Seminars in Fetal & Neonatal Medicine 22 (2017) 354–358

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Bronchopulmonary dysplasia: Myths of pharmacologic management

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Keywords:
Bronchodilators
Bronchopulmonary dysplasia
Corticosteroids
Diuretics
Gastroesophageal reflux
Newborn
Vasoactive agents

A B S T R A C T

Bronchopulmonary dysplasia (BPD) is the leading cause of long-term respiratory morbidity in newborns who require respiratory support at birth. BPD is a multifactorial disorder, and infants are frequently subjected to treatment with multiple pharmacologic agents of dubious efficacy and questionable safety, including diuretics, bronchodilators, corticosteroids, anti-reflux medications, and pulmonary vasodilators. These agents, with narrow therapeutic indices, are widely used despite the lack of an evidence base, and some may do more harm than good. It is incumbent on the clinician to establish a risk:benefit ratio and to avoid drugs that have little efficacy and a high rate of toxicity.

1. Introduction

Bronchopulmonary dysplasia (BPD) is the leading cause of long-term respiratory morbidity in newborns who require respiratory support at birth. This disorder was originally described in 1967 by Northway et al. in a 13-patient series of infants who had survived respiratory distress syndrome (RDS) [1]. These infants ranged from 30 to 39 weeks gestational age and had birth weights between 1474 and 3204 g. In the ensuing years, BPD was seen in term or late preterm infants subjected to high ventilator pressures and oxygen concentrations. Radiographic changes included overinflation, cystic emphysema, and fibrosis. The histopathologic changes showed interstitial and alveolar edema, small airway disease, extensive inflammation, and pulmonary fibrosis. Pulmonary arteriolar thickening and pulmonary hypertension were common features.

As the demographics of the neonatal intensive care unit (NICU) population changed over the decades since Northway's report, so too did the characteristics of BPD. In 1999, Jobe coined the term "new BPD" to describe the transition. Affected infants now tend to be very low birth weight and require only modest ventilator and oxygen support. Their chest radiographs demonstrate diffuse haziness or a fine, lacy pattern. Histopathologically, there is decreased alveolarization, minimal small airway disease, and less inflammation and fibrosis than the "old BPD" [2].

2. Scope of the problem

The incidence of BPD is inversely proportional to birth weight or gestational age. It occurs in more than half of surviving infants between 500 and 750 g, in a third of infants 751–1000 g, 14% of infants 1001–1250 g, and 6% of infants 1251–1500 g [3]. BPD remains an important cause of mortality and morbidity in the NICU population. Affected infants have prolonged and recurrent hospitalizations and higher rates of other serious complications of prematurity. It is estimated that there are 14,000 new cases in the USA each year [4]. An alarming trend is the increasing prevalence of BPD in all weight strata. Since 1993–94, the proportion of survivors with BPD in infants 24–28 weeks has increased; since 1998, the same trend has been noted for infants 29–30 weeks [5]. Long-term follow-up has revealed alterations in lung function, with small airway damage and hyperinflation persisting to age 8–10, airway obstruction in adult life, increased susceptibility to viral respiratory infections (particularly respiratory syncytial virus), and there is a strong association with cerebral palsy and neurodevelopmental delays.

3. Pathogenesis of bronchopulmonary dysplasia

Bronchopulmonary dysplasia is a multifactorial disorder (Fig. 1). Preterm birth results in delivery of a baby with incomplete lung development and a reduced number of alveoli. This necessitates the initiation of chronic ventilator support and oxygen exposure. Unfortunately, the lungs of these babies are structurally and biochemically immature and may react adversely to treatments with

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http://dx.doi.org/10.1016/j.siny.2017.08.002
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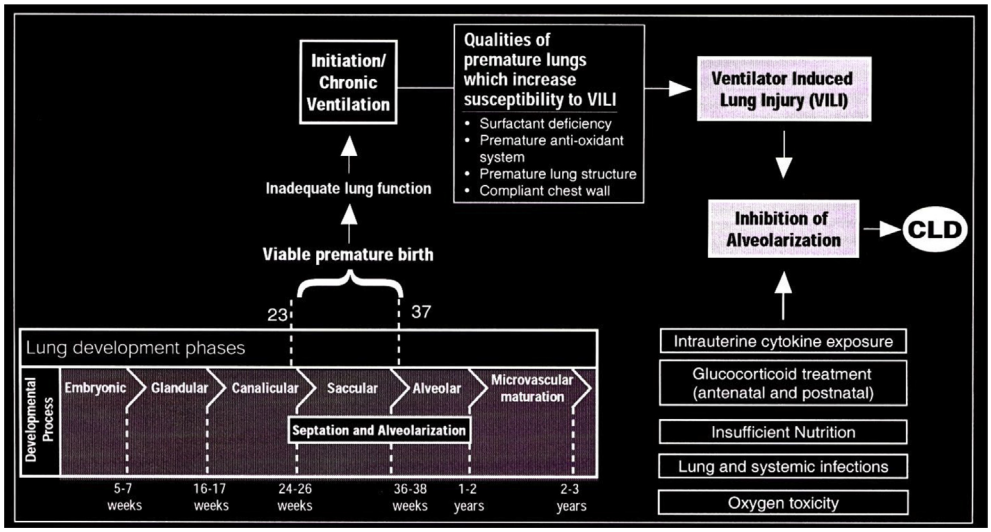

Fig. 1. The effect of ventilator-induced lung injury (VILI) and other factors on lung development and their relationship to chronic lung disease (bronchopulmonary dysplasia). CLD, chronic lung disease. [From Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. Semin Neonatol 2002; 7:353–60, copyright Elsevier Science, Ltd, with permission.].

resultant ventilator-induced lung injury (VILI). Infection, inflammation, oxygen toxicity, inadequate nutrition, and corticosteroid exposure may also result in diminished alveolarization, and when coupled with VILI lead to the development of BPD [6].

4. Pharmacologic management

The management of infants with BPD is controversial and has an almost non-existent evidence base. This is nicely demonstrated by the following case report:

A 5-month-old, former 25-week gestation female infant was transferred to our institution for further management of intractable respiratory failure from BPD. She was ventilator-dependent and required 55% oxygen. She weighed only 1.87 kg. Box 1 lists the medications she was receiving at the time of transfer.

A pediatric pulmonologist was consulted and wrote, "Given that she has cystic BPD, diuretics are an important part of her plan of care. The determination of whether to use furosemide or chlorothiazide can be made based on her potassium level, given that fluid overload may further compromise her respiratory status."

Box 1
Medications frequently used to treat infants with bronchopulmonary dysplasia

Hydrodiuril
Spironolactone
Furosemide
NaCl
KCl
Metaclopramide
Lansoprazole
Dexamethasone
Midazolam
Ipratropium bromide (inhalational)
Fluticasone (inhalational)
Morphine sulfate (intermittent)
Lorazepam (intermittent)

4.1. Can diuretic therapy prevent BPD?

There has been a long-held belief that infants with BPD tolerate excessive fluid intake poorly and tend to accumulate lung water. This stems from the observation of "old BPD," with the severe inflammatory and fibrotic changes. Water and salt intake were limited to the minimum necessary to provide adequate calories to support metabolic needs and growth. Deductive reasoning led to the use of diuretics to enable administration of more fluid and calories and better growth, but is this appropriate for the "new BPD?" A systematic review by Laughon and Bose noted that two Cochrane reviews included small studies of single-dose or short-term therapy and that only short-term outcomes (extubation rates, change in lung compliance, or oxygen requirement) were reported. They concluded that the evidence does not support the "preventative" use of diuretics [7].

4.2. Can diuretics treat BPD?

Perhaps the larger question regarding diuretics is whether they effectively treat established BPD. The answer appears to be "no." Two comprehensive reviews of diuretic therapy indicate some short-term improvement in pulmonary function, but without any substantial reduction in ventilator support or duration of treatment. No long-term benefits, such as a reduction in mortality, duration of positive pressure ventilation or oxygen use, or length of hospital stay have been shown [8,9].

4.3. Physiology of diuretic therapy

Administration of diuretics to an infant with BPD will generally result in a diuresis, with subsequent loss of salt and water. Chronic use will lead to hyponatremia, hypokalemia, hypochloremia, calciuria, and a contraction alkalosis. This is often followed by salt and water repletion, which in turn leads to fluid retention and subsequently more diuretic. It is truly a situation of the dog chasing its tail. Calcium loss, exacerbated by corticosteroid and anti-reflux