Inhaled Drugs and Systemic Corticosteroids for Bronchopulmonary Dysplasia

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KEYWORDS

• Bronchopulmonary dysplasia • Inhaled corticosteroids • Inhaled bronchodilators
• Systemic corticosteroids • Dexamethasone • Hydrocortisone • Pharmacology

KEY POINTS

- A contemporary definition of bronchopulmonary dysplasia (BPD) that correlates with neurodevelopment and respiratory morbidity in childhood is desirable.
- Despite some positive effects on BPD, more information about the long-term effects of early inhaled corticosteroids is required to assess the overall efficacy and associated risks.
- Clinicians should balance the risks of neurodevelopmental impairment owing to systemic corticosteroids against those of BPD itself.
- Too little evidence is currently available to show positive or negative effects of bronchodilators for BPD.
- Future research focusing on the design of appropriate aerosol delivery systems and on the pharmacokinetics of inhaled drugs and systemic corticosteroids is needed.

DEFINING BRONCHOPULMONARY DYSPLASIA

In 1967, Northway and colleagues[1] described a previously unrecorded abnormality of the lung after hyaline membrane disease in preterm infants that were relatively mature and coined the term bronchopulmonary dysplasia (BPD). In their view, the disease seemed to be a prolongation of the healing phase of respiratory distress syndrome combined with an injury triggered by mechanical ventilation and oxygen. They characterized BPD by its clinical course, radiographic findings, and histopathology. Twelve

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years later, Tooley[2] introduced a functional definition and suggested that oxygen use at 28 days of age might better identify preterm infants with BPD. The emphasis on the functional abnormality was reinforced by Shennan and colleagues,[3] who aimed for a definition that could separate those who would be normal from abnormal in the long term. They proposed, in 1988, that the best predictor of abnormal pulmonary outcomes at 2 years of age among very preterm infants was the clinical use of oxygen at 36 weeks postmenstrual age (PMA) with a corresponding accuracy of 85%. To address the problem of a definition that treats BPD as a dichotomous "yes" or "no" diagnosis, the National Institute of Child Health and Human Development proposed a consensus definition that includes 3 levels of severity (mild, moderate, and severe) based on an assessment at 36 weeks PMA.[4] This is preceded by an assessment that included the use of oxygen for at least 28 days (not necessarily consecutive). To control for the variable clinical use of targeted oxygen saturations, Walsh and colleagues[5] suggested an alternative definition, the so-called physiologic definition. They defined BPD as the requirement for positive pressure support, the requirement for supplemental oxygen at a fraction of inspired oxygen exceeding 0.3, or, in infants receiving low amounts of oxygen, an inability to maintain an oxygen saturation value of greater than 90% during a structured, short period of saturation monitoring coupled with gradual weaning from oxygen to ambient air (the oxygen reduction test).

All of these definitions have their limitations and shortcomings. Recently, Isayama and colleagues[6] conducted a retrospective cohort study in the Canadian Neonatal Network with the objective to identify the optimal definition of BPD that best predicts respiratory and neurodevelopmental outcomes in preterm infants. They concluded that defining BPD by the use of oxygen alone is inadequate and suggested a combined criterion of oxygen and/or positive pressure respiratory support. Furthermore, they proposed to apply this criterion at 40 weeks PMA rather than at 36 weeks PMA because of a better ability to predict serious respiratory morbidity and neurosensory morbidity at 18 to 21 months. This finding was confirmed by another study that assessed the contribution of the prevalence (mild, moderate, or severe) and the time of diagnosis of BPD in the prediction of neurodevelopmental impairment at the corrected age of 2 years in a single-center, retrospective analysis of 754 children with a gestational age (GA) of less than 30 weeks who were born between 2000 and 2013. (Malavolti AM, Bassler D, Arlettaz-Mieth R, et al. Severe bronchopulmonary dysplasia is a better predictor of neurological impairment in very preterm infants when diagnosed at 40 compared to 36 postmenstrual weeks. Submitted for publication.) Additionally, this group found that severe BPD was a better independent predictor of neurodevelopmental impairment at the age of 2 years than mild or moderate BPD.

SHORTCOMINGS OF CURRENTLY AVAILABLE BRONCHOPULMONARY DYSPLASIA DEFINITIONS

The use of different definitions for BPD has been an ongoing challenge. In addition, contemporary changes in management of infants such as high-flow nasal cannula pose further challenges and limit application of existing definitions, which may result in misclassifications. In a scoping review, Hines and colleagues[7] found that the incidence of BPD ranged from 6% to 57%, depending on the definition chosen and that studies that investigated correlations with long-term pulmonary and/or neurosensory outcomes reported moderate-to-low predictive values regardless of the BPD criteria. In their review, these authors concluded that a comprehensive and evidence-based definition for BPD is needed for benchmarking and prognostic use. Poindexter and colleagues[8] applied 3 commonly used definitions of BPD to surviving