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REVIEW

Bronchopulmonary Dysplasia: An Overview

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Abstract: Bronchopulmonary dysplasia (BPD) is the most common long-term respiratory morbidity of infants born prematurely. Historically thought to be a direct consequence of lung injury from mechanical ventilation and exposure to high concentrations of oxygen, recent evidence suggests that the BPD of today may be the result of altered lung development and altered alveolarization. In this paper, we will review historical and contemporary definitions of BPD as well as frequently used prevention and management strategies.

Keywords: prematurity, respiratory distress syndrome, lung injury, bronchopulmonary dysplasia

Definition

The initial description of bronchopulmonary dysplasia (BPD) was first reported by Northway et al in 1967, who linked the radiologic features to the clinical status in a small group of modestly preterm infants who had been mechanically ventilated.[1,2] As a consequence of preterm birth, these infants were in the late saccular stage of lung development.[1,2] However, as both the demographics of the neonatal intensive care unit (NICU) and neonatal clinical practices have evolved, so has the definition of BPD.

In 1988 Shennan et al proposed a definition based on supplemental oxygen need at 36 weeks' postmenstrual age (PMA).[3] They reported that this clinical definition was a better predictor of later respiratory morbidity.[2–4] Currently, treatment with supplemental oxygen at 36 or 40 weeks' PMA is the most widely accepted definition of BPD.[5] This "new" BPD reflects the increasing survival of extremely premature infants, whose lungs may be between the canalicular and saccular stages of lung development at the time of birth, leading to a developmental arrest of the lung, and impaired alveolarization.[5–8]

Pathogenesis and Etiology

The BPD first described by Northway et al was believed to result from the aftermath of severe respiratory distress syndrome, the toxic effects of oxygen, and damage from positive-pressure ventilation.[1] Preterm infants are now known to be at risk for mechanical, oxidant, and inflammatory injury because of lung underdevelopment and insufficient quantities of biochemical protectants, such as surfactant, antioxidants, and protease inhibitors.[2,5,9]

Infants born between 24–28 weeks' gestation are just beginning to develop alveolar ducts during the saccular stage of lung development. Alveolarization occurs in parallel with development of the lung capillary bed.[6,10] The "new" BPD represents an arrest of lung organogenesis, with abnormal alveolar septation and

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vascular development in the distal lung.[2,8,11–13] Histologic evaluation of the "new" BPD shows that affected infants have fewer and larger alveoli, leading to decreased lung surface area, confirming an arrest of septation.[8,14] This extremely premature lung is also prone to injury from lack of biochemical protectants, as well as mechanical stress caused by ventilation and the use of supplemental oxygen. When the alveolar capillary wall is injured by these stressors, a fibroproliferative response produces the classic histopathologic findings.[15,16]

Incidence and Prevalence

Despite efforts to prevent preterm birth, prematurity continues to contribute disproportionately to neonatal mortality and subsequent physical and neurodevelopmental morbidities.[17–20] BPD remains the most prevalent sequela of preterm birth in the United States, affecting 41–46% of infants born at <29 weeks' gestation or 10,000–14,000 preterm infants annually in the United States.[3,4,6,21–25] Although the use of antenatal steroids, surfactant, and sophisticated ventilator strategies have improved survival, the rates of BPD have remained relatively constant.[6,26,27] Member institutions in the Vermont-Oxford Network (VON) reported an average incidence of BPD of 29%, but the rates at individual sites varied from 13.4–66% in 2001 and 4–58% in 2003. Because BPD is so closely linked to prematurity, the improving survival of extremely low birth weight and extremely premature infants must be considered in interpreting the incidence and prevalence.[6]

Perinatal Risk Factors

Prenatal factors producing fetal growth restriction can also influence lung function and the development of BPD. These include maternal diet, intrauterine tobacco exposure, male sex, and family history of asthma.[6,9,28–30] An increased risk for BPD in infants who are small for gestational age (SGA) is greatest among those born at 26–30 weeks' gestation.[31]

Chorioamnionitis is another important cause of preterm birth, and may initiate a fetal systemic inflammatory response.[2,32–35] Observational studies by Watterberg et al established an association between chorioamnionitis and BPD.[6,32] Perinatal risk factors for BPD are also indicative of increased severity of illness at the time of delivery and initial resuscitation, and include the failure to receive antenatal steroids, low Apgar scores, and perinatal depression.[6]

Prevention

Prenatal

Steroids

Glucocorticoids induce structural and biochemical maturation of the lung by thinning the mesenchyme and inducing the production of surfactant.[7,36–38] However, they are also potent inhibitors of protein synthesis and can thus interfere with alveolarization. A meta-analysis evaluating outcomes of infants born to women treated with antenatal steroids showed a significantly reduced risk for developing neonatal respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and early-onset sepsis.[39] Antenatal steroids have not, however, been shown to reduce the risk for BPD in randomized controlled trials (RCTs) (RR 0.86, 95% CI 0.42–1.79) or larger observational studies.[39–41]

Tocolytics

Following the American College of Obstetrics and Gynecology recommendation to administer antenatal steroids to women with an anticipated delivery between 24 0/7 weeks to 33 6/7 weeks at risk for delivering in the next 7 days, there was an increase in the utilization of tocolytics to treat preterm labor.[42] Tocolytics are not used to prolong pregnancy, but rather to prevent immediate delivery, allowing the steroids to have more time to work.[43]

Neonatal

The fetal lung is a still-developing organ between 24 and 28 weeks.[7,11,44] This may explain why aggressive ventilation (eg, high inspiratory pressure, low positive end-expiratory pressure, and high ventilation rates leading to hypocarbia) contribute to lung injury and the eventual development of BPD.[6] The practice of permissive hypercapnia has been widely adopted in an attempt to avoid these injurious mechanisms despite randomized trials finding no improvement in outcomes.[45–47]

To complicate this further, not only does over-distension contribute to the development of BPD, but atelectasis and under-inflation also play a role. Ventilation of an atelectatic lung causes parenchymal injury through the shearing stress of repeatedly re-inflating collapsed alveoli.[6,48] This creates damage through inflammatory mediators and is referred to as biotrauma.[16,49,50]

Noninvasive Ventilation

To avoid repetitive stress to the developing preterm lung, the use of continuous positive airway pressure (CPAP) and

its derivatives has been recommended by some.[2,9] Evidence to support the use of CPAP is promising, suggesting that the use of CPAP in selected populations reduces the risk of developing BPD.[45] The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was designed to evaluate early CPAP versus early surfactant treatment in extremely preterm infants on the primary outcomes of death or BPD.[51] Newborns either received CPAP or early intratracheal surfactant followed by a conventional ventilation strategy.[51] Investigators found no statistically significant difference in the rates of BPD between the two study group.[51]

Similarly, the randomized, controlled Continuous Positive Airway Pressure or Intubation at Birth (COIN) trial evaluated the use of CPAP versus intubation and ventilation on the primary outcomes of death or BPD at 36 weeks.[52] Authors reported that half of the patients initially treated with CPAP were later intubated, and that there was no statistically significant difference in the primary outcomes of death or BPD at 36 weeks' gestational age.[52]

The VON Delivery Room Management (DRM) Trial was a multicenter randomized trial that evaluated three different approaches to initial respiratory management in infants born between 26–29 weeks' completed gestation.[53] Prophylactic surfactant followed by a period of mechanical ventilation (PS) versus prophylactic surfactant with rapid extubation to bubble nasal CPAP (nCPAP) versus nCPAP with selective surfactant treatment.[53] Their goal enrollment was 876 infants (292 in each treatment arm), due to declining enrollment the study analyzed outcomes from a total of 648 infants enrolled and randomized to a treatment group.[53] The study group found no statistically significant difference in the relative risk of BPD or death between surfactant with extubation to nCPAP versus PS with a relative risk of 0.78 (95% CI 0.59–1.03) and nCPAP with selective surfactant versus PS with a relative risk of 0.83 (95% CI 0.64–1.09).[53] Dunn et al concluded that intubation and unnecessary surfactant administration could thus be avoided and similar outcomes achieved with early initiation of nCPAP.[53]

A Cochrane review by Subramaniam et al evaluated whether the use of prophylactic nCPAP initiated immediately after birth reduced the use of intermittent positive pressure ventilation and the incidence of BPD.[54] They evaluated four trials comparing CPAP versus supportive care (765 infants), and three trials (SUPPORT, COIN, and DRM) comparing CPAP versus mechanical ventilation (2364 infants).[54] They found that in the CPAP versus supportive care analysis there was no reduction in BPD or mortality.[54] In the comparison between CPAP versus mechanical ventilation (with or without surfactant), CPAP reduced the incidence of BPD at 36 weeks (typical RR 0.89, 95% CI 0.79–0.99), and death or BPD (typical RR 0.89, 95% CI 0.81–0.97).[54]

There is also an increasing use of non-invasive positive-pressure ventilation (NIPPV) in this population, as a primary or rescue mode of ventilation. However, no studies have been published to date to definitively suggest that its use reduces the incidence of BPD.[40,55]

Based on the evidence discussed the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn made the recommendation to use CPAP immediately after birth with selective administration of surfactant.[56] They also stated that if the infant is likely to require a ventilator for respiratory support that "early administration of surfactant with rapid extubation is preferable to prolonged ventilation.[56]"

Volume-Targeted Ventilation

Barotrauma, or pressure-induced injury, plays a role in the mechanisms causing BPD, but it is more likely that volutrauma, or alveolar over-distension, is a larger contributor.[6] Taking into account this and the rapid changes in lung compliance over the first days of life, volume-targeted ventilation may be the preferred modality for ventilating premature infants, as it automatically weans pressure in response to improved compliance.[41] To further support this, a 2017 Cochrane review found moderate quality of evidence supporting the use of volume-targeted ventilation to reduce the rates of death or BPD, pulmonary air leaks, and the duration of mechanical ventilation.[57]

High-Frequency Ventilation (HFV)

High-frequency ventilation is capable of oxygenating and ventilating patients at lower mean airway pressure than conventional ventilation, while maintaining distending pressure, making it an attractive option for ventilating fragile lungs. A study done on preterm baboons described improved ventilation and lung mechanics with high-frequency oscillatory ventilation (HFOV) compared to conventional ventilation, but continued interference with lung development persisted.[8,58] A 2015 Cochrane review evaluated the use of HFOV as the primary ventilation strategy compared to conventional ventilation in preterm or low birth weight infants.[59] The Cochrane review found a small reduction in death or BPD and BPD alone, but also

found that air leaks (pneumothorax or pulmonary interstitial emphysema) were more common in the HFOV-treated patients.[59] One large trial which found a benefit of HFOV may have been flawed by using synchronized intermittent mandatory ventilation in the conventional group, rather than assist-control.[60]

Diuretics

High fluid intake, and lack of weight loss during the first week of life have been associated with a higher risk of the combined outcome of death and BPD.[45,61,62] Diuretics are one of the most commonly prescribed medications in the NICU, used to prevent BPD or manage patients with established BPD. Commonly used diuretics include loop, thiazide, and potassium-sparing diuretics.

The intention of diuretic use is to "improve" the fluid balance of the premature infant by reducing pulmonary edema, and thus improving lung mechanics.[62] Furosemide, a loop diuretic, enhances lung fluid absorption.[63–65] Systematic reviews of diuretic use have found that these improvements in lung mechanics are short-lived, with no meaningful improvement in ventilator requirements.[62,66] Moreover, chronic use may result in electrolyte disturbances, nephrocalcinosis, nephrolithiasis, and contraction alkalosis.

The Premature and Respiratory Outcomes Program (PROP) reported that of 835 infants born 23 0/7–28 6/7 weeks, 483 were exposed to at least one dose of a diuretic during their NICU hospitalization.[67] Blaisdell et al reported that respiratory requirements did not improve following diuretic therapy.[67] Contrariwise, they found that respiratory requirements actually increased in the 1–7 days after diuretics were initiated.[67]

Slaughter et al evaluated the use of diuretic therapy in NICUs. They reported that the use of one diuretic was associated with the use of an additional diuretic.[64] Specifically, they found strong positive correlations between chlorothiazide and spironolactone ($R = 0.85$, $P < 0.0001$), and hydrochlorothiazide and spironolactone ($R = 0.89$, $P < 0.0001$).[64] These combinations of medications may be an attempt to correct the contraction alkalosis that occurs with diuretics secondary to increased potassium excretion. This contraction alkalosis causes increased carbon dioxide retention, necessitating increased respiratory support, leading to more pulmonary injury and edema, and a vicious cycle.

Individual diuretics have their own side effect profiles. Furosemide increases local prostaglandin production leading to pulmonary vasodilation,[64,68–70] and this enhanced prostaglandin production also leads to increased patency of the ductus arteriosus.[62,64,71–73]

A systematic review of the use of diuretics in preterm infants with respiratory distress syndrome (RDS) showed no effect on the outcomes of death, BPD, or duration of mechanical ventilation.[63,66] Thus, their routine use must be discouraged.

Steroids

Because of low serum cortisol levels in the first week of life, and the role of inflammation in the development of BPD, postnatal steroids are frequently used in premature infants.[74–77] The most frequently used corticosteroids are dexamethasone and hydrocortisone, with the most studied being dexamethasone. The use of steroids has been stratified into early (<7 days of age) or late (>7 days of age) administration. A Cochrane meta-analysis of 32 clinical trials of early systemic steroid use found a correlation with a lower rate of extubation failures, decreased duration of intubation, and decreased risk of BPD.[40,78,79]

The use of systemic steroids is unfortunately not without side effects. The Cochrane meta-analysis of early steroid use also reported increased rates of intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure.[17,23,45,78,80,81] The Cochrane review also suggests that early steroid use is linked to a higher risk of adverse neurologic outcomes compared to later administration.[78]

The use of inhaled corticosteroids for the prevention of BPD has also been studied. A Cochrane review concluded that

> "the trials did not demonstrate significant change on the BPD rate at 28 days or 36 weeks' PMA regardless of whether the therapy was given early (<7 days) or late. (>7 days)."[23,79,82]

In 2002 an AAP policy statement on the use of postnatal corticosteroids for prevention or treatment of BPD concluded that routine use could not be recommended.[83] Several reports suggest that the severity of BPD increased during this time period.[84] The 2010 AAP policy statement does not recommend the routine use of high-dose dexamethasone, low-dose dexamethasone, or high-dose hydrocortisone based on a lack of randomized trials and insufficient evidence.[84] The policy statement regarding early hydrocortisone, however, states that

> "early hydrocortisone treatment may be beneficial in a specific population of patients; however, there is

insufficient evidence to recommend its use for all infants at risk of BPD."[84]

Surfactant

The initiation of, and continued use of mechanical ventilation in the surfactant-deficient lung may cause injury.[15,85,86] The administration of rescue surfactant within 2 hours of delivery reduces the risk of BPD as well as the composite risk of death or BPD.[87] A Cochrane review of early versus late surfactant with a brief period of ventilation versus prolonged ventilation showed a reduction in the incidence of air leak and BPD (defined as oxygen therapy at 28 days) with early administration of surfactant, relative risk (RR): 0.51; 95% confidence interval (CI): 0.26–0.99.[88,89]

With the known benefits of surfactant administration in the reduction of respiratory distress syndrome, and BPD, new approaches to its administration, less invasive surfactant administration (LISA) and minimally invasive surfactant therapy (MIST), are gaining clinical interest worldwide, and in some regions considered standard of care.[87,90,91] Kribs et al first described LISA, a method for delivering surfactant to infants on CPAP in 2007 with placement of a catheter through the vocal cords under direct laryngoscopy.[90,91] While this approach does not require intubation with an endotracheal tube, it does require laryngoscopy. MIST does not require laryngoscopy, or endotracheal intubation, and instead utilizes a laryngeal mask to direct a catheter and subsequently surfactant down the trachea, but without laryngoscopy and secure advancement past the vocal cords, there is no way to ensure the full dose enters the airways.[87,90] Despite several RCTs evaluating the safety, efficacy, and long-term outcomes of patients receiving surfactant via LISA or MIST techniques showing either no difference, or decreased rates of BPD when compared to INSURE, a survey of 472 neonatologist in the United States, published in 2019, provided evidence that only 10% of respondents felt that there was adequate evidence to recommend it as a standard of care.[91] 4% of respondents reported utilizing LISA in their NICUs, 4% stated that they sometimes use it, and 7% reported using it as part of a research study.[91]

Methylxanthines

Methylxanthines are one of the few therapeutic classes of medications that have been associated with a reduction in the rate of BPD. The most commonly utilized methylxanthine is caffeine. Schmidt et al evaluated the short- and long-term effects of caffeine when initiated in the first ten days of life for the treatment of apnea of prematurity in the Caffeine Therapy for Apnea of Prematurity (CAP) Trial.[92] The trial randomized over 2000 infants to receive caffeine or placebo until caffeine use for the treatment/prevention of apnea of prematurity was no longer indicated, approximately 34–35 weeks' post-menstrual age.[92] The CAP Trial Group reported that caffeine therapy significantly reduced the risk of BPD, 36% in the treatment group vs 47% in the placebo group [odds ratio (OR): 0.63; 95% CI: 0.52–0.76; P<0.001].[92] Theophylline and caffeine have positive short-term effects on pulmonary mechanics in infants who do have BPD by decreasing airway resistance, increasing dynamic compliance, and improving diaphragmatic excursion.[63,93] Patients treated with caffeine have also been shown to have a reduced need for supplemental oxygen, continuous positive airway pressure, and mechanical ventilation compared to placebo, with support able to be discontinued one week earlier.[92]

iNO

Inhaled nitric oxide (iNO) is a potent pulmonary vasodilator that can improve oxygenation of patients in hypoxemic respiratory failure. Its use has been studied prophylactically, for prevention of BPD, or as rescue therapy. The results of these studies have opposing conclusions.

The Nitric Oxide to Prevent Chronic Lung Disease (NO CLD) trial evaluated the routine use of iNO at 20 ppm for infants with continued mechanical ventilation requirements at 7 to 21 days of life.[94] Infants were initiated on 20 ppm for 48 to 96 hours, then decreased sequentially to 10, 5, and finally 2 ppm weekly, with a minimum duration of therapy of 24 days. They reported that iNO improved survival without BPD, but the results were barely statistically significant (P=0.04, 95% CI 1.01–1.51).[94]

More recently Hasan et al published a randomized, placebo controlled clinical trial evaluating whether iNO improved the rate of survival without BPD in infants born at <30 weeks' gestation with birth weight <1250 g who required mechanical ventilation at 5 to 14 days' postnatal age.[95] Patients randomized to the treatment arm received iNO at 20 ppm for 72 to 96 hours, which was then decreased to 10 ppm until day 10 to 11, at which time it was decreased to 5 ppm until completion of the study, after receiving 24 days of treatment.[95] Four hundred fifty-one infants were studied, and the investigators concluded that

prophylactic use of iNO did not improve survival without BPD (OR 1.17; 95% CI 0.79–1.73).[95]

A Cochrane review evaluating the use of iNO for respiratory failure in preterm infants on death, BPD, or IVH was completed by Barrington et al. Eight studies evaluating rescue treatment found no significant effect of iNO on mortality or BPD (RR 0.94, 95% CI 0.87–1.01).[96] An evaluation of four studies using iNO routinely found no significant reduction in the rates of death or BPD (RR 0.94, 95% CI 0.87–1.02).[96] With these mixed results, the routine use of iNO for the prevention or treatment of BPD cannot be recommended.

Antibiotics

Ureaplasma parvum and *Ureaplasma urealyticum* are the most commonly isolated organisms from infected placentas and amniotic fluid, and infection with them has been associated with the development of BPD.[7,97,98] Azithromycin is a macrolide antibiotic that has both anti-bacterial and anti-inflammatory properties.[99,100] One theory for this anti-inflammatory effect is that azithromycin inhibits neutrophil chemotaxis and cytokine release.[99,100]

The utility of azithromycin and clarithromycin to treat infants infected with these bacteria to help treat or prevent associated pulmonary inflammation has been studied.[101] A systematic review and meta-analysis evaluated the utilization of azithromycin in neonates.[102] The review found eleven studies, four of which were RCTs, three utilized azithromycin (one used erythromycin versus azithromycin) and two of these were placebo controlled.[102] Meta-analysis of the 3 studies administering azithromycin only reported decreased BPD as well as BPD/death in patients who received prophylactic azithromycin (RR 0.83, 95% CI 0.71–0.98).[102] There was no significant difference in the adverse event rate between the treatment and placebo/nil arms of the three RCTs evaluated.[102] The potential benefit of these medications needs to be weighed against the FDA warning about their arrhythmia potential, although this effect was not found in a study of 171 preterm infants completed by Viscardi et al.[101]

Vitamin A

Vitamin A is involved in the regulation, differentiation, and promotion of multiple cell lines, including cells in the lung.[63] Preterm infants lack the ability to recycle retinol and require a constant exogenous supply.[5,103] Supplementing vitamin A in premature infants is associated with a significant reduction in the composite outcome of death or oxygen requirement at one month of age and among survivors at 36 weeks' corrected age.[63,104,105] For these reasons, administration of intramuscular vitamin A is one of the few evidence-based pharmacologic agents recommended for the prevention of BPD,[40] but it is infrequently used, possibly because of the need for intramuscular injection. Recent difficulties in the supply have also been problematic.

Patent Ductus Arteriosus

Because of the pulmonary over-circulation associated with a patent ductus arteriosus (PDA), there is a correlation between the presence of a PDA and the later development of BPD.[40,61,62,106] Indomethacin and ibuprofen are the most commonly utilized medications to attempt to close the PDA non-surgically. The Trial of Indomethacin Prophylaxis in Preterms (TIPP) evaluated the benefits of early PDA treatment in very low birth weight infants.[107] The trial reported no significant reduction in the incidence of BPD, despite a significant reduction in the incidence of PDA.[107] A meta-analysis performed by Jensen et al evaluating prophylactic indomethacin found no increased or decreased risk of BPD.[108] A Cochrane Review by Ohlsson and Shah evaluating the use of ibuprofen for the prevention of PDA found that prophylactic use of ibuprofen probably decreased the incidence of PDA on day 3 or 4 (typical RR 0.39, 95% CI 0.31–0.48; typical RD −0.26, 95% CI −0.31 – −0.21; NNT to benefit 4, 95% CI 3–5), but increased the risk of oliguria, elevated creatinine levels, and gastrointestinal hemorrhage, while having no benefit in the rates of mortality or BPD.[109] Similarly, a Cochrane review by Cooke, Steer, and Woodgate evaluating the use of indomethacin for asymptomatic PDAs found a reduction in PDAs becoming symptomatic, and duration of supplemental oxygen, but no effect on BPD (RR 0.91, 95% CI 0.62–1.35).[110] A retrospective study attempting to determine risk factors for developing BPD by Palta et al found no difference in the risk of oxygen dependence in patients with PDAs treated medically, surgically, or left untreated.[62] These results, combined with the known adverse effects of indomethacin and ibuprofen on decreased blood flow to the brain, kidneys, and intestines, suggest that prevention or treatment of a PDA should be done with caution.

Management

Ventilation

Oxygenation

The previously discussed SUPPORT trial that evaluated CPAP versus invasive ventilation and the development of

BPD, also evaluated two different pulse oximetry target ranges and the primary outcome of retinopathy of prematurity.[111] A secondary outcome of this portion of the study was the development of BPD.[111] Investigators reported that while patients in the lower-oxygen-saturation group had lower oxygen requirements, the rates of BPD at 36 weeks were not statistically different.[111]

The Benefits of Oxygen Saturation Targeting (BOOST) study and Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial showed that higher oxygen saturation targets begun after 32 weeks' PMA were associated with worse pulmonary outcomes as measured by duration of oxygen exposure at 38 weeks' PMA and 3 months' PMA.[82,112,113] The BOOST trial found that infants receiving more oxygen were more likely to be prescribed postnatal steroids, diuretics, and had more readmissions, and pulmonary-related deaths.[112]

A systematic review and meta-analysis of five randomized controlled trials evaluating the utility of varying pulse oximetry target ranges reported no difference in the rate of BPD, ROP, death, or disability at 24 months of age.[114]

For these reasons the AAP Committee on Fetus and Newborn concluded that the ideal physiologic target range for oxygen saturation is "likely patient-specific and dynamic and depends on various factors…[115]" The utilization of oxygen needs to account for the effects of hyperoxemia and hypoxemia.

However, since the publication of the AAP recommendations a large, 5000 patient, multicenter study by the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration has been published which evaluated the effects of lower oxygen saturation targets, 85–89%, or higher, 91–95%, on the primary outcome of a composite of death or major disability at 18 to 24 months' corrected age.[116] BPD, defined as oxygen requirement at 36 weeks postmenstrual age was included as a secondary outcome.[116] The group reported no significant difference in the primary composite outcome of death or major disability at 18 to 24 months.[116] They did find reduced mortality and NEC in the higher oxygen saturation target group, but also reported increased rates of ROP and BPD in this group (25% in the lower target group versus 30% in the high, Risk difference −5.6, 95% CI −8.5 – −2.7; RR 0.81, 95% CI 0.74–0.9).[116]

Pharmacologic Agents

Diuretics

As noted above, pulmonary edema plays a role in the development of BPD.[45] Slaughter et al found that diuretics are commonly used in NICUs across the country, but that patterns vary extremely widely by institution.[64] During hospitalization, PROP found that the use of diuretics decreased significantly over time, while the use of inhaled bronchodilators and steroids increased.[22] Without evidence that diuretic use helps in the prevention of BPD, with side effect profiles previously discussed, they are likely "one of the most abused (drugs) without evidence of substantive benefit.[82]"

Bronchodilators

Hyperreactivity of airway smooth muscle can occur in neonates with BPD.[117] Albuterol, a β2-agonist, is the most commonly prescribed bronchodilator.[22] Bronchodilators have short-term benefits with decreased airway resistance but have not been shown to prevent, treat, or decrease the severity of BPD.[117] PROP found that the use of bronchodilators increases over time during hospitalization and that they are the most commonly prescribed respiratory medication at the time of discharge.[22]

Post-hoc nonrandomized analysis of the Neonatal European Study of Inhaled Steroids (NEuroSIS) found that prophylactic use of inhaled bronchodilators alone, or in combination with inhaled corticosteroids, did not reduce the composite outcome of BPD or death at 36 weeks' PMA.[118] Denjean et al evaluated the use of inhaled bronchodilators on outcomes in patients at risk for BPD in a prospective, randomized, double blind, placebo controlled, multicenter study.[119] One hundred seventy-three infants born at <31 weeks' gestation, who required mechanical ventilation on the tenth postnatal day, were randomized to receive inhaled salbutamol, inhaled salbutamol plus beclomethasone, or placebo for 28 days. They found no significant effect of treatment on survival, diagnosis or severity of BPD, or duration of ventilator or oxygen requirement.[119] Slaughter et al also surveyed neonatologists in the United States about bronchodilator use.[117] The one association they demonstrated was that the longer a baby was treated with mechanical ventilation, the greater the likelihood that a bronchodilator would be prescribed.[117] This suggests that they may merely be drugs of desperation.

Steroids

Delayed (>7–21 days) postnatal steroid therapy for the treatment of BPD has not been shown to have any effect on overall mortality in patients who develop BPD.[63,120] One proposed mechanism for determining indications for

delayed steroid administration is determining risk of BPD. Doyle et al reported that postnatal steroid therapy significantly increased the chance of death or CP when used in patients with a risk of BPD <35%, but reduced the chance of death or CP in infants with a >65% risk of BPD.[121] A study evaluating steroid use over time found that the median age at steroid initiation moved from 13 to 22 to 33 days between 1997–1999, 2000–2003 and 2004–2006.[122] Importantly when comparing these epochs, the rates of BPD increased.[111] The potential side effects cannot be understated, even when being used for the management of BPD.[17,23,80] For these reasons the delayed use of dexamethasone should be done with caution in patients at highest risk of developing BPD, with the inability to wean from high ventilator or oxygen support.[79]

Late Surfactant

Surfactant administered late (>7 days) in patients with a secondary surfactant deficiency and high risk for BPD has also been studied.[45,123,124] An RCT comparing the administration of a delayed dose of surfactant versus placebo found that patients who received full therapeutic doses of surfactant had decreased fraction of inspired oxygen at 24 hours after dosing, but found no difference in the incidence of mortality or BPD between the groups.[123]

Nutrition

Malnutrition during respiratory illness may cause respiratory muscle fatigue prolonging mechanical ventilation, increasing trauma to the developing lung, and continuing this vicious cycle.[15,45,125,126] The diet and nutrition of all premature infants have direct implications on their long-term outcomes. Infants fed exclusively maternal breast milk compared to formula are less likely to develop BPD.[40,127,128] Growth of normal lung tissue is a key element in overcoming BPD.

Pulmonary Hypertension

The changes in lung and vascular development secondary to prolonged ventilator and/or oxygen requirement have cardiac implications as well. Echocardiography has shown a relatively high incidence of right ventricular hypertrophy, increased pulmonary vascular resistance, and pulmonary artery hypertension (PAH).[7,129,130] The development of PAH results from proliferation of smooth muscles of the pulmonary arteries, with incorporation of fibroblasts within the vessel wall, increasing pulmonary vascular resistance, and vasoreactivity.[131,132] Patients with PAH are more likely to be born at lower birth weight, be small-for-gestational age, born to African-American mothers, and born to mothers with a history of hypertension.[133]

The incidence of PAH in patients with BPD based on two studies is 18–25%.[11,134–136] There are both acute and chronic management approaches for PAH. In the acute setting to improve oxygenation, increasing the fraction of inspired oxygen up to 1.0, use of iNO to relax pulmonary vascular smooth muscle and decrease pulmonary artery pressure, diuretics to decrease pulmonary over-circulation, and milrinone to improve right ventricular function have been utilized.[137] Diuretics and milrinone may also decrease systemic vascular resistance, and should be used with caution as they may exacerbate already decreased blood flow to the pulmonary vasculature. Sildenafil, a PDE-5 inhibitor, is commonly used for chronic treatment of PAH. PDE-5 inhibitors increase the concentrations of cyclic GMP, promoting pulmonary vasodilation.[131,138] Patients with PAH have higher rates of tracheostomy and gastrostomy tube placement (27% vs 9%, 80% vs 46%, respectively, $p < 0.001$).[133]

Home Oxygen

According to the most recent VON report from June 2020, 19% of infants born between 22–29 weeks are discharged home on respiratory support.[139] The American Thoracic Society considers oxygen "a safe and relatively convenient means for maximizing growth and development" in infants with BPD.[140] DeMauro et al evaluated this statement, and compared medical and developmental outcomes at two years in 1039 patients with BPD discharged on supplemental oxygen to 1039 patients discharged in room air.[140] Patients discharged on home oxygen were more likely to require re-hospitalization for respiratory illness, had a higher median number of hospitalizations, and were more likely to require tracheostomy between discharge and follow-up.[140] The study found a small improvement in growth among infants discharged on home oxygen compared to those discharged in room air, but there was no difference in developmental outcomes.[140]

Tracheostomy and Home Ventilation

The incidence of ventilator-dependent BPD has been reported to be 0.5–2% of patients with birth weights <1500 g, and up to 6.9% in patients who weigh less than <1000 g at birth.[141,142] Patients who require tracheostomy continue to have a high mortality rate. Mandy et al

reported that 5 of 22 patients (23%) died following tracheostomy, but prior to discharge from the hospital.[142] Gien et al reported improved survival and morbidity in patients with home ventilator-dependence when a multidisciplinary approach was taken to support these infants and their families.[143]

Cristea et al did a retrospective review of patients discharged on home ventilation with tracheostomy between 1984 and 2010.[141] The most common reason for re-hospitalization in their cohort was respiratory-related. They reported that at the time of review 19 of 102 (18.6%) patients had died.[141] Among survivors, 69 of 83 (83%) were able to be weaned from positive pressure ventilation (PPV), and 60 of 69 (97%) were able to be decannulated, with a median age of liberation from PPV of 24 months, and a median age at decannulation of 37.5 months.[141]

Outcomes

Preterm infants who develop and survive with BPD are often predisposed to chronic respiratory and cardiovascular impairments, growth failure secondary to increased nutritional requirements, and neurodevelopmental delay.[40,78,129,140,141,144,145] Smyth et al followed preterm infants with BPD into childhood to evaluate pulmonary function. They reported that eight of nine children had abnormally increased residual volume/total lung capacity, indicative of air trapping.[129] Although all children had improvements in their spirometry results during the study period, only one child could be considered "normal".[129] Preterm infants with BPD are also twice as likely to be re-hospitalized during their first year of life and have more than doubled odds of late death compared to preterm infants without BPD.[140]

Infants with BPD are at increased risk of requiring hospitalization if they become infected with respiratory syncytial virus (RSV), as well as other respiratory viruses. For this reason, BPD is one indication for infants to receive Palivizumab for RSV prophylaxis.[145] The recommendation is to administer Palivizumab during the first year of life for patients with BPD, and during the second year if the patient continues to require supplemental oxygen, diuretics, or chronic steroids.[145]

Conclusion

BPD is a multi-factorial disease. It is unlikely that a single intervention-short of preventing preterm birth will effectively prevent or treat the condition. Improvements in outcome will require a dedicated approach to the principles of evidence-based medicine (and the maintenance of equipoise) and continued multi-center collaborative research.

Disclosure

The authors report no conflicts of interest in this work.

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