

Summary Proceedings From the Bronchopulmonary Dysplasia Group

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

ABSTRACT

Despite improvements in neonatal care, bronchopulmonary dysplasia (BPD) continues to occur in approximately one third of newborns who have birth weights of <1000 g and contributes to significant morbidity in this population. Gaps in knowledge about the prevention and treatment of BPD remain, resulting in unintended short- and long-term sequelae. In addition to chronic lung disease, preterm newborns with BPD are more likely to develop language delay, cerebral palsy, and cognitive impairments compared with preterm newborns without BPD. The pulmonary group identified 3 critical needs to enhance the design of clinical trials in neonates with BPD: (1) identify the stages of BPD; (2) define BPD more clearly; and (3) identify subtypes of BPD patients. The group determined that trials are needed for 3 areas of BPD: (1) prevention of BPD; (2) treatment of evolving BPD; and (3) treatment of established BPD. The severity of BPD is defined as mild, moderate, and severe, and subgroups among those with BPD are described. Here we identify gaps in basic science and pharmacologic knowledge that hamper investigators' ability to conduct effective BPD clinical trials and provide a list of drugs to be studied in BPD trials. Priorities for drug-class evaluation by stage of BPD are given. The pulmonary group proposes a BPD clinical-trials framework that varies according to the different stages of BPD and describes characteristics of the overall design for BPD clinical trials. Finally, we discuss trial-design issues that are common to all neonatal studies.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-0620I

doi:10.1542/peds.2005-0620I

The views presented in this article do not necessarily reflect those of the Food and Drug Administration (FDA). This article reflects discussions of designing clinical trials in newborns and should not be construed as an agreement or guidance from the FDA. Drug development and clinical-trial design must be discussed with the relevant review division within the FDA.

Key Words

bronchopulmonary dysplasia, therapeutics

Abbreviation

BPD—bronchopulmonary dysplasia

Accepted for publication Oct 17, 2005

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275); published in the public domain by the American Academy of Pediatrics

BRONCHOPULMONARY DYSPLASIA (BPD) is an evolving process of lung injury and recovery that can result in chronic pulmonary impairment requiring oxygen therapy. The incidence of BPD varies according to birth weight, with BPD increasing as birth weight decreases.¹ Infants who weigh <1250 g at birth constitute 97% of the infants with this condition. The development of BPD is a multifactorial process. The impact of injury and repair on immature lungs and any imbalance in the processes leads to BPD that may have lifelong consequences for the infant.

Although neonatal care has improved substantially over the past 3 decades, BPD continues to occur in ~30% of newborns with birth weights of <1000 g and contributes to significant morbidity in this population.² Because of the gaps in knowledge about the prevention and treatment of BPD in newborns, children treated in NICUs may develop unintended short- and long-term sequelae. For example, in addition to the chronic lung disease of BPD, preterm newborns with BPD are more likely to develop language delay, cerebral palsy, minor neuromotor dysfunction, and cognitive impairments than are preterm newborns who do not develop BPD.

STUDY-DESIGN ISSUES

Before the workshop, the pulmonary group identified 3 areas that are critical to the design of clinical trials in neonates with BPD: (1) identification of the stage of BPD; (2) definition of BPD; and (3) identification of subtypes of patients among those with BPD.

Three Stages of BPD

Because BPD is an evolving process of lung injury, the pathophysiology is likely to differ at different times. Therefore, optimal therapeutic agents may differ at different stages of the disease (see Table 1). The pulmonary group found it useful to conceptualize BPD in 3 stages and agreed that trials are needed in all 3 stages.

- Stage 1: prevention of BPD
 - Perinatal: before birth and up to 4 days of age
 - Early postnatal: up to the first 7 days
- Stage 2: treatment of evolving BPD
 - Beginning at 7 to 14 days of age
- Stage 3: treatment of established BPD
 - Beginning at 28 ± 7 days of age

In stage 1, injury begins with inflammation playing a prominent role. Therefore, preventive strategies that use antiinflammatory treatments are attractive. Major therapeutic classes that may prove useful in stage 1 include antenatal corticosteroids and early use of postnatal corticosteroids, antioxidant therapies, and other antiinflammatory strategies. Corticosteroids have been studied extensively for infants who are at risk of BPD. Although

TABLE 1 Priorities for Drug-Class Evaluation According to Stage of BPD

Drug Class	Stage 1: Prevention	Stage 2: Evolving	Stage 3: Established
Steroids	X	?	X
Antiinflammatory agents	X	X	X
Bronchodilators		X	X
Diuretics		X	X

antenatal steroids do not consistently decrease the incidence of BPD in survivors, they confer a clear survival advantage for very low birth weight infants, and some of these survivors are at high risk of developing BPD.³ Antenatal steroids can arrest alveolar septation and pulmonary microvascular development (animal models), which may contribute to the pathogenesis of BPD.⁴ The clinical data are relatively compelling that betamethasone and dexamethasone are not equivalent for antenatal treatment and that betamethasone is the drug of choice because it is associated with better clinical responses and fewer adverse effects.⁵ Repetitive courses of betamethasone are being evaluated in multicenter trials that are in progress worldwide. The dose, regimen, and choice of betamethasone preparation used for current treatments may be excessive, and those are issues that can be resolved with adequate and well-controlled clinical trials.

After birth, corticosteroids may play a role. However, the use of high-dose dexamethasone (0.5 mg/kg) for short or longer intervals is associated with adverse short-term outcomes (gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure) and long-term outcomes (adverse neurosensory outcome) without a clear reduction in BPD.⁶ Lower-dose dexamethasone (≤0.15 mg/kg) and hydrocortisone treatments begun shortly after birth have been associated with gastrointestinal perforations, which may result from an apparent drug interaction with the simultaneous use of indomethacin.⁷ Nevertheless, some very low birth weight infants have low cortisol levels, and the logic of replacing what seems to be a physiologic deficit resulting from adrenal immaturity is compelling.⁸ The choice of corticosteroid, the dose, patient selection (possibly to include screening for inadequate cortisol levels before treatment), and the potential for drug interactions need to be considered carefully. In designing such studies, it is important to prospectively collect data about the severity and chronicity of chorioamnionitis and other antenatal conditions that may contribute to postnatal corticosteroid responses and adverse events.

Infants with evolving BPD who are oxygen- and ventilator-dependent have rapid and often dramatic responses to corticosteroid treatments that permit achievement of important short-term clinical goals such as

extubation.^{3,9} Corticosteroids may also decrease mortality. Concerns about their potential for neurodevelopmental impairment have limited their use. The available follow-up data on neurodevelopmental impairment are concerning but selective, incomplete, and inadequate. Nevertheless, the recent statement from the American Academy of Pediatrics and Canadian Paediatric Society that suggests limiting the use of postnatal steroids may make future studies more difficult to perform.⁸

In stage 2, the goal is treatment of evolving BPD in an attempt to abort the development of the disease. Therapies that are directed at controlling inflammation and lung water might have the most impact on this stage. Therapeutic agents of interest include systemic or inhaled corticosteroids, other antiinflammatory agents, and diuretics. It is currently unknown whether some patients have a major component of the disease from excess lung water while others have inflammation as the predominate feature. It is logical to assume that patients with different predominate disease pathophysiology might respond to different directed therapies. Trial design must include an assessment of these different pathophysiologic mechanisms.

In stage 3, BPD is established. The underlying predominate mechanisms may include overly reactive airways, lung fluid retention, and an oxygenation defect. Methods to identify the extent to which any component is contributing to established BPD in an individual patient do not currently exist. The development of such techniques would allow the use of more targeted therapies. Neonates with established BPD are frequently managed with systemic and/or inhaled corticosteroids during their initial hospitalization and after hospital discharge. The use of corticosteroids for this indication is essentially unstudied. Another commonly used treatment in established BPD is the use of β -adrenergic aerosolized bronchodilators.¹⁰ Virtually all evaluations of bronchodilators have been of short-term duration in small numbers of infants. There are no trials that have assessed the ability of bronchodilators to modify the course of disease.

Definition of BPD

The pulmonary group agreed to use the definition developed by the National Institute of Child Health and Human Development (NICHD) Workshop on BPD in 2001.¹ The NICHD definition is stratified by postmenstrual age with different end points for infants who are born at <32 weeks' and those who are born at \geq 32 weeks' postmenstrual age. The following end points are for infants who are born at <32 weeks' postmenstrual age:

- Mild BPD: oxygen requirement for the first 28 days but in room air at 36 weeks' postmenstrual age

- Moderate BPD: oxygen requirement for the first 28 days and oxygen <30% at 36 weeks' postmenstrual age
- Severe BPD: oxygen requirement for the first 28 days and oxygen >30% and continuous positive airway pressure or mechanical ventilation at 36 weeks' postmenstrual age.

The definitions for infants who are born at >32 weeks' postmenstrual age is adjusted for the time end point of 56 days of life rather than 36 weeks' postmenstrual age.² The group agreed that this definition should be augmented with a physiologic definition of BPD in selected infants with oxygen-saturation monitoring during a room-air challenge to adjust for differences in the diagnosis that are introduced by differences in oxygen-prescription practices.¹¹ The group felt that these 2 definitions worked well together to provide information on the severity of disease at 36 weeks' postmenstrual age as a short-term end point.

Subgroups Within BPD

The pulmonary group identified opportunities to study subgroups among those with BPD. Infants with a high likelihood of mortality or very severe morbidity might qualify for studies of agents with a higher-risk adverse-effect profile, such as systemic corticosteroids. Another subgroup is those infants with BPD who have a strong family history of asthma. It is possible that their response to therapeutic agents may differ from those without such a history. Finally, there is a need to evaluate groups for potential maternal protective factors and risk factors (eg, antenatal steroids, tobacco, asthma, chorioamnionitis).

GAPS IN KNOWLEDGE

The pulmonary group identified gaps in basic science and pharmacologic knowledge that hamper investigators' ability to conduct effective BPD clinical trials.

Basic Science

Knowledge is limited in the following areas of basic science:

- normal and abnormal lung development in the smallest infants and how those are perturbed by introduction too soon into the air environment
- basic biology of BPD, including:
 - biomarkers validated for the short-term outcome of oxygen requirement at 36 weeks' postmenstrual age to monitor the pathology of the disease and response to treatment; biomarkers that have proven useful in the study of asthma include exhaled nitric oxide, serum eosinophilic cationic protein, serum IgE, and total blood eosinophil count

- critical windows for intervention for targeted therapy
- genetic susceptibility using genetic analysis and proteomics
- preclinical science studies, particularly using juvenile animal models

Pharmacologic Knowledge

Current gaps in pharmacologic knowledge are extensive. Data are lacking on safety, efficacy, pharmacokinetics, and potential drug interactions of even the most commonly used agents. The safety of drug excipients (vehicles, emulsifiers, or preservatives) in preterm infants needs to be evaluated. Because some common metabolic pathways are immature in premature infants, ingredients that are inactive in term infants and older children may produce toxicities in preterm infants. A notorious example of this is benzyl alcohol, which produced a gasping syndrome, metabolic alkalosis, and death in preterm infants in the 1980s. Among infants at risk of BPD, the use of inhaled bronchodilators and chronic diuretics is widespread, but evidence for efficacy and safety is lacking. Patients with established BPD are frequently treated with multiple drugs simultaneously with no understanding of drug interactions. Furthermore, similarities in pathophysiology to asthma and extensive preclinical work on the role of inflammation in BPD suggest that antiinflammatory strategies may be beneficial. However, these strategies remain largely unstudied, and with the exception of corticosteroids, major drug classes have not been explored for use in this patient population.

Specific areas worthy of additional study include:

- medications used to treat asthma;
- safety and efficacy of commonly used agents including inhaled bronchodilators and diuretics;
- population-based pharmacokinetic and pharmacodynamic studies for all drugs that are used to treat BPD including steroids and antiinflammatory agents;
- safety, efficacy, and pharmacokinetic data analyzed by both postnatal age and postmenstrual age;
- impact of renal and hepatic insufficiency on pharmacokinetics;
- pharmacogenomics/proteomics;
- drug-drug interactions for commonly used and proposed new therapies; and
- safety of drug excipients including benzyl alcohol, propylene glycol, and polysorbates.

DRUG PRIORITIES

The pulmonary group developed a list of drugs to be studied in BPD trials. The drug classes to be studied vary according to the stage of disease.

Clinical trials of these drug classes should use parallel groups and placebo controls. The use of open-label drugs and the potential for drug-drug interactions will need to be addressed in the study design. Stratification by postmenstrual age and disease severity is desirable. To ensure that trials do not produce short-term benefits with long-term harm, trials should assess long-term pulmonary and neurodevelopmental outcomes including language development.

PROPOSED CLINICAL-TRIAL FRAMEWORK

The pulmonary group's proposed BPD clinical-trial framework would vary according to the different stages of BPD. However, the overall design would include the characteristics that are listed in Table 2.

TRIAL-DESIGN ISSUES COMMON TO ALL NEONATAL STUDIES

The pulmonary group discussed issues that applied not only to studies on BPD but also to the other neonatal diseases that were addressed in the workshop. Common trial-design issues included:

- More funding is needed for preclinical studies as well as phase 1 clinical trials.
- The participation of neonatologists is needed in trials of unproven but existing and widely used therapies (eg, diuretics).

TABLE 2 Framework for a Study of the Treatment of BPD in Newborns

Type of study	Placebo-controlled, randomized clinical trial with no crossover so that long-term outcomes can be assessed
Entry criteria	The entry criteria would differ according to the phase of disease studied; generally, entry criteria would focus on infants of <32 weeks' gestational age; in addition to disease, entry criteria would focus on severity and potentially would have more strict criteria for drugs such as corticosteroids that have a higher potential for harm
Exclusion criteria	Exclusion criteria would include Newborns with major anomalies, including pulmonary, cardiac (excluding patent ductus arteriosus), airway, genetic, and lethal anomalies Confirmed sepsis Inability to comply with follow-up Infants expected to die within 72 h of the enrollment window
Exit criteria	To minimize and discourage the use of open-label drugs, the pulmonary group supported stringent predefined criteria for failure
Duration of outcome assessment	The work group supported the following parameters for outcome assessment Longitudinal evaluations at a minimum of 2 y of age Ideally, longer-term assessments at 8–10 y of age, when cognition and lung function can be assessed more accurately, would be included, particularly if the study involved steroids Duration would depend on drug class studied (eg, shorter for diuretics than corticosteroids)

- Investigators are increasingly encountering the perception among families that clinical research is experimentation on their children. Educating the public, parents, and other groups about neonatal research is an important issue that applies to all Newborn Drug Development Initiative groups. Although considerable publicity surrounds the dangers of conducting research in this population, little information is disseminated about the danger of not performing the right studies in neonates and the uncontrolled experiments that are conducted daily with off-label use of drugs in infants. The scientific community needs to educate the public about neonatal research rather than let the media and less educated persons take charge of the issue, with potentially detrimental effects.
- The research infrastructure for conducting neonatal drug trials must include a biopharmacologist, a toxicologist, and a statistician. The participation of an ethicist should be considered.
- Multidisciplinary research teams that include specialists in neonatology, pulmonology, and neurodevelopment are needed.
- Methods and funding are needed to track families for long-term assessments.
- Better tools are needed for assessing the structure and function of the lung and brain. Newer and less expensive alternatives (eg, telephone/journal contact) to the current standard long-term follow-up programs need evaluation. It may be fruitful to study the potential of MRI at term gestation to act as a surrogate for later neurodevelopment. Standardized measures of pulmonary outcome have been developed for use in other neonatal conditions, such as infants with cystic fibrosis; it may be fruitful to explore the use of these tools in the study of BPD. Infant pulmonary-function testing exists but is limited in its availability and by the need for sedation.
- Better measures to evaluate overall health status and functional outcome are needed.

FUTURE DIRECTIONS

The pulmonary group identified the following new drugs/proteins for future study:

- antiinflammatory agents such as superoxide dismutase, interleukin 10, tumor necrosis factor α antagonists, and inhaled nitric oxide;
- new surfactant components (eg, surfactant protein-B) and investigation of the role of repeated surfactant doses at 10 to 14 days of age;
- clara cell secretory protein (CC-10);
- bombesin-blocking antibody; and
- new preparations of vitamin A that can be administered orally or intravenously with high bioavailability.

ACKNOWLEDGMENTS

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

Our thanks go to the reviewers for helpful comments.

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