been shown clearly to be unreliable in documenting apnea episodes.

### TABLE 2 Clinical Study Design

<table>
<thead>
<tr>
<th>Type of study</th>
<th>The study should be a randomized, blinded, multicenter, placebo-controlled trial with well-defined criteria for rescue therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratification</td>
<td>Neonatal groups would be stratified by the following criteria</td>
</tr>
<tr>
<td></td>
<td>&lt;800 g</td>
</tr>
<tr>
<td></td>
<td>800 to &lt;1200 g</td>
</tr>
<tr>
<td></td>
<td>1200 to 1500 g</td>
</tr>
<tr>
<td>Sample size</td>
<td>The pulmonary group proposed a range of sample sizes based on a first-pass power analysis, given neurodevelopmental outcome vs control (80% power)</td>
</tr>
<tr>
<td></td>
<td>3000 patients to discern a 5% difference in neurodevelopmental impairment (eg, 30% vs 25%)</td>
</tr>
<tr>
<td></td>
<td>500 patients to discern a 5-point difference in the Bayley score (SD: 15)</td>
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<tr>
<td>Entry criteria</td>
<td>Entry criteria would require consideration of the following issues</td>
</tr>
<tr>
<td></td>
<td>Use of perintubation caffeine</td>
</tr>
<tr>
<td></td>
<td>Use of prophylaxis, particularly for very immature infants to prevent intubation</td>
</tr>
<tr>
<td></td>
<td>Use of a nonprophylaxis strategy that might require defining frequency and duration</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Infants with the following characteristics would be excluded from the study</td>
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<tr>
<td></td>
<td>Apnea judged to be caused primarily by an alternative etiology (not AOP; eg, intraventricular hemorrhage, sepsis)</td>
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<tr>
<td></td>
<td>Congenital anomalies</td>
</tr>
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<td></td>
<td>Prior study-drug exposure</td>
</tr>
<tr>
<td>Assessment parameters</td>
<td>The pulmonary group identified the following assessment parameters for efficacy, safety, and pharmacokinetics</td>
</tr>
<tr>
<td></td>
<td>Short-term parameters include</td>
</tr>
<tr>
<td></td>
<td>Frequency, severity, and duration of apnea episodes at specific times throughout hospitalization, with direct measures of actual apnea and the associated heart rate and SpO2</td>
</tr>
<tr>
<td></td>
<td>Pharmacokinetic information for various gestational ages and postconceptional ages</td>
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<td>Intermediate parameters include</td>
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<td></td>
<td>Various assessments of duration (eg, duration of hospitalization, assisted ventilation [both continuous positive airway pressure and intermittent positive pressure ventilation], O2)</td>
</tr>
<tr>
<td></td>
<td>Morbidities (necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, retinopathy of prematurity)</td>
</tr>
<tr>
<td></td>
<td>Long-term parameters include</td>
</tr>
<tr>
<td></td>
<td>Cognitive and psychomotor assessment</td>
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</tbody>
</table>
One pulmonary group member is conducting studies to assess the role of xanthines and is not specifically addressing apnea. Although the pulmonary group’s study would build on any results from this study, it would explore new territory by asking whether an association exists between AOP and impaired neurodevelopmental outcome and, if so, whether the association is causal. If apnea is related to or results in impaired neurodevelopmental outcome, treatment to reduce apnea would provide direct benefit to the patient.

The pulmonary group did not discuss the issue of the potential confounding effect of xanthine therapy, which might affect growth and, thus, long-term outcome. The group did suggest that one approach to addressing the issue was to record growth-rate velocity.

The framework will address differentiation between central and obstructive apnea by obtaining nasal airflow measurements. This assessment would not be conducted for the entire study, because it is impractical to measure airflow on a continuing basis.

The pulmonary group considered the issue of nonapnea desaturation and was unable to resolve concerns about defining AOP in a way that would miss apnea events <10 seconds in duration. The final design of the study will need to address whether to include all events, including 2- to 3-second apneas.

ACKNOWLEDGMENTS
We gratefully acknowledge financial and administrative support from the National Institutes of Health and the Food and Drug Administration.

Our thanks go to Keith Barrington, MD, and Barbara Schmidt, MD, for helpful comments.

REFERENCES
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*Pediatrics* 2006;117;S47

DOI: 10.1542/peds.2005-0620H

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