

# Prevalence, Prevention and Management of Bronchopulmonary Dysplasia

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**Abstract:** Bronchopulmonary dysplasia (BPD) is a complex pulmonary condition that arises in preterm infants secondary to a constellation of adverse exposures contributing to impaired lung development and repair. In many developed countries, the incidence of BPD continues to rise despite the increasing use of evidence-based therapies and efforts to minimize adverse post-natal exposures. Refinement of perinatal care practices that reduce mortality in the most immature infants is likely contributing to this trend; however, a growing population of survivors with respiratory morbidity significantly burdens individuals and health-care systems. Racial and socioeconomic disparities also result in unequal distribution of morbidity within society. In this review, we will outline trends in the incidence of BPD over the last decade and review important risk factors for adverse pulmonary outcomes. The consequences of BPD for long-term health will be described, followed by a comprehensive summary of evidence-based therapies and potential future treatments that can be applied to reduce the incidence, and the prevalence of BPD.

**Keywords:** chronic lung disease, prematurity, invasive mechanical ventilation, non-invasive respiratory support, surfactant, steroids, oxygen, inflammation

## Introduction

Bronchopulmonary dysplasia (BPD) was first described over 50 years ago as a predominantly fibrocystic lung disease occurring in late preterm infants requiring invasive mechanical ventilation (IMV) and high concentrations of O<sub>2</sub> for management of respiratory distress syndrome (RDS).<sup>1,2</sup> Subsequent advances such as surfactant replacement and antenatal steroid administration have altered the disease phenotype<sup>3</sup> and allowed for increases in long-term survival of extremely preterm infants.<sup>4,5</sup> Although our understanding of the patho-mechanisms of BPD has increased rapidly in the last two decades, there remains a paucity of therapeutic interventions proven to reduce the incidence of both short- and long-term respiratory dysfunction.<sup>6,7</sup> This situation is reflected by reports indicating that the incidence of BPD is increasing in several high-income countries,<sup>4,5,8</sup> often despite increased adoption of evidence-based practices. As BPD is associated with significant long-term morbidity<sup>9–11</sup> and increased health-care costs,<sup>12</sup> the lack of significant progress in preventing this most common complication of prematurity has serious implications for individual and population health.

Prevalence of BPD-related morbidity in pediatric and adult populations is challenging to estimate, as individuals born preterm without BPD may also demonstrate differences in lung function<sup>13</sup> and increased respiratory morbidity.<sup>14,15</sup> The term post-prematurity respiratory disease (PPRD) can be used to describe ongoing morbidity in survivors of preterm birth. While BPD remains an important risk factor for PPRD, other factors such as lower gestational age (GA)<sup>16</sup> and birth weight (BW),<sup>14</sup> respiratory infections early in life<sup>17</sup> and maternal smoking<sup>14,18</sup> are also important. The first part of this review will address current trends in the incidence of BPD and describe the impact of PPRD on individuals and health-care systems. The second part summarizes evidence-based interventions and approaches used to prevent and manage early, evolving and established BPD.

## Prevalence of BPD

### Trends in the Incidence of BPD and Associated Risk Factors

Over the last 5–10 years, increases in survival continue to be reported in extremely low BW (ELBW) infants,<sup>4,5,8,19</sup> including those born between 22 and 23 weeks GA.<sup>4,5,20,21</sup> Although reductions in mortality have been accompanied by decreases in other neonatal morbidities such as necrotizing enterocolitis (NEC)<sup>4</sup> and severe intraventricular hemorrhage (IVH),<sup>4</sup> increasing trends in the incidence of BPD have been recognized in several populations.<sup>4,5,8</sup> The most recent report on care practices and outcomes of extremely preterm infants cared for in hospitals that are part of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) described an overall increase in BPD from 44.7% in 2008–2012 to 49.8% in 2013–2018 (adjusted difference 4.3%, 95% CI: 2.8–5.8%).<sup>4</sup> Outcomes reported by the NRN of Japan that included 19,370 infants born between 22 and 27 weeks GA demonstrated a significant increase in BPD from 41.4% (95% confidence interval or CI: 36.4–46.4%) in 2003 to 52% (95% CI: 48.2–55.9%) in 2016.<sup>5</sup> The composite outcome of BPD and mortality prior to 36 weeks post-menstrual age (PMA) also increased from 52.5% (99% CI: 48–57%) in 2003 to 55.9% (99% CI: 52.2–59.5%) in 2016, indicating that improvements in survival rates may not be sufficient to explain the increase in pulmonary morbidity.<sup>5</sup> Of concern, a lack of improvement in BPD rates has been noted despite more frequent use of practices that have been linked to reductions in respiratory morbidity. These practices include decreased prophylactic administration of surfactant,<sup>22</sup> increased use of post-natal steroids,<sup>23</sup> decreased exposure to IMV<sup>5</sup> and increased use of non-invasive respiratory support (NRS).<sup>24,25</sup> It appears that the relative weight of different risk factors and injurious exposures need to be further explored with ongoing refinement of treatment strategies.

Several recent studies have identified important risk factors associated with adverse respiratory outcomes (Table 1). Demographic characteristics such as low GA, low BW and male sex continue to be strongly associated with increased risk for BPD.<sup>4,5,26–29</sup> Duration of exposure to IMV continues to be a strong predictor of adverse outcomes.<sup>27–31</sup> Specifically, IMV exposure in the delivery room (DR)<sup>24</sup> and first 3–7 days of life<sup>27,28,32</sup> has been linked with increased risk for BPD. These observations indicate that this time-period is of particular importance in determining long-term pulmonary outcomes.<sup>33</sup> Adverse consequences of early exposure to inflammation are reflected in associations between chorioamnionitis,<sup>5</sup> elevated C-reactive protein (CRP)<sup>30</sup> and presence of Gram-negative organisms<sup>30</sup> or *Ureaplasma* species (*spp.*)<sup>34</sup> in respiratory cultures with BPD. Placental insufficiency is linked to the development of BPD and BPD associated pulmonary hypertension (BPD-PH).<sup>35</sup> Gestational diabetes mellitus has also been associated with increased risk for BPD<sup>30</sup> and BPD-PH.<sup>36</sup>

The presence of risk factors can be used to identify infants with a high likelihood of developing BPD<sup>32</sup> and specific adverse pulmonary phenotypes such as BPD-PH. Retrospective studies can only demonstrate associations between exposures and outcomes and not causation. Parallel efforts in pre-clinical research to identify the specific molecular pathways driving these observations are also critical for the development of novel treatments.<sup>6</sup>

### Limitations of Current Clinical Definitions of BPD

As BPD continues to be defined by clinician-prescribed support at 36 weeks<sup>37–39,43</sup> or 40 weeks<sup>41</sup> PMA, differences in the use of respiratory support modalities or changes in criteria may result in alterations in reported incidence.<sup>44,45</sup> The NRN 2019 definition developed by Jensen et al<sup>37</sup> has been reported to be better than previously used criteria<sup>38,39,43</sup> in predicting long-term respiratory<sup>37,44,46</sup> and neurodevelopmental<sup>37,47</sup> morbidity, although this has not been consistently seen across all studies.<sup>48–50</sup> Grading of BPD severity using NRN 2019 definition was found to correlate more closely with health-care costs such as increased length of stay, costs related to the initial admission and hospital charges sustained in the first year of life<sup>45</sup> than either the NICHD 2018<sup>43</sup> or the Canadian Neonatal Network (CNN) definitions.<sup>51</sup> Severity of BPD by NRN 2019 definition does not, however, constitute the only risk factor for PPRD. When the ratio of peripheral oxygen saturation and fraction of inspired O<sub>2</sub> (FiO<sub>2</sub>) was measured in 1005 preterm infants at 36 weeks PMA, lower values were significantly associated with a greater degree of prematurity in infants without BPD.<sup>16</sup> These findings indicate that a greater degree of respiratory immaturity at birth could have a significant impact on ongoing pulmonary function. Respiratory viral and bacterial infections sustained early in life can increase risk for pulmonary morbidity,<sup>52</sup>

**Table 1** Summary of Studies Evaluating Trends in BPD Incidence and/or Relationships with Associated Risk Factors

Study Population	Time Period of Study	BPD Criteria	BPD Outcome (% Population)	Significant Trends Identified During Study Period (RR, 95% CI)	Associations with BPD (OR, 95% CI)	Ref
10,877 infants born at 22–28 weeks GA in US hospitals belonging to NICHD NRN	2013–16 Comparison: 2008–2012 outcomes	NRN <sup>37</sup>	BPD: 49.8% Grade 1: 31.8% Grade 2: 21% Grade 3: 8%	BPD increased: 44.7–49.8%, (AD: 4.3, 2.8–5.8) Survival increased: 76.0–78.4%, (AD: 2.0, 1.0–2.9) Exposure to IMV decreased: 87.0–84.3%, (AD: –2.1, –3.2 to –0.9) Exposure to PNS increased 12.2–18.6%, (AD: 4.0, 3.1–4.9)	N/A	[4]
19,370 infants born at 22–27 weeks GA in hospitals affiliated with the Neonatal Research Network of Japan	2003–16 2003 outcomes compared to 2016	NICHD 2001 <sup>38</sup>	2003–16: 45.5% 2003: 41.4% (n=660) 2016: 52% (n=1122)	BPD increased: 41.4–52%, (p≤0.001) Mortality rates decreased (19–8%, (p≤0.001) IMV ≥4 weeks decreased: 70.3–57.3%, (p≤0.001) NIPPV ≥4 weeks increased: 13.9–64.6%, (p≤0.001) Higher % adverse perinatal factors: SGA, chorioamnionitis, BW <750g in 2016 population versus 2003	Supplemental O <sub>2</sub> ≥4 weeks (aOR: 6.98, 5.8–8.41) IMV ≥4 weeks (aOR: 3.42, 3.04–3.86) BW <750g (aOR: 1.62, 1.43–1.84) SGA (aOR: 1.40, 1.22–1.61) NIPPV ≥4 weeks (aOR: 1.38, 1.25–1.52) Chorioamnionitis (aOR: 1.29, 1.17–1.43) GA<26 weeks (aOR: 1.18, 1.04–1.33) Treated PDA (aOR: 1.12, 1.02–1.23) Center volume <20 cases/yr (aOR: 1.16, 1.06–1.27)	[5]
40,268 infants born at 22–32 weeks GA at Hospitals in CA, USA	2008–2017	Shennan 1988 <sup>39</sup>	BPD: 23.5% overall <28 weeks: 44.9%	Overall incidence of BPD unchanged BPD in infants >26 weeks GA decreased: (18.1% in 2008–2011 vs 16.6% in 2014–17, p =0.002 for trend) BPD in infants <750g decreased: (18.5% in 2008–2011 vs 16.6% in 2014–17, p <0.001 for trend) Mortality decreased: (31.6/100 live births to 25.5/100 live births (p<0.001 for trend) IMV in DR decreased by 46% (p=0.002) NRS increased by 75% (p<0.001)	IPPV in DR (aOR: 2.64, 2.22–3.13) predicted probability of BPD: 13.96, (10.54–18.27) NRS in DR (aOR 1.73, 1.46–2.05) Predicted probability of BPD 9.53 (7.1–12.69) IMV after DR (aOR: 10.01, 7.4–13.58) Predicted probability of BPD: 14.83 (10.97–19.75) iNO use: (aOR 3.79, 3.3–4.35) Predicted probability of BPD: 31.6 (24.23–40.01) Surfactant: (aOR: 2.88, 2.68–3.09) Predicted probability of BPD 14.94 (11–19.91)	[24]

(Continued)

**Table 1** (Continued).

Study Population	Time Period of Study	BPD Criteria	BPD Outcome (% Population)	Significant Trends Identified During Study Period (RR, 95% CI)	Associations with BPD (OR, 95% CI)	Ref
Infants 24–27 <sup>+6</sup> weeks GA born in Germany with data in National Database	Epoch 1: 2010–2013 n=9058 Epoch 2: 2014–2017 n=10,924	NICHD 2001 <sup>38</sup> moderate to severe with O <sub>2</sub> needs targeting SpO <sub>2</sub> ≥90% <sup>40</sup>	Epoch 1: 34.9% Epoch 2: 24.2%	Mortality decreased: 15.1–12.7%, (RR: 0.841, 0.784–0.901, p<0.0001) BPD decreased: 34.9–24.2%, (RR 0.693, 0.662–0.727, p<0.0001) % requiring NRS only increased: 20.7–27.8% (RR 1.342, 1.276– 1.411)	N/A	[19]
379 Infants <28 weeks GA born at a single US academic center	Epoch 1: prophylactic surfactant 2010–2014 n=233 Epoch 2: Selective surfactant n=146	Shennan 1988 <sup>39</sup> NICHD 2001 <sup>38</sup> CNN <sup>41</sup> NRN <sup>37</sup>	Epoch 1: Shennan: 32% NICHD 2001: 68% Moderate or severe: 39% CNN: 16% NRN: 41% Grade 2/3: 21% Epoch 2: Shennan: 35% NICHD 2001: 58% Moderate or severe: 37% CNN: 22% NRN: 49% Grade 2/3: 19%	Significant differences in incidence were noted with varied use of definition within each epoch No significant differences noted between epochs in BPD incidence Use of PNS increased: 6–17% (p=0.002) Intubation in DR decreased: 87–52% (p<0.001) CPAP days increased: 22±16 to 40±19 (p<0.001) NIPPV days decreased: 22±17 to 14±13 (p=0.007) IMV decreased but not significantly	N/A	[22]

481 Infants <32 weeks and <1500g born in a 2 NICUs in Jerusalem, Israel	Epoch 1: 2012–2013 Epoch 2: 2018–2019	NICHD 2001 <sup>38</sup>	Epoch 1: Moderate or Severe: 11% <28 weeks GA Moderate or Severe: 36% Epoch 2: Moderate or Severe: 14% <28 weeks GA Moderate or Severe: 40%	No significant changes in BPD rates Mortality rates decreased: 13.1–10.7% IMV rates increased: 33–47%, $p = 0.016$ Average NRS days increased: 9.24–14.08 days $p=0.016$ % infants receiving any respiratory support increased: 63–77% ( $p=0.001$ ) O <sub>2</sub> use decreased: 10.02±17.49 vs 5.47±11.13 days ( $p=0.001$ ) Total duration of respiratory support was unchanged	BW: OR: 0.0998 (0.996–0.999, $p=0.003$ ) IMV days: OR: 1.21 (1.14–1.30, $p<0.001$ )	[42]
9181 Infants born at 23–28 <sup>+6</sup> weeks GA, BW 501–1250g born in US Hospitals belonging to NICHD NRN	2011–2017	NRN <sup>37</sup>	BPD:60% Grade 1:34.3% Grade 2:18.8% Grade 3:6.7% n=8129 survivors at 36 weeks PMA	N/A	On DOL 1 BW was most predictive of death or BPD severity Mode of respiratory support most predictive factor on days 3,7,14 and 28	[32]
24,896 Infants born at 22–29 weeks GA at 715 US hospitals belonging to VON	2018	NRN <sup>37</sup>	BPD:45.4% Grade 1/2: 36.9% Grade 3: 3.7% n=22,322 survivors to 36 weeks PMA	N/A	Incidence of mortality and grade 3 BPD decreased proportionally as GA increased Grade 1 or 2 BPD diagnosis peaked at 25 weeks GA (51.8%) Various morbidities higher in survivors with BPD versus those with No BPD including IVH or cystic PVL, surgical NEC, LOS, severe ROP and need for home oxygen therapy	[26]
266 ELBW infants ≤28 weeks cared for at a tertiary center in Singapore	2012–2015	NICHD 2001 <sup>38</sup>	Moderate or severe BPD 67%	N/A	IMV on DOL 7: (OR: 1.97, 1.3–3.1) was the only independent risk factors for the composite outcome of mortality or BPD Significant factors on univariate analysis included: Low GA, Low BW, PDA needing treatment, air leaks, FiO <sub>2</sub> >0.25	[28]

(Continued)

Table 1 (Continued).

Study Population	Time Period of Study	BPD Criteria	BPD Outcome (% Population)	Significant Trends Identified During Study Period (RR, 95% CI)	Associations with BPD (OR, 95% CI)	Ref
202 VLBW infants born ≤32 weeks GA at a Level III NICU in Spain	January 1st 2013-August 30th 2020	NICHD 2001 <sup>38</sup>	BPD: 28.7% Moderate or severe: 10.4%	N/A	IMV DOL 1: (OR 5.39, 1.54–18.89, $p=0.008$ ) IMV DOL 3: (OR 9.99, 2.47–40.44, $p=0.001$ ) LOS: (OR: 9.51, 2.99–30.28, $p<0.001$ ) IMV through DOL 1 and DOL 3 and LOS were independent risk factors for moderate-severe BPD	[27]
1755 preterm infants with BPD born in public and private hospitals included in a national database Median GA 27.1 weeks	January 2016-August 2020	NICHD 2001 <sup>38</sup>	Mild: 52.5% Moderate: 25.3% Severe:22.2%	N/A	Factors associated with increased risk for moderate/severe versus mild BPD: Male sex (OR: 1.425, 1.134–1.791, $p=0.003$ ) Oligohydramnios (OR: 1.547, 1.120–2.212, $p=0.009$ ) Histological chorioamnionitis (OR: 1.714, 1.250–2.348, $p=0.001$ ) FiO <sub>2</sub> >0.3 at birth (OR: 1.434, 1.098–1.874, $p=0.008$ ) FiO <sub>2</sub> >0.6 at birth (OR:1.607, 1.211–2.132, $p<0.001$ ) IMV exposure: (OR:1.515, 1.104–2.604, $p=0.01$ ) Nosocomial pneumonia: (OR:3.231, 2.192–4.764, $p<0.001$ ) Received iNO: (OR1.76, 1.189–2.079, $p=0.005$ )	[29]
471 <32 weeks GA infants with BPD admitted to Level IV NICU in Shanghai, China	2016–2020	NICHD 2001 <sup>38</sup>	Mild: 59.2% Moderate 31.2% Severe: 9.6%	N/A	GDM: (aOR: 2.272, 1.080–4.780, $p=0.031$ ) Initial FiO <sub>2</sub> : (aOR: 1.032, 1.012–1.052, $p=<0.001$ ) IMV: (aOR: 2.593, 1.400–4.802, $p=0.002$ ) pH-min: (aOR: 0.005, 0.001–0.189, $p=0.005$ ) Cl-min: (aOR: 0.904, 0.851–0.961, $p=0.001$ ) CRP-max: (aOR: 1.026, 1.016–1.036, $p<0.001$ ) Gram negative organism in respiratory culture: (aOR: 2.311, 1.273–4.197, $p=0.006$ ) PDA: (aOR: 6.328, 2.937–13.631, $p<0.001$ )	[30]

**Abbreviations:** GA, gestational age; US, United States; BPD, bronchopulmonary dysplasia; CI, confidence interval; RR, relative risk; AD, adjusted difference; aOR, adjusted odds ratio; OR, odds ratio; BW, birth weight; SGA, small for gestational age; NIPPV, nasal intermittent positive pressure ventilation; NRS, non-invasive respiratory support; IMV, invasive mechanical ventilation; IPPV, invasive positive pressure ventilation; NICHD, National Institute for Child Health and Human Development; NRN, Neonatal Research Network; NICU, Neonatal Intensive Care Unit; PDA, patent ductus arteriosus; iNO, inhaled nitric oxide; PNS, post-natal steroids; CNN, Canadian Neonatal Network; CPAP, continuous positive airways pressure; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; LOS, late onset sepsis; ROP, retinopathy of prematurity; FiO<sub>2</sub>, fraction of inspired oxygen; O<sub>2</sub>, oxygen; SpO<sub>2</sub>, oxygen saturation; DR, delivery room; Cl, chloride; CRP, C-reactive protein.

while socioeconomic disparities have also been linked to increased frequency of symptoms and health-care utilization in those born preterm.<sup>53–55</sup> Non-Hispanic black infants and those receiving public insurance were found to have increased odds of tracheostomy placement for BPD relative to non-Hispanic white infants or infants with private coverage (adjusted odds ratio (aOR) 1.25, 95% CI: 1.09–1.43) and (aOR 1.25, 95% CI 1.09–1.43), respectively.<sup>56</sup> Active efforts to both further characterize and address factors driving interracial and socioeconomic disparities in pulmonary outcomes are urgently needed.

Infants who remain on respiratory support at 36 weeks PMA have been shown to vary widely in terms of their clinical presentation and response to therapy.<sup>57</sup> Specific BPD phenotypes characterized by central airway malacia and PH are disproportionately associated with morbidity and mortality.<sup>58,59</sup> There remains a continued need for an objective consensus definition for BPD that allows for more accurate prediction of long-term outcomes and benchmarking between institutions.<sup>33</sup>

## Impact of BPD on Individuals and Healthcare Costs

Analysis of data from a US insurance commercial claims database revealed that 29% of infants born  $\leq 28$  weeks GA required one of the following in the first year after discharge: pulmonary medications for  $\geq 30$  days, supplemental O<sub>2</sub>, hospital readmission or emergency room (ER) visit for respiratory indications.<sup>15</sup> BPD was present in 86.7% of these infants and was associated with markedly elevated health-care costs.<sup>15</sup> Extrapolation of this data to the total US population of infants born at  $\leq 28$  weeks in 2015 suggests that nearly 8000 extremely preterm infants would be expected to sustain respiratory complications each year.

Within the population of infants meeting criteria for BPD, there exist several, often overlapping, clinical phenotypes that are differentially associated with adverse outcomes.<sup>58,60,61</sup> Impairment of alveolar development that leads to a paucity of abnormally distended airspaces typically presents with impairment of gas exchange and prolonged dependency on supplemental O<sub>2</sub>.<sup>60,61</sup> BPD-PH affects up to 25% of infants with moderate-to-severe BPD<sup>62</sup> and is associated with both increased morbidity and mortality.<sup>58,62</sup> Prolonged exposure to invasive positive pressure can disrupt normal central airway development, leading to varying degrees of tracheomalacia, bronchomalacia and tracheomegaly.<sup>63</sup> In one multi-center study population, tracheobronchomalacia was associated with longer duration of IMV, greater likelihood of tracheostomy placement and increased incidence of co-morbidities such as gastroesophageal reflux and pneumonia.<sup>59</sup> Findings from a single-center study also identified central airway disease along with BPD-PH as phenotypes associated with higher rates of tracheostomy placement, use of pulmonary vasodilator therapies and mortality prior to discharge.<sup>58</sup> Other clinical phenotypes that have been described include interstitial lung disease and peripheral airway involvement that is associated with increased airway resistance and wheezing in later life.<sup>57,60,61</sup>

Although the prevalence of symptomatic PPRD decreases after the first 3 years of life, studies continue to demonstrate that children and adults with BPD have reduced exercise tolerance,<sup>64</sup> lower quality of life scores,<sup>65,66</sup> increased airflow obstruction<sup>67,68</sup> and earlier decline in pulmonary function tests (PFTs).<sup>67,69</sup> An obstructive pattern of lung disease, characterized by a reduced functional expiratory volume in 1 sec (FEV<sub>1</sub>) or a reduced ratio of FEV<sub>1</sub> to forced vital capacity (FVC) is the phenotype most frequently identified in pediatric and adult survivors of prematurity.<sup>52</sup> Clinically, increased airway resistance likely contributes to the elevated frequency of asthmatic symptoms noted in preterm-born children,<sup>15,70,71</sup> which in turn, contribute to increased usage of medications such as bronchodilators,<sup>71</sup> inhaled and systemic steroids<sup>72</sup> and antibiotics,<sup>70</sup> in addition to more frequent hospitalizations for respiratory indications.<sup>15,70,72</sup>

Continued alveolar development in early childhood typically results in improvement in symptoms and weaning from respiratory support;<sup>33</sup> however, differences in lung function remain persistent throughout adolescence and early adulthood.<sup>73,74</sup> A recent study that compared the exercise capacity, lung function and habits of children with BPD to term-born controls revealed that while oxygen consumption parameters by body weight were comparable between groups, children with BPD demonstrated a greater degree of airflow limitation.<sup>75</sup> Children with BPD achieved lower levels of workload on cardiopulmonary exercise test and were over twice as likely to report difficulties in physical exercise and symptoms such as wheezing and shortness of breath on exertion than term-born controls.<sup>75</sup> These findings indicate that while alveolar growth may result in improvements in gas exchange, the involvement of peripheral airways



may have lasting consequences for future cardiopulmonary and metabolic health. Patterns of early decline in FEV<sub>1</sub>/FVC in adolescents and young adults with either a history of BPD or extreme prematurity raise concern that PPRD may be a precursor to early development of chronic obstructive pulmonary disease (COPD) in some patients with severe parenchymal involvement.<sup>74,76</sup> Severe BPD is linked with neurodevelopmental impairment<sup>47,77</sup> which places an additional burden on patients and caregivers. Recent studies continue to report associations between BPD and neurodevelopmental disabilities in infants,<sup>47,78</sup> toddlers,<sup>78</sup> school-age children<sup>79</sup> and adolescents.<sup>80</sup>

Both respiratory and neurological morbidities associated with BPD contribute to marked increases in health-care costs.<sup>12,79</sup> A retrospective study utilizing data obtained from infants born in California between 2008 and 2011 calculated median hospitalization costs during the first year of life for a <30 week GA infant with BPD to be \$377,871 compared with \$175,836 for an infant without BPD.<sup>81</sup> Severe BPD was associated with a median total incremental admission cost of \$35,773 (95% CI: \$32,018 - \$39,528) making this second most expensive complication of prematurity after surgical NEC.<sup>82</sup> A microsimulation model based on mortality and morbidity data noted in populations of preterm infants with and without BPD estimated that patients with BPD would incur an average lifetime healthcare cost in Canadian Dollars (CAD) of \$716,912 (95% CI: CAD \$416,000 - \$1,275,000).<sup>9</sup> Coordinated efforts to prevent BPD both through optimization of existing treatment strategies and through the development of new therapies therefore have strong potential to conserve healthcare spending.

## Prevention of BPD

Recent updated evidence-based guidelines are included in [Table 2](#), which is adapted from recommendations we have previously published.<sup>33</sup> While individual interventions by themselves are important, it is critical that they are adopted in a systematic manner with multi-disciplinary team input and involvement. Quality improvement (QI) projects provide critical guidance on how approaches can be combined and implemented to improve local/institutional outcomes. [Table 3](#) provides a summary of the results of several recently published QI projects that described success in improving respiratory outcomes.<sup>83–85</sup> Each QI team placed an emphasis on optimization of DR management with standardized, GA specific protocols for surfactant replacement, initiation of caffeine, NRS and invasive ventilatory support.<sup>83–85</sup> The results of these and other recent QI projects demonstrate the impact of systematic initiation of GA-specific approaches that begin at birth. Integration of evidence-based practices described in the following section using a QI-based framework is therefore strongly recommended.

## Prenatal Strategies

Exposure to antenatal steroids (ANS) is associated with reductions in multiple complications including RDS, IVH, NEC and mortality.<sup>126</sup> These benefits have been shown to be relevant in populations born at <24 weeks GA.<sup>127</sup> The early advantages gained by prenatal steroid exposure have not, however, been shown to result in improvement in long-term respiratory outcomes.<sup>128</sup> Of note, receipt of repeated courses of ANS in the absence of preterm delivery has been linked to adverse respiratory and neurological outcomes in term infants.<sup>129</sup> Current European perinatal guidelines advocate for routine administration of ANS at 24–33<sup>+6</sup> weeks gestation in pregnant women deemed at high risk for preterm delivery in the next 7 days.<sup>130</sup> ANS can be offered between 22 and 24 weeks GA when active management of the infant is anticipated.<sup>130</sup>

## DR Strategies: Optimal Diagnosis and Management of RDS

Pooled meta-analysis data from four randomized clinical trials (RCTs) comparing early initiation of continuous positive airway pressure (CPAP) with prophylactic surfactant administration for infants 24–28 weeks GA,<sup>131–134</sup> showed an association between early CPAP and reduced risk for BPD [relative risk (RR) 0.90, 95% CI: 0.83–0.98, risk difference (RD) –0.04, 95% CI: –0.08 –0.00], number needed to treat (NNT)=25].<sup>131,132,135</sup> Given the strong link between early exposure to IMV and development of BPD,<sup>27</sup> a greater advantage might be expected. Rates of CPAP failure approaching 50%<sup>131–134</sup> were thought to explain the small effect size. Receipt of surfactant within 2 hr of birth is associated with significant reductions in the risk for BPD and the combined outcome of BPD and mortality.<sup>88</sup> Delayed surfactant administration in patients who failed CPAP, may therefore, have contributed to lung injury.<sup>136</sup> Factors predicting CPAP



**Table 2** A Summary of Evidence-Based Recommendations for Prevention and Management of BPD

Therapeutic Intervention	Current Status	Evidence Level	Recommendation Level
<b>Early phase (up to 1 postnatal week)</b>			
Oxygen supplementation	Resuscitation: Titrate supplemental oxygen to obtain preductal oxygen saturation >80% by five minutes of life <sup>86</sup> Maintain oxygen saturations 90–95% <sup>87</sup>	I I	B A
Ventilatory strategy	Trial of CPAP for spontaneously breathing infants Aim to give surfactant within 2 hours of life <sup>88,89</sup> Surfactant administration for infants requiring intubation in DR <sup>89</sup> Consider surfactant administration if FiO <sub>2</sub> remains consistently ≥0.3 on PEEP +6 cm H <sub>2</sub> O <sup>89–91</sup> Use InSurE/LISA technique to administer surfactant <sup>89</sup> Use early NIPPV <sup>92</sup> Lung protective strategies: Consider volume targeted ventilation strategies – TV 4–6mL/kg <sup>93</sup> or HFOV <sup>94</sup> Use short inspiratory times (0.3–0.4 s), <sup>95</sup> rapid rates (40–60 per min) and low PIP on pressure control settings (14–20 cm H <sub>2</sub> O), moderate PEEP (4–6 cm H <sub>2</sub> O) <sup>96</sup> PaO <sub>2</sub> : 40–60mmHg; PaCO <sub>2</sub> :45–55 mmHg <sup>97</sup> No proven advantage to higher CO <sub>2</sub> limits <sup>98</sup> Trial of extubation to NIPPV prior to 7 days in infants who tolerate weaning to minimal settings <sup>99</sup>	I I I II II I I I III	A A A A A B A A B
Methylxanthines	Administration of caffeine within first 3 days of life decreases BPD, <sup>100,101</sup> improves neurodevelopmental outcome <sup>102</sup> Improves successful extubation rate <sup>103</sup>	II-2 I I	B A A
Intratracheal administration of budesonide and surfactant	Associated with an increase in BPD free survival (NNT 4.1 [95% CI: 2.8–7.8]) <sup>104</sup> Studies to date not adequately powered to assess long term neurodevelopmental outcome	I	B
Vitamin A	Improves BPD free survival with reported NNT 14–15 <sup>105</sup> Not associated with long term improved respiratory outcome <sup>106</sup> Dose: 5000 IU given intramuscularly 3 times a week for 4 weeks	I	A
Low dose hydrocortisone	Low dose hydrocortisone (total dose 8.5mg over 10 days) is associated with increased BPD free survival <sup>107</sup> Increased risk of late onset sepsis in infants <26 weeks <sup>107</sup> Increased risk of SIP in infants who receive indomethacin <sup>107</sup>	I	C
Antibiotics	Consider withholding early antibiotic treatment in infants delivered in the absence of preterm labor, preterm ROM or concerns for chorioamnionitis <sup>108</sup>	II	B
Fluids	Avoiding excessively positive fluid balance may prevent BPD <sup>109,110</sup>	II-2	B
Nutrition	Exclusive human milk feeding reduces the risk for BPD <sup>111</sup> Provide increased energy intake <sup>110,112</sup>	I II-2	A A
<b>Evolving BPD (&gt; 1 postnatal week to 36 weeks PMA)</b>			
Dexamethasone	Low dose dexamethasone (0.89 mg/kg over 10 days) facilitates extubation but does not reduce BPD <sup>113</sup> High dose dexamethasone (0.5mg/kg – 1mg/kg) reduces BPD but may increase the risk of NDI and CP <sup>114</sup> Greatest global benefit is for infants with combined risk of mortality and Grade 2/3 BPD >52% - ie those who remain intubated at 3–4 weeks post-natal age. <sup>115</sup>	I I	C C

(Continued)

Table 2 (Continued).

Therapeutic Intervention	Current Status	Evidence Level	Recommendation Level
Ventilatory strategy	Avoid endotracheal tube ventilation, encourage non-invasive support strategies (NIPPV, SNIPPV, nCPAP) <sup>116</sup> Blood gas targets: pH 7.25–7.35; PaO <sub>2</sub> 50–70mmHg; PCO <sub>2</sub> 50–60 mmHg <sup>97</sup> No advantage to allowing higher CO <sub>2</sub> limit <sup>98</sup> Continue CPAP/NIPPV/NIV-NAVA until 32 weeks PMA may help optimize FRC <sup>117</sup>	I I II II	A A B A
Diuretics	May improve respiratory mechanics and facilitate weaning of support. Do not prevent BPD. Continue use only if clear response demonstrated <sup>118</sup>	I	B
Antibiotics	Same as for early phase Preterm infants remain at risk for sepsis, but antibiotics used in the absence of infection can increase risk for BPD <sup>119</sup> Strongly consider discontinuing antibiotics at 48h if cultures are negative	I	A
Nutrition	Same as for early phase		
Methylxanthines	Same as for early phase	I	A
<b>Established phase (&gt;36 weeks PMA)</b>			
Echocardiographic screening for BPD PH	25% of infants with moderate or severe BPD have echocardiographic evidence of pulmonary hypertension <sup>120</sup>	III	A
Ventilatory strategy	SIMV or NAVA modalities over HFOV Use large tidal volumes (8–15mL/kg), long I-time (0.5–1s), low respiratory rates (12–20 per minute), high PEEP (8–12 cmH <sub>2</sub> O) Wean slowly, with goals to reduce work of breathing, improve growth and participation in developmental therapies	III   	A   
Bronchodilators	May improve symptoms in subpopulations of affected infants <sup>121</sup>	II-3	B
Inhaled steroids	Later use may improve symptoms in subpopulations of infants <sup>121</sup>	III	B
Systemic steroids	Brief use of prednisolone may help wean support or provide symptomatic relief during exacerbation <sup>122</sup>	II	B
Diuretics	Chronic therapy as for the evolving phase <sup>118</sup> Consider allowing infant to outgrow dose <sup>121</sup>	I III	B B
Nutrition	Monitor linear growth closely <sup>123</sup> Adjust approach according to clinical phase, avoid holding of enteral feeds <sup>124</sup> Avoid excessive weight gain.	II III	A A
Immunization	Prophylaxis against RSV and influenza decreases re-hospitalization and morbidity RSV prophylaxis is cost-effective <sup>125</sup>	II-2 I	A A

**Note:** Adapted by permission from BMJ Publishing Group Limited. Diagnosis and management of bronchopulmonary dysplasia. Gillfillan M, Bhandari A, Bhandari V, 375:n1974, copyright notice 2021.<sup>33</sup>  
**Abbreviations:** nCPAP, nasal continuous positive airway pressure; FiO<sub>2</sub>, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; InSurE, intubation, surfactant administration, extubation; LISA, less invasive surfactant administration; TV, tidal volume; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PIP, peak inspiratory pressure; NIPPV, nasal intermittent positive pressure ventilation; SIP, spontaneous intestinal perforation; NDI, neurodevelopmental impairment; CP, cerebral palsy; RSV, respiratory syncytial virus; FRC, functional residual capacity; NIV-NAVA, non-invasive ventilation-neurally adjusted ventilatory assist.

**Table 3** A Summary of the Strategies and Results of three Recent QI Projects That Successfully Reduced Adverse Pulmonary Outcome

Site and Population	Global Aim	Key Drivers	Bundle Components	Outcomes	Ref
42 bed level III NICU, USA 132 infants <32 weeks GA admitted during study period Mean GA 29 weeks	To reduce number of patients discharged on supplemental O <sub>2</sub>	Limitation of high PIPs on conventional IMV Consistency in use of different IMV modalities Consistency in use of medications Consistency in delivery room management	<b>1st PDSA Cycle: (January 2018 – April 2019)</b> Indications for initial surfactant administration and repeat dosing HFOV as primary mode in infants <28 weeks GA, HFOV until extubation or ≥2 weeks of age Caffeine on admission in all infants <32 weeks GA <b>2nd PDSA Cycle (May 2019-January 2020)</b> Indications for DR intubation: PPV for >5 mins or FiO <sub>2</sub> >0.6 SIMV-VG as primary mode in infants ≥28 weeks GA, limit PIPs to 24–25cmH <sub>2</sub> O <b>Extubation and reintubation guidelines</b> -Settings for pressure and rate that should prompt extubation -Failure defined by blood gas parameters and frequency of apneic events -Guidelines regarding NRS initiation and weaning process, CPAP until 32 weeks for infants who fail RA trial - Bronchodilators and diuretics limited to patients who showed benefit	Infants <32 weeks GA discharged on O <sub>2</sub> : 19.5% to 8.3% Grade II/III BPD in infants <32 weeks: 54.4% to 28.6%	[84]
24-bed, Level III NICU, USA 449 infants<33 weeks admitted during study period Mean GA 28.5 weeks	Decrease BPD according to VON BPD <33wk criteria (O <sub>2</sub> dependency at 36 weeks PMA in infants <33 weeks GA)	A shared mental model that BPD is preventable Consistent GA and PMA specific practices	<b>Initial Responses (2010–2014)</b> <b>“Shared mental model that BPD is avoidable but requires aggressive preventative care”</b> – Enhanced communication re protocol compliance, consensus building regarding management changes <b>GA and PMA specific interventions:</b> Early CPAP, surfactant administration guidelines, SIMV-VG as primary mode, HFOV for rescue Extubation criteria, CPAP or NIPPV phasing into NIV-NAVA post extubation, delay weaning to HFNC until 32 weeks PMA Caffeine, Vitamin A and IVIG for ELBW and <28 weeks GA, dexamethasone criteria and protocol, inhaled medications as rescue, avoidance of diuretics, Azithromycin prophylaxis pending cultures, limit use of other antibiotics MBM/DBM as base for feeds with bovine supplements <b>Additions to protocols - Full implementation (2015–2019)</b> “No BPD Roadmap”, Surfactant criteria expanded, HFOV as primary mode for ELBW <28 weeks, NIV-NAVA until 32 weeks PMA, human milk for both base and fortifier, avoid pharmacological treatment of reflux and PDA	BPD in infants <33wk (VON): 31% to 1.6% (p <0.001) BPD in infants <28 wk (VON): 50% to 1.2% (p <0.001) BPD in infants <26 wk VON): 35.7 to 2.6% (p=0.03) O <sub>2</sub> at D/C:13.8 to 2.2% (p =0.03)	[83]
49 bed academic Level III NICU, USA 611 infants <32 weeks GA admitted during the baseline and study periods Median GA 29 weeks	Decrease moderate to severe BPD by NICHD 2001 criteria <sup>38</sup> by 35%	Effective team communication re: DR plan and preparation Standardization of DR resuscitation Awareness of InSurE guideline Comfort using NRS equipment Standardization of orders sets Care team guideline support Uncertainty regarding optimal timing of surfactant	<b>DR care bundle Q1 2017-Q4 2017</b> -Pre-delivery huddle before every <32 weeks GA delivery -GA specific guidelines for initiation and escalation of NRS and threshold for surfactant administration -Caffeine within 24 hr of life <b>Compliance with weaning pathway Q1 2018-Q2 2020</b> -Maintain infants <32 weeks GA on NRS until at least ≥32 weeks PMA <b>Revision of surfactant guideline Q3 2020-Q1 2021</b> -Revised GA specific protocol to include early selective surfactant administration determined by NRS requirements in the DR and at 90 minutes of age -Surfactant in all infants intubated unless for respiratory depression -Surfactant by InSurE method for infants on NRS meeting selective treatment criteria	Moderate to severe BPD: 38 to 15% (p <0.0001) Moderate to severe BPD or death: 48 to 26% (p =0.0009) IMV requirement: 52 to 27% (p = 0.0025) Postnatal steroids: 19 to 10% (p = 0.02)	[85]

**Abbreviations:** NICU, neonatal intensive care unit; USA, United States of America; GA, gestational age; O<sub>2</sub>, oxygen; PIP, positive inspiratory pressure; IMV, invasive mechanical ventilation; PDSA, “plan, do, study, act” cycle; HFOV, high frequency oscillatory ventilation; DR, delivery room; FiO<sub>2</sub>, fraction of inspired oxygen; PPV, positive pressure ventilation; SIMV-VG, synchronized intermittent ventilation volume guarantee; NRS, non-invasive respiratory support; RA, room air; VON, Vermont Oxford Network; NIV-NAVA, non-invasive ventilation-neurally adjusted ventilatory assist; PMA, post menstrual age; IVIG, intravenous immunoglobulin; ELBW, extremely low birthweight (<1000g); MBM, maternal breast milk; DBM, donor breastmilk; mins, minutes; NICHD, National Institute of Child Health and Human Development; InSurE, Intubate Surfactant Extubate; PDA, patent ductus arteriosus; Q, quarter.

failure include lower GA, lower BW,<sup>90,91</sup> lack of receipt of ANS,<sup>90</sup> evidence of severe RDS on chest radiograph,<sup>90</sup> and  $\text{FiO}_2 \geq 0.3$ .<sup>90</sup> CPAP failure is associated with a significantly increased risk of pneumothorax, BPD and mortality<sup>90,91,137</sup> suggesting that earlier interventions could be beneficial. The current European guidelines recommend surfactant administration for  $\text{FiO}_2 \geq 0.3$  in infants supported by CPAP;<sup>138</sup> however, more accurate predictive tools are needed. In USA, RDS-NExT workshop conducted by an expert panel of health-care providers has recently made specific recommendations for surfactant administration based on a clinical score, respiratory support status,  $\text{FiO}_2$  requirement and blood gas values.<sup>89</sup> Lung ultrasound (US) performed at the bedside has been shown to be effective in diagnosing RDS and predicting need for surfactant treatment.<sup>139</sup> While this approach shows promise, there is currently no direct evidence of any long-term impact in reducing BPD.

Techniques that allow for timely receipt of surfactant while minimizing exposure to IMV have been associated with reduced risk for BPD.<sup>51,140</sup> The “Intubate, Surfactant, Extubate” (InSurE) strategy describes delivery of surfactant through an endotracheal tube (ETT) after which the tube is removed quickly and the infant placed back on NRS. Less invasive surfactant administration (LISA) involves delivery of surfactant into the airway via a thin flexible catheter during spontaneous breathing. Recent meta-analyses of RCTs comparing LISA to either InSurE or intubation with continued IMV reported both a decreased risk of BPD and a reduction in the combined outcome of BPD and mortality.<sup>140,141</sup> Although pooled results from clinical trials suggest an advantage for LISA over InSurE, a direct comparison between these two methods in extremely preterm infants has not been made, as in many investigations a variable duration of IMV occurred following the procedure. There have also been concerns raised regarding the safety and effectiveness of LISA, after a recent RCT showed a trend towards increased mortality in infants 25–26 weeks GA who received minimally invasive surfactant therapy.<sup>142</sup> These findings are in contrast with those of a large retrospective study of 6542 infants 22–26<sup>+</sup> weeks GA cared for in centers that are part of the German Neonatal Network.<sup>143</sup> In this population, LISA was associated with reduced risks of all-cause death [OR: 0.74, 95% CI: 0.61–0.9.0;  $p=0.02$ ], BPD (OR: 0.69, 95% CI: 0.62–0.78;  $p<0.001$ ), and BPD or death (OR: 0.64, 95% CI: 0.57–0.72;  $p<0.001$ ).<sup>143</sup> Reduced risk for BPD and mortality remained significant in all GA groups even when adjusted for adverse perinatal characteristics.<sup>143</sup> LISA has been readily adopted in Germany and other European countries as part of a bundled approach to transitional care that includes delayed cord clamping to support hemodynamic transition, minimal handling, and avoidance of procedural pain.<sup>144</sup> Of note, Germany is one of the few developed countries where a decrease in the incidence of BPD has occurred despite increases in survival.<sup>19</sup> The context in which LISA is used, together with the skill level of the clinician administering therapy are likely to have an important influence on outcome. Careful investment in training and guidelines for safe use of LISA are, however, necessary to avoid complications.<sup>145</sup>

## DR Strategies: Use of O<sub>2</sub> During DR Resuscitation

The amount of O<sub>2</sub> required during DR resuscitation and during the first few hours of life has been linked to increased risk for BPD. To date, there remains little evidence linking specific regimens of O<sub>2</sub> titration with reduced risk for BPD. Failure to achieve saturations >85% and/or heart rate >100 bpm by 5 min of life was linked with higher risk of both BPD and death in a recent multi-center RCT.<sup>146</sup> Therefore, clinicians attending deliveries of extreme preterm infants should approach resuscitation with the goal of achieving cardio-pulmonary stability within this timeframe.

## Early Course: First Week of Life – Early NRS Strategies to Reduce BPD

Retrospective study data suggest early attempts at extubation have potential to prevent BPD in the most immature infants.<sup>147,148</sup> However, other reports indicate that the success of these attempts plays a pivotal role in determining outcome.<sup>149</sup> Hence, efforts to maximize success of extubation are important; however, the most optimal NRS strategy for use in preterm infants at risk of BPD has not been conclusively identified. In “Bubble CPAP”, continuous distending pressure is generated by submersion of the expiratory limb of the circuit in varying levels of water.<sup>150</sup> The variability in pressure caused by bubbling in the water-seal chamber has been linked to enhanced alveolar recruitment and surfactant production in animal studies.<sup>150</sup> Results from pooled RCTs have not, however, shown any advantage of bubble CPAP above flow-driver delivered CPAP in terms of reducing pneumothorax or BPD.<sup>151</sup> Nasal intermittent positive pressure ventilation (NIPPV) is a technique where an increased positive inspiratory pressure (PIP) is provided transiently,

typically between 20 and 40 times a minute, over a set of positive end expiratory pressure (PEEP).<sup>116</sup> These cycles are not synchronized with the infant's spontaneous breaths but act to improve recruitment of small airspaces and enhance respiratory drive.<sup>116</sup> Although meta-analysis data suggest that NIPPV may be superior to CPAP in terms of prevention of BPD and/or the composite outcome of BPD and mortality,<sup>51</sup> this advantage may be due to the higher mean airway pressure (MAP) generated by intermittent rises in PIP rather than the support strategy itself. Increased use of NIPPV was not associated with increased survival without moderate-to-severe BPD in a recent multicenter cohort study evaluating the outcomes of 6735 VLBW infants who did not require intubation during their NICU stay.<sup>152</sup> In a recent Cochrane review, early NIPPV (ie within 6 hr after birth) reduced the risk of respiratory failure and the need for intubation and IMV in very preterm infants (GA  $\geq$  28 weeks) with RDS, compared to CPAP. It was also noted that there was a slight decrease in the rate of BPD (RR 0.70, 95% CI 0.52–0.92).<sup>92</sup> However, this may not apply to extremely preterm infants that are most at-risk of BPD.<sup>92</sup> Hence, additional studies are required to evaluate the efficacy of NIPPV in preventing BPD in extreme preterm populations.

Nasal high-frequency ventilation (NHFV) employs rapid oscillatory changes in pressure around a set MAP to enhance recruitment of small airways in preterm infants.<sup>150</sup> This technique, although less widely used than either NIPPV and nasal or NCPAP, has been shown to be a safe option in preterm infants. Results from a recent RCT comparing NHFV to CPAP and NIPPV as a post-extubation support modality, suggested that NHFV may be more effective in reducing the duration of IMV than either CPAP or NIPPV.<sup>153</sup> Subgroup analysis of participants in the treatment group who either were born at  $<29$  weeks GA and/or had evidence of a more severe degree of respiratory failure demonstrated significantly reduced incidence of moderate-severe BPD relative to infants in the CPAP group (range,  $-12\%$  to  $-10\%$ ; NNT 8–9 infants).<sup>154</sup> These results suggest that NHFV is safe and may have some advantages over more frequently used NRS modalities.

Neurally adjusted ventilatory assist (NAVA) utilizes electrical signals from the diaphragm detected by a sensor implanted in a specially designed feeding tube to adjust the intensity of inflations and synchronize these cycles to the patient's own respiratory effort.<sup>150</sup> This strategy can be applied to infants receiving IMV or NRS (non-invasive ventilation or NIV-NAVA). Small crossover trials have shown that NIV-NAVA is associated with reduced work of breathing and improved oxygenation at a lower delivered PIP when compared with other NRS strategies.<sup>155,156</sup> Two small prospective RCTs associated NIV-NAVA with reduced rates of extubation failure when compared to CPAP<sup>157</sup> and NIPPV;<sup>158</sup> however, no long-term benefits in terms of a reduction in BPD have been noted.<sup>157</sup> While NIV-NAVA has been adopted with apparent success in several centers,<sup>83,159</sup> evidence from larger prospective trials is needed in order to demonstrate a clear advantage of NIV-NAVA over other NRS modalities.

### Early Course: First Week of Life – Early Invasive Respiratory Support Modalities

Infants who require initiation of IMV during the first week of life represent a group at high risk for BPD.<sup>27,31</sup> Delivery of excessive tidal volume is known to be highly injurious to the developing lung and opening of atelectatic areas also leads to a potent inflammatory response.<sup>160</sup> Volume targeted conventional mechanical ventilator modalities aim to avoid both excessive airspace distension and collapse through automated adjustment of PIPs to achieve a set tidal volume. Interventions that lead to improvements in lung compliance such as surfactant administration can therefore lead to automated weaning of inspiratory pressure. Meta-analysis data indicate that volume targeted ventilation is associated with reduced risk for BPD when compared to pressure limited ventilation.<sup>93</sup> Retrospective study data suggest that this advantage may also be applicable to infants born between 22 and 25 weeks GA, therefore a volume targeted strategy on a conventional ventilator is a reasonable first-line approach in this population.<sup>161</sup> High-frequency oscillatory ventilation (HFOV) represents an alternative lung protective support strategy in preterm infants at risk for BPD. Movement of a piston is used to generate rapid low volume oscillations that are superimposed over a constant MAP at rates of 300–900 cycles per minute.<sup>162</sup> A Cochrane review comparing HFOV to conventional IMV demonstrated an association between reduced risk of BPD and HFOV use (RR: 0.86, 95% CI: 0.78–0.96) but increased risk for pulmonary air leak (RR: 1.19, 95% CI: 1.05–1.34).<sup>94</sup> BPD outcomes were noted to be highly inconsistent between studies even after subgroup analysis was performed to take into account the use of different lung recruitment strategies.<sup>94</sup> As most of the trials compared HFOV to pressure limited conventional IMV, it is not clear if this strategy offers superior lung protection to volume targeted IMV strategies. A follow-up study of participants in the HIFI trial<sup>163</sup> demonstrated an association between

HFOV and improved small airway function at 11–14 years.<sup>164</sup> No significant differences in lung function parameters were, however, noted when trial subjects were assessed at 18–21 years of age.<sup>165</sup> Despite these caveats, primary use of HFOV has been adopted as a QI bundle intervention in several units that have successfully reduced their BPD rates.<sup>83,84</sup> Earlier initiation of a higher frequency (15–20 Hz), tidal volume limited HFOV strategy as a rescue therapy for preterm infants failing conventional IMV was associated with increased survival free of grades 2/3 BPD (OR 2.93, 95% CI: 1.41–6.05) and reduced hospital admissions and respiratory treatments post discharge (aOR 2.33, 95% CI: 1.10–4.93).<sup>166</sup> Further application of this HFOV-volume guarantee approach may be helpful in limiting early lung damage and preventing BPD; however, efficacy of this modality is yet to be evaluated in a prospective trial.

High-frequency jet ventilation (HFJV) has been frequently considered by several centers as an alternative lung protective strategy for use in high-risk preterm infants.<sup>159</sup> PEEP delivered by a conventional ventilator is used to maintain lung recruitment, while high-velocity pulsations generated by a pinch valve are delivered via a second ETT attachment.<sup>162</sup> These pulsations generate turbulence and encourage molecular diffusion to occur in small airspaces. Although there is no evidence from prospective RCTs that primary application of HFJV prevents BPD, centers that use this strategy have reported improved outcomes, particularly in the most immature infants 22–25 weeks GA.<sup>167,168</sup>

A proactive approach to weaning support should be strongly considered as continued IMV dependency on day of life (DOL) 7 has been consistently associated with increased risk for BPD.<sup>28,148,169</sup> Use of NAVA has been associated with more rapid weaning of the ventilator when compared to the use of pressure limited strategies,<sup>170</sup> suggesting this could be a helpful transitional strategy. Readiness for extubation should be considered carefully in the most immature infants, given the association with early failure and multiple adverse outcomes.<sup>149</sup>

### Early Course: First Week of Life – Caffeine

Caffeine is a methylxanthine medication that has been used for over 5 decades with the purpose of preventing central apnea in preterm infants. Data from a multicenter RCT demonstrated an association between early caffeine use and reduced risk for BPD (OR: 0.63, 95% CI: 0.52–0.76;  $p < 0.001$ )<sup>100</sup> with follow-up studies also demonstrating positive effects on neurodevelopmental outcome.<sup>102,171</sup> The protective effects of caffeine appear to be most apparent in infants treated within the first 3 days of life.<sup>101,172–175</sup> Early initiation of caffeine is, to date, the only BPD preventive strategy that has been associated with both improved respiratory and neurodevelopmental outcomes.<sup>171,176,177</sup> Long-term benefits include increased survival without disability at 18–21 months of age<sup>171</sup> and reduced incidence of developmental coordination disorder along with improved lung function at 11 years of age.<sup>177,178</sup>

Caffeine use has been associated with increased likelihood of successful extubation<sup>179</sup> and reduced duration of IMV.<sup>101,173</sup> These observations are likely due to enhancement of respiratory drive and diaphragmatic contractility.<sup>180</sup> Early caffeine use is also associated with a reduction in medical management of the patent ductus arteriosus (PDA)<sup>100,172,173</sup> as well as diuretic, anti-inflammatory,<sup>181,182</sup> pro-angiogenic<sup>183,184</sup> and antioxidant<sup>184–186</sup> effects. Caffeine citrate is typically initiated with a loading dose of 20 mg/kg with maintenance therapy, then started 24 hr later at 5–10 mg/kg/day.<sup>187</sup> For infants either weaning on IMV or receiving NRS, dose is usually titrated according to the frequency and severity of apneic events. Such a titration does not usually occur in the most immature, critically ill infants who require higher levels of IMV support. Several studies indicate that increased loading (>20 mg/kg) and/or maintenance doses (>5 mg/kg/day) may be more beneficial in preventing BPD.<sup>188</sup> Some studies have reported increased rates of tachycardia with higher caffeine doses,<sup>189,190</sup> with other side-effects including feeding intolerance, hyponatremia, hypertension and hyperglycemia.<sup>191</sup> In some centers, a maintenance dose of 8–10 mg/kg/day is used with weekly weight adjustment of maintenance dose in the range of 8–20 mg/kg/day to prevent extubation failure.<sup>192</sup> Further work evaluating the pharmacodynamics of caffeine along with outcomes in different populations is needed to optimize the preventive properties of this treatment.

### Early Course: First Week of Life – Vitamin A

A RCT conducted in ELBW infants demonstrated an association between early vitamin A administration and reduced risk for the composite outcome of death prior to 36 weeks PMA and BPD (55% versus 62%, RR: 0.89, 95% CI: 0.80–0.990, NNT 14–15).<sup>105</sup> Despite the significant effects noted by this trial, differences in the perceived benefits of vitamin A by



clinicians have led to inconsistent uptake of this approach in clinical practice.<sup>193</sup> Pain from repeated intramuscular injections together with the significant financial cost of vitamin A may also contribute to this finding. The failure of subsequent studies to demonstrate long-term pulmonary benefits from parenteral vitamin A supplementation,<sup>106</sup> coupled with the observation that BPD rates remained stable during a national vitamin A shortage,<sup>194</sup> adds weight to the argument that this is a less efficacious strategy to prevent BPD. Even a small reduction in the risk of BPD in a high-risk population may, however, offset a substantial part of the cost of this therapy. A more recent meta-analysis not only showed an association between vitamin A and reduced dependency on supplemental O<sub>2</sub> at 36 weeks PMA (pooled risk ratio: 0.88, 95% CI: 0.77–0.99; 4 trials, 841 infants, moderate certainty of evidence) but also suggested that vitamin A use is linked to reduced length of hospital stay (mean difference, –49.9; 95% CI: –88.78 to –11.02; 1 trial, 20 infants, low certainty of evidence).<sup>195</sup> This may be another area where this treatment may prove cost-effective. Although vitamin A should be strongly considered as part of a bundle for BPD prevention in ELBW infants, this strategy is unlikely to be pivotal in reducing adverse respiratory outcomes.

### Early Course: First Week of Life – Low Dose Hydrocortisone

Hydrocortisone initiated at low doses to counteract relative adrenal insufficiency during the first week of life is associated with a reduction in the composite outcome of mortality and BPD (RR: 0.90, 95% CI 0.82–0.99).<sup>107</sup> Low dose hydrocortisone is not, however, associated with a reduction in BPD (RR: 0.92, 95% CI: 0.81–1.06).<sup>107</sup> A single patient meta-analysis indicated that female sex,  $\geq 26$  weeks GA and exposure to chorioamnionitis were factors linked to increased odds of BPD-free survival following receipt of hydrocortisone.<sup>196</sup> Risks associated with early low-dose hydrocortisone therapy include gastrointestinal perforation, which is more likely with concomitant use of indomethacin and early onset sepsis, which was noted more frequently in infants  $< 26$  weeks GA.<sup>197</sup> A cortisol nomogram developed using data compiled from a large RCT of early hydrocortisone therapy<sup>197</sup> suggested that infants with high baseline cortisol levels exposed to hydrocortisone were at increased risk for spontaneous intestinal perforation and severe IVH compared to those with comparable results who received placebo.<sup>198</sup> These findings suggest the presence of a “Goldilocks phenomenon” where either inadequate<sup>199</sup> or excessive<sup>198</sup> mineralocorticoid stimulation is associated with adverse effects. Until there is improved delineation of the patients most likely to benefit from treatment, early hydrocortisone therapy should be approached with caution.

### Early Course: First Week of Life – Targeted Medical Management of the PDA

Although there is considerable evidence to suggest that prolonged patency of the ductus arteriosus contributes to adverse respiratory outcomes in preterm infants,<sup>200–203</sup> recent RCTs and QI studies have not demonstrated that use of cyclooxygenase inhibitors to induce earlier closure of a hemodynamically significant PDA (hsPDA) reduces BPD.<sup>204–206</sup> Failure of medications to reliably induce ductal closure in preterm infants  $< 26$  weeks GA, combined with significant rates of spontaneous closure and open-label treatment, pose limitations on the accuracy of information obtained from RCTs.<sup>204</sup> Of note, data from a recent QI project that implemented a “Targeted Prophylactic Indomethacin” treatment approach for infants either born  $< 25$  weeks GA or  $\geq 25$  weeks GA and requiring IMV at 72 hr of life did show a significant decrease in the duration of ductal patency when compared with expectant management.<sup>204</sup> Reduction in exposure to a PDA in this study was not, however, associated with decreased incidence of BPD.<sup>204</sup> The impact of a hsPDA does, however, seem to be modulated by the duration of IMV.<sup>207</sup> Infants exposed to IMV for  $< 10$  days were found to have a reduced risk for grade 2–3 BPD regardless of the presence of a hsPDA. Exposure to a hsPDA for  $> 11$  days was, however, associated with almost 2 times the rate of a Grade 2–3 BPD diagnosis in infants who required  $> 10$  days of IMV (PDA exposure  $> 11$  days 79% with Grade 2–3 BPD versus 40% with PDA exposure  $< 11$  days,  $p < 0.01$ ).<sup>207</sup> It is possible that longer exposure to IMV sensitizes the airspaces and pulmonary vasculature to the additional stress of a significant left-to-right shunt. Closure of a PDA should therefore be considered in patients likely to require IMV beyond the first week of life.

Results from centers who have adopted and developed techniques in early hemodynamic screening suggest that proactive identification and management of a PDA may benefit infants  $< 24$  weeks GA who have been underrepresented in RCTs.<sup>208</sup> Ongoing efforts to further define PDA-related risk factors for BPD,<sup>209</sup> to develop alternative therapies to



induce ductal closure<sup>210</sup> and to identify subgroups of infants who may benefit from treatment<sup>211</sup> may, however, have a significant impact in improving respiratory morbidity.

### Early Course: First Week of Life – Judicious Use of Antimicrobial Therapy

A recently published retrospective study that included 196 infants <28 weeks GA suggested that babies with airway cultures or PCR positive for *Ureaplasma spp.* on admission may have over 4 times the risk of developing BPD compared to those without a positive test.<sup>212</sup> These findings are supported by data from previous clinical and pre-clinical studies that link *Ureaplasma spp.* infection to increased risk for BPD.<sup>213,214</sup> RCTs evaluating the strategy of early eradication of *Ureaplasma spp.* with azithromycin have not, however, shown consistent benefit in reducing BPD.<sup>215–217</sup> Although there is some evidence that treatment of infants who test positive for *Ureaplasma spp.* can reduce the risk of BPD,<sup>217</sup> a prophylactic approach could lead to many more infants being exposed to a therapy that could be harmful. Disturbances in the airway microbiome at birth, with increased Gram-negative Gammaproteobacteria relative to Gram positive *Lactobacilli* has been associated with BPD.<sup>218</sup> The combination of dysbiosis and hyperoxia has also been linked to more severe disturbances in lung architecture in animal models.<sup>219,220</sup> Exposure to antibiotics both in the first week of life<sup>221,222</sup> and throughout the NICU stay<sup>119</sup> is associated with BPD, with evidence of a dose–response relationship.<sup>119</sup> Significantly higher odds of moderate-severe BPD were noted in a cohort of infants <32 weeks GA without risk factors for infection who were exposed to antibiotics within the 24 hr of life (OR: 2.30, 95% CI: 1.21–4.38).<sup>108</sup> These results suggest that movement towards a selective approach to early antibiotic treatment may be a more effective BPD preventive strategy. In centers where turnaround time for *Ureaplasma spp.* detection is less than 48 hr, prophylaxis with azithromycin may be reasonable. Treatment could also be considered if there is also high clinical and radiographic suspicion of active infection.<sup>223</sup>

### Early Course: First Week of Life – Fluid Management and Nutritional Strategies

Subgroup analysis of the multicenter Preterm Erythropoietin Neuroprotection Trial (PENUT) revealed that higher peak fluid balance (calculated by percentage change in weight from BW) was associated with increased risk for IMV on DOL 14 and in the combined outcome for BPD and mortality.<sup>109</sup> Every 10% increase in peak fluid balance was associated with 103% increased odds of receipt of IMV on DOL 14 (aOR: 2.03, 95% CI: 1.64–2.51).<sup>109</sup> Current evidence suggests that keeping the baby “dry” (ie BW loss in the range of 6–15% and maintaining serum sodium levels at the lower end of normal) from DOL 1–10 might be helpful in the prevention of BPD.<sup>224</sup> Additional information from prospective trials is required to identify optimal fluid management practices preventing BPD.

Suboptimal nutritional intake in the first 2 weeks of life has been linked to both short-<sup>110,225</sup> and long-term<sup>112</sup> pulmonary outcomes. Standardized feeding protocols that optimize components of parenteral nutrition whilst promoting timely advancements in enteral feeding have been shown to be effective in reducing time to full enteral feeds and improving growth parameters in preterm infants.<sup>226–228</sup> Human milk, particularly colostrum, contains many immunomodulatory protective components that act to promote a more favorable microbiome and help prevent BPD. Results from a prospective cohort study investigating the impact of own mother’s milk (OMM) on neonatal outcomes reported a 9.5% reduction in the odds of developing BPD for every 10% increase in receipt of OMM [aOR 0.905, 95% CI: 0.824–0.995].<sup>229</sup> Systemic racism and socioeconomic hardship have been shown to have a negative impact on provision of OMM.<sup>230</sup> It is imperative that these disparities are considered when planning initiatives to encourage provision of OMM to ensure equitable improvement in outcome.

### Evolving Course: DOL 7 – 36 Weeks PMA

Evidence strongly points towards the perinatal period and first post-natal week as being an exquisitely sensitive time for determination of both short- and long-term pulmonary outcomes. Interventions adopted to reduce BPD beyond this time-period have typically focused on reducing duration of IMV as this represents a major risk factor for respiratory morbidity.<sup>29,231</sup> Results of recent studies that have shown increasing trends in BPD rates, even with similar to reduced duration of IMV and increased usage of NRS,<sup>5,25</sup> indicate that other factors, such as maintenance of an adequate growth trajectory and avoidance of atelectasis may also be important. The use of invasive ventilatory strategies that limit volutrauma while maintaining adequate functional residual capacity (FRC) such as volume targeted ventilation<sup>93</sup> and

HFV<sup>159,168</sup> may be more helpful in avoiding respiratory morbidity infants who are not yet ready to tolerate extubation and/or are <23 weeks GA.<sup>232</sup> Tolerating a mild degree of permissive hypercapnia (PaCO<sub>2</sub> 55–65 mmHg), particularly in infants maintained on NRS should be strongly considered, but not at the expense of maintaining adequate lung recruitment and growth.<sup>33</sup>

Selective treatment of preterm infants dependent on IMV after 7 days of life with low-dose dexamethasone has been shown to be effective in facilitating extubation.<sup>113</sup> This specific benefit of steroid treatment may underly findings from the latest Cochrane review that suggest an association between dexamethasone treatment after 7 days of life and a reduction in O<sub>2</sub> dependency at 36 weeks PMA [RR 0.76, 95% CI: 0.66–0.870].<sup>114</sup> Unlike treatment during the first 7 days of life, exposure to dexamethasone after 7 days was not associated with increased risk of the combined outcome of cerebral palsy and mortality.<sup>114</sup> This may reflect key differences in the characteristics of infants undergoing late treatment, as exposure to dexamethasone reduces the composite risk for death or neuro-disability in patients at high risk of developing BPD.<sup>115,233</sup> Given concerns regarding adverse effects on neurodevelopmental outcomes noted with early use of dexamethasone, treatment is rarely given before 21 days of life and often postponed further. Of concern, increasing trends in the use of post-natal steroids were not associated with reduced incidence of BPD, indicating a need for further study and refinement of treatment strategies.<sup>23</sup> Evidence from a retrospective analysis indicates that infants who received dexamethasone between 21 and 28 days of life were more likely to avoid a diagnosis of severe BPD than those treated after DOL 50.<sup>234</sup> No significant differences in neurodevelopmental outcomes were noted between infants in the earlier and later treatment groups.<sup>234</sup> Receipt of steroids >36 days of life was associated with approximately twice the risk for Grade 2 or 3 BPD when compared to exposure between 8 and 21 days of life [aOR: 2.0, 95% CI: 1.1–3.70] in a retrospective study conducted by centers enrolled in the Children's Hospital Neonatal Consortium (CHNC).<sup>235</sup> Although it seems surprising that almost half of the patients in this cohort received their first dose of systemic corticosteroids in the 8–21-day timeframe, a much higher proportion of infants in this group received hydrocortisone (77.9%) versus dexamethasone (22.1%) when compared with those that received later treatment.<sup>235</sup> Clinicians may be more willing to use hydrocortisone before 21 days of life as unlike dexamethasone, early postnatal hydrocortisone use has not been linked to neurodevelopmental impairment.<sup>107,236,237</sup> No evidence of adverse outcomes has been noted in the follow-up of participants in the SToP BPD Trial, who received later, higher doses of hydrocortisone;<sup>237</sup> however, there is as yet no evidence from RCTs that treatment with hydrocortisone beyond the first week of life is helpful in reducing BPD even for higher risk populations.<sup>238–240</sup> In summary, treatment with systemic steroids with the goal of reducing risk for BPD should be strongly considered in preterm infants who remain IMV dependent at or approaching 21 days of life.

Diuretic therapy is another strategy that is frequently used to improve lung compliance and reduce respiratory support requirements. In a large retrospective analysis, longer duration of furosemide exposure from DOL 7 to 36 weeks PMA was associated with a significantly lower risk of BPD, suggesting a potential benefit.<sup>241</sup> Unfortunately, electrolyte losses caused by loop diuretics also increase the risk for metabolic bone disease, nephrocalcinosis and growth failure.<sup>242</sup> In the absence of RCT data indicating a relationship between diuretic use and reduced risk for BPD, short-term use of these medications should be restricted to infants with clinical or radiographic evidence of pulmonary edema.<sup>33</sup> Long-term use of diuretics should be restricted to patients who have demonstrated objective evidence of improvement. Assessment of pulmonary edema using lung US is a potentially useful strategy to guide selective medication administration and to determine the degree of response.<sup>243</sup>

Initiation of inhaled bronchodilators and inhaled steroids between 7 days to 36 weeks PMA varies widely between different neonatal units. To date, the use of these medications during this time-period has not been either associated with a reduction in BPD or an increase in any specific adverse outcome. For this reason, no firm recommendations on their use can be made.

### Evolving Course: DOL 7 – 36 Weeks PMA – Maintain Growth Trajectory

Strategies that promote growth in preterm infants must involve measures to reduce unnecessary energy expenditure such as adherence to incubator weaning protocols and provision of adequate respiratory support. The practice of maintaining extremely preterm infants on NRS until they reach 32 weeks PMA has been included as a bundle intervention in quality improvement projects that successfully reduced BPD.<sup>83,85</sup> This approach could be explained by data suggesting that

weaning by transition to high flow nasal cannula (HFNC) is associated with increased duration of O<sub>2</sub> exposure and increased length of stay.<sup>244–246</sup> Another assumption behind the practice of routine prolonged CPAP administration is that this may help conserve energy and facilitate pulmonary growth and repair. This is supported by the results of a small RCT (n=44 analyzed) that linked extended CPAP with improvement in FRC measurements.<sup>117</sup> There are, however, legitimate concerns regarding the impact of long-term continuous distending pressure on the developing lung.<sup>247</sup> The utility of routine extension of CPAP until 32 weeks PMA or 1250g versus gradual weaning from CPAP to HFNC will be tested objectively in a clinical trial that is currently recruiting patients (NCT05557139). Information from this study may help further inform NRS practices used beyond 7 days of life.

Feeding protocols that standardize optimization of nutritional intake throughout the NICU stay, with continued daily tracking of caloric intake and weight gain, have not been directly associated with a reduction in BPD but are likely to be of benefit.<sup>248</sup> Continued research to identify specific nutritional strategies to optimize growth is necessary to inform practice and mitigate long-term health outcomes.

### Emerging Treatments

Increasing trends in the incidence of BPD reflect the need for novel therapies to protect the developing lung and promote growth and repair. Current treatments have relatively non-specific effects and often do not show the same degree of benefit in infants <25 weeks GA. Table 4 provides a summary of emerging therapies that are currently being evaluated in RCTs. Parallel research to identify important predictive markers of specific BPD phenotypes is also important for direct interventions towards patients who will demonstrate the most benefit.<sup>7</sup>

### Established BPD: > 36 Weeks PMA – Multidisciplinary Approach

Infants with established BPD, especially those with moderate-to-severe disease, benefit from a multidisciplinary approach. The core team should at a minimum include neonatologists experienced in the care of infants with BPD, a dedicated clinical pharmacist and dietician in addition to support from physical and occupational therapist. The expertise of other pediatric subspecialists is also required to optimize outcomes. Pediatric pulmonologists well-versed in the care of infants with established BPD can help determine the most appropriate long-term ventilatory strategy, evaluate for airway pathology with bronchoscopy and ease the transition from inpatient care to outpatient management. Infants with either concern for or established BPD-PH should be followed closely by a pediatric cardiologist to determine the frequency of surveillance and need for medications and/or cardiac catheterization. Pediatric otolaryngologists play an essential role in the evaluation and management of infants who have airway complications necessitating corrective surgery or a tracheostomy. Involvement of a pediatric general surgeon may also be necessary, since infants may develop oral aversion or have aspirations that require a gastrostomy tube.<sup>262</sup> This interdisciplinary team-based approach that begins during the initial hospitalization and continues post-discharge has been shown to decrease the incidence of moderate-to-severe neurocognitive impairment and decrease the rates of readmission.<sup>263</sup> A US institution that adopted a multidisciplinary approach to infants with BPD-PH was able to achieve resolution of PH in all their patients, with minimal vasodilator therapy (8%) and low mortality (5%).<sup>264</sup> Various institutions have also found that a multidisciplinary approach to the care of infants with ventilator-dependent BPD results in improved survival until discharge.<sup>262,265</sup> Development of a multidisciplinary approach is therefore deemed to be essential in delivering optimal care to infants with BPD who require long-term IMV. Physical, Occupational and Speech therapy should all be instituted, while infants with established BPD are still in the hospital to provide early, age-appropriate interventions that optimize neurodevelopmental outcomes. Physical therapists can provide input regarding tolerance and engagement with age-appropriate activities that help determine the adequacy of respiratory support. Feeding difficulties are common in infants with established BPD and early referral to a speech therapy team should be considered. Some infants with established BPD may have recurrent aspiration further compromising pulmonary status. As aspiration can occur without clinical symptoms; therefore, a swallow study may be necessary to evaluate the safety of oral feedings and to prevent continuing lung injury. After discharge, infants require ongoing neurodevelopmental follow-up to promptly identify and address areas of concern.<sup>262</sup>

**Table 4** A Summary of Emerging Therapies for BPD Currently Being Evaluated in Clinical Trials

Novel Treatment	Current Evidence	Mechanisms of Benefit	Future Directions
High dose vitamin C to pregnant smoking women 500mg/day	RCT n=159 newborns. Increased ratio of time to peak tidal expiratory peak flow and increased compliance/kg in newborns. Decreased wheezing in first year of life. <sup>249</sup> RCT n=222 Increased forced expiratory flows at 3 months of age and at 12 months of age in prenatal high dose vitamin C group. <sup>250</sup>	Reduces effect of nicotine in promoting increased collagen deposition in small airways of fetus. Exposure to vitamin C alters DNA methylation patterns. Hyper-methylation of DIP2C, APOH/PRKCA genes noted in placental DNA specimens from women who received vitamin C was associated with decreased wheezing and improved lung function. <sup>251</sup> Potential reduction in morbidity from small airway disease phenotype of BPD.	RCT with more patients enrolled currently underway. Follow up of lung function tests from infancy to adolescence. Tracking of DNA methylation patterns linked with maternal smoking. (NCT03206710)
N-Acetylcysteine (NAC) to women with chorioamnionitis at risk of preterm delivery	RCT n=67. NAC exposed newborns required less intensive resuscitation at birth. BPD reduced: 3% versus 32% (RR:0.1, 95% CI:0.01–0.73). <sup>252</sup>	NAC acts as a free radical scavenger and inhibitor of histone deacetylase. Has anti-fibrotic and anti-inflammatory properties. Potential to reduce early sensitization of the lung to further inflammatory exposures such as IMV and supplemental O <sub>2</sub> .	Needs evaluation in a larger prospective RCT.
Budesonide mixed with surfactant for RDS	RCT n=265 VLBW infants with RDS. 0.25mg/kg budesonide associated with reduced risk for BPD and mortality (RR 0.58, 95% CI: 0.44–0.77; $p < 0.001$ ), NNT 4.1 (95% CI 2.8–7.8)]. <sup>104</sup>	Reduces cytokine expression in TA aspirates of preterm infants. <sup>104,253</sup> Modulates inflammatory responses induced by prenatal <sup>254</sup> and postnatal <sup>255</sup> inflammatory stimuli and accelerates lung maturity <sup>256</sup> in preterm lambs. Benefits lung parenchyma and small airways.	Existing RCTs underpowered for long term outcomes. Phase 3 RCT currently underway (NCT04545866).
rhIGF-I/rhIGFBP-3 infusion from birth to 29 <sup>+</sup> 6 weeks GA	RCT n=121 EP 23–27+6 wks GA. Associated with reduced BPD (23% vs 44.9%, $p = 0.04$ ). <sup>257</sup>	rhIGF-I/rhIGFBP-3 preserved alveolar development and RV remodeling in rats exposed to two different experimental models of BPD-PH. <sup>258</sup> Potential to benefit parenchymal, interstitial and pulmonary vascular development.	Phase 2b RCT underway. (NCT03253263)
Mesenchymal stem cell (MSC) based therapies	Phase II RCT n=66. Infants 23–28 wks GA on IMV randomized at 5–14 days of life to intra-tracheal administration of umbilical cord blood MSCs. Moderate to severe BPD reduced in 23–24 weeks GA subgroup (53–18%) but not in the 25–28 wks GA subgroup. <sup>259</sup>	Multiple data from animal studies indicate the benefits derived from MSC exposure are mediated by the content of exosomes. <sup>260</sup> Exosomes contain miRs and regulatory proteins that reduce inflammation. Pulmonary vascular and alveolar development is maintained even in the presence of inflammatory and anti-angiogenic insults. <sup>261</sup> Potential to preserve normal alveolar and pulmonary vascular development.	Multiple Phase I and Phase 2 RCT studies underway. (NCT04255147) (NCT03645525) (NCT03631420) (NCT03392467)

**Abbreviations:** RCT, randomized controlled trial; DIP2C, disco interacting protein 2 C; APOH, apolipoprotein; PRKCA, protein kinase C alpha; DNA, deoxyribonucleic acid; NAC, N-acetylcysteine; VLBW, very low birth weight; RDS, respiratory distress syndrome; rhIGF-I, recombinant human insulin growth factor-I; rhIGFBP3, recombinant human insulin binding protein 3; GA, gestational age; wks, weeks; IMV, invasive mechanical ventilation; EP, extremely preterm; BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; RR, relative risk; NNT, number needed to treat; CI, confidence interval; miR, microRNA; MSC, mesenchymal stem cells.

### Established BPD: > 36 Weeks PMA – Respiratory Support

Optimization of respiratory support in the phase of established BPD requires a shift from a preventive-focused approach to a strategy that prioritizes somatic growth and developmental progress. Rapid weaning and avoidance of IMV are no longer the primary aims and may be counterproductive. The optimal approach to delivering respiratory support in this

population has not been extensively studied, and therefore the reliance is on physiologically sound approaches informed by results from high-volume centers.<sup>262,266</sup> Infants with a milder degree of respiratory compromise can be adequately supported with low-flow NC or NRS; however, infants with severe forms of BPD may require IMV for months to years.<sup>267</sup> Weaning from their current level of support should only be initiated once comfortable breathing, growth and tolerance of developmental therapies have been demonstrated.<sup>262,266</sup> Any reduction in settings should be performed in incremental steps, no more frequently than once or twice a week.<sup>262,266</sup>

Chronic exposure to supplemental oxygen and positive pressure during the evolving phase of the disease transforms the properties of the lungs of an infant with severe BPD to the extent that IMV strategies that were previously successful are unlikely to be effective.<sup>268</sup> Although specific respiratory phenotypes vary between patients, common pathologic findings in infants with grade 3 BPD include parenchymal edema, inflammation of the small airways, and alveolar oversimplification.<sup>269,270</sup> These factors combine to create the heterogeneous pattern of a multicompartiment lung. The fast compartment of the lung consists of areas that have relatively normal alveolar dead space, airway resistance, and emptying times. In contrast, the slow compartment of the lung is characterized by larger alveolar dead space, increased airway resistance, and longer emptying times.<sup>271</sup> In most infants with severe BPD, the slow compartment predominates; therefore, tailoring strategies to the properties of this part of the lung is ideal.<sup>266,268</sup> Moreover, infants may suffer from additional comorbidities, such as airway disease or PH, that need to be addressed when selecting the appropriate IMV strategy.<sup>271</sup>

Most experts who treat a larger number of infants with grade 3 BPD agree that synchronized IMV (SIMV), whether volume or pressure controlled, is the preferred mode of delivery of IMV for a large part of this severe BPD population.<sup>266</sup> HFOV or HFJV do not allow for sufficient expiration and ultimately can lead to more air trapping and impaired ventilation. Most often, infants with established BPD need large target volumes with long inspiratory times and a low rate. Larger targeted volumes (8–15 mL/kg)<sup>272</sup> delivered with a long inspiratory time (0.5–1 sec)<sup>266</sup> should help overcome the increased alveolar dead space and airway resistance in the slow compartment. Likewise, the low respiratory rate (12–20 bpm) allows for the increased emptying time present in these slow compartments; an I:E ratio of 1:5 is preferable.<sup>272</sup> The amount of PEEP (7–12 cmH<sub>2</sub>O) required will also vary based on disease phenotype. If an infant appears to have a significant component of airway malacia, higher PEEPs are often necessary.<sup>266,268</sup> This may seem counterintuitive, but the presence of hyperinflation may be evidence that the current level of PEEP is insufficient to keep the airway open during expiration, leading to increased air trapping.<sup>266</sup>

No large-scale or long-term RCTs have been aimed at determining the most effective NRS strategies for established BPD. A small study looking at 20 infants with evolving and established BPD found no difference in the work of breathing infants when comparing CPAP and HFNC,<sup>273</sup> however, long-term use of these modalities was not assessed. Successful use of both invasive and NIV-NAVA, defined as achievement of respiratory stability at a lower level of respiratory support, has been reported in several centers caring for high volumes of infants with severe BPD.<sup>274</sup> This approach has not, however, been evaluated in prospective clinical trials.

### Established BPD: > 36 Weeks PMA – Approach to Tracheostomy

Severe BPD has been noted to be the most frequent indication for tracheostomy in infants, accounting for almost 50% of cases.<sup>267,275</sup> There is no unifying guideline as to when and in whom tracheostomy is indicated. A retrospective cohort study from 16 centers of the NICHD NRN found that 83% of patients with tracheostomies experienced the composite outcome of death or neurodevelopmental impairment compared with 40% of patients without a tracheostomy [aOR 3.3, 95% CI: 2.4–4.6].<sup>276</sup> In a retrospective study, a tracheostomy was performed on average on DOL 118 (95% CI: 107–128).<sup>277</sup> Infants who had a tracheostomy before, rather than after, 120 days of life had a lower risk of death or neurodevelopmental impairment (aOR 0.5, 95% CI: 0.3–0.9), suggesting that timing has an important influence on outcome.<sup>276</sup> A survey of providers in the CHNC revealed that the most common factors prompting consideration of tracheostomy were as follows: airway malacia (13%), need for higher PEEP (8%), endotracheal positive pressure (11%); PH (16%); multiple courses of systemic corticosteroids (11%); failure to thrive on non-invasive support (11%); and poor growth and feeding (10%).<sup>275</sup> Some of the baseline clinical parameters that would prompt providers to begin considering tracheostomy in patients included PCO<sub>2</sub> ≥76–85 mmHg, FiO<sub>2</sub> ≥0.6, PEEP ≥9–11 cmH<sub>2</sub>O, respiratory rate ≥61–70 bpm, PMA ≥ 44 weeks, and weight <10th



percentile at 44 weeks PMA.<sup>275</sup> These findings demonstrate factors that are important to clinicians; however, the decision as to whether a tracheostomy is the best option requires consideration and input from various members of the team and the patient's family. Factors that should be deliberated include the uncertain duration of the need for IMV, risks associated with surgery, the need to commit the infant to multiple serial procedures, together with the risk of accidental decannulation or obstruction at home.<sup>267,278</sup>

### Established BPD: > 36 Weeks PMA – Long-Term O<sub>2</sub> Therapy

Long-term home O<sub>2</sub> therapy in infants with established BPD has not been sufficiently studied. Both the American Thoracic Society (ATS)<sup>279</sup> and the European Respiratory Society (ERS)<sup>121</sup> have recommended the use of home O<sub>2</sub> in infants with BPD complicated by chronic hypoxemia. This guideline is based on very low-quality evidence from a few small studies that showed better growth, improved mean pulmonary artery pressures and improved sleep quality and duration for hypoxemic infants who receive supplemental O<sub>2</sub>. The use of low flow supplemental O<sub>2</sub> also allows patients to be discharged home. The ERS suggests a target goal of 90% SpO<sub>2</sub> or higher extrapolating from the BOOST II trial that showed an increased mortality in infants born <28 weeks who had a target of 85–89% SpO<sub>2</sub>.<sup>280</sup> While the ATS suggests SpO<sub>2</sub> goal of ≥92%, the lower threshold of 90% of the ERS limits unnecessarily prolonging hospitalization and the added associated risks.<sup>121</sup>

### Established BPD: > 36 Weeks PMA – Use of Medications

The paucity of evidence regarding optimal pharmacological management of established BPD has led to marked variations in prescribing patterns between centers.<sup>281,282</sup> Patients with different clinical phenotypes of BPD vary considerably in their response to specific therapies,<sup>57</sup> therefore an individualized approach to care is strongly recommended.<sup>33</sup> Infants with extensive small airway involvement may respond favorably to the anti-inflammatory effects of inhaled corticosteroids. However, two RCTs evaluating the effects of inhaled fluticasone failed to demonstrate objective evidence of long-term benefit.<sup>283</sup> Although obstructive patterns of lung disease are common in patients with BPD,<sup>52</sup> response to bronchodilator therapy is variable.<sup>284–286</sup> Unlike in asthma, where reversible airway narrowing arises due to eosinophilic inflammation, the obstructive lung disease seen in BPD is more closely related to fixed structural abnormalities that limit small airway caliber.<sup>52</sup> Trials of inhaled medications should therefore be considered in infants with established BPD; however, continuing therapy in the absence of a clinical response is not recommended.<sup>287</sup>

Use of both loop and thiazide diuretics has been shown to result in transient improvements in lung compliance; however, these changes have not been linked to weaning from respiratory support.<sup>118,288</sup> Adverse reactions to chronic diuretic use include electrolyte imbalances, calciuria, nephrocalcinosis, ototoxicity, and delayed closure of PDA.<sup>283</sup> As in the evolving phase of BPD, use of diuretics should be targeted at patients who demonstrate a response to therapy and weaned as tolerated following discharge.<sup>287</sup>

The use of systemic corticosteroids in the management of infants with established BPD has not been well studied. Short courses of prednisolone have been effectively used to wean off supplemental oxygen prior to discharge<sup>122</sup> and short courses of corticosteroids can also be used during BPD exacerbations due to viral illnesses to decrease airway inflammation and reduce work of breathing.<sup>287</sup> A pulse dose of methylprednisolone has also been shown to improve pulmonary severity score, in the 5 months following administration,<sup>289</sup> with benefits most marked in infants with grades 2–3 BPD.<sup>289</sup> Adverse side effects of chronic systemic corticosteroid use include significant hyperglycemia, hypertension, immune suppression, intestinal perforation, cardiomyopathy, growth retardation, and adverse neurodevelopmental outcome. There is also evidence from animal studies that alveolar development is impaired following chronic glucocorticoid exposure.<sup>290</sup> For these reasons, prolonged use of systemic corticosteroids is not recommended.

### Established BPD: > 36 Weeks PMA – Surveillance for BPD-PH

It is estimated that 25–37% of infants with BPD will develop BPD-PH, a diagnosis that is associated with increased risk for mortality<sup>291–293</sup> and tracheostomy placement.<sup>58,294</sup> A proactive approach to the detection of BPD-PH is therefore of critical importance. Different screening algorithms have been described.<sup>120,295</sup> The European Pediatric Pulmonary Vascular Disease Network (EPPVDN) recommends screening all infants with established BPD with transthoracic echocardiography at 36 weeks PMA and before discharge.<sup>120</sup> Screening should also be considered in any infant with chronic O<sub>2</sub> dependency and in those who demonstrate suboptimal growth or lack of expected clinical improvement.<sup>120</sup>

Confirmation of BPD-PH should lead to consultation with cardiology and consideration for pulmonary vasodilator therapy with or without cardiac catheterization.<sup>120</sup> Screening for PH should continue post-discharge. The Pediatric PH Network recommends evaluation with an echocardiogram every 4–6 months if the patient is requiring supplemental O<sub>2</sub> or develops increasing respiratory support needs.<sup>296</sup>

### Established BPD: > 36 Weeks PMA – Nutritional Strategies

A specific nutritional approach to an infant with established BPD should be informed by disease severity, respiratory support requirement, age and level of activity.<sup>124</sup> Enteral feeding should be maintained as long as possible as this provides the most optimal source of energy, vitamins and minerals and contributes to maintenance of gut integrity. Continuing enteral feeds during acute deteriorations in status and in patients requiring sedation and paralysis has been recommended by experts who manage high volume of patients with severe BPD.<sup>124</sup> This team also advocate for an approach that is sensitive to the various clinical phases of severe BPD that they describe as the acute, transitional, and pro-growth stages.<sup>124</sup> Table 5 provides a brief description of each phase with specific expert recommendations.<sup>124</sup>

Ongoing monitoring of anthropometric data should occur throughout both inpatient and outpatient phases of care along with screening for metabolic bone disease<sup>297</sup> and anemia of prematurity. Electrolyte abnormalities are common in patients receiving diuretic therapy and should be identified and treated accordingly. Recommended goals for daily weight gain in preterm infants are 15–20 g/day with weekly linear growth of 0.9–1.1 cm per week and should be considered when tracking the progress of infants with established BPD. Maintenance of adequate growth should be a priority for infants with established BPD and multi-center trials on nutritional practices should be strongly considered.

### Established BPD: > 36 Weeks PMA – Lung Transplantation

Between the years 2000–2020, a total of 37 patients with BPD as a diagnosis underwent a lung transplant.<sup>298</sup> Overall, these patients had a younger median age at the time of transplant when compared to other lung transplant recipients, 22 years (interquartile range (IQR) 7–34 years) versus 58 years (IQR 48–64 years), respectively. When comparing the BPD lung transplant recipients born in the pre-surfactant era (SE) to the post-SE, the post-SE patients were significantly younger, 7.5 years (IQR 1–13.35 years) versus 34 years (IQR 29–37 years). Post-SE patients were also more likely to be

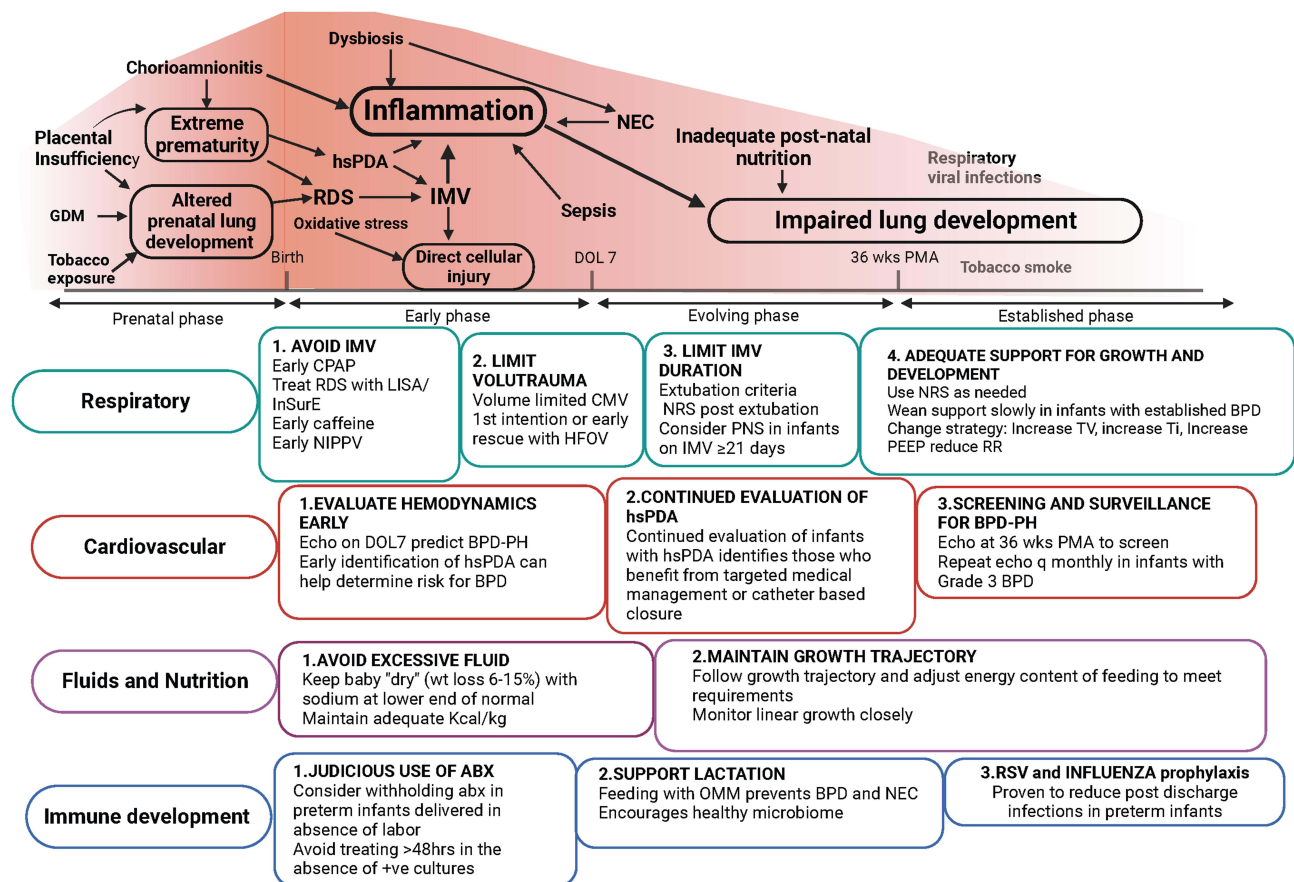
**Table 5** Summary of the Approach Used for Patients with Established BPD at Nationwide Children's Hospital, Columbus, Ohio, USA

BPD Phase	Clinical Characteristics	Relative Cardiopulmonary Support Requirements	Nutritional Recommendations
I: Acute	Frequent desaturations Increased work of breathing Irritability Unable to tolerate developmental therapy Variable weight gain Poor linear growth	Increased FiO <sub>2</sub> Increased positive pressure Systemic corticosteroids Pulmonary vasodilators in setting of BPH-PH Sedation Pharmacological paralysis	Fluids: 120–150mL/kg/day Energy: 120–150kcal/kg/day Protein: 4g/kg/day 24–26kcal/oz FBM or formula 24–30kcal/oz Consider MCT oil or liquid protein
II: Transitional	Improved work of breathing Brief time periods in quiet alert state Tolerates low-level activities Improving weight trend Slow linear growth	FiO <sub>2</sub> typically ≤0.6 Tolerates slow weaning of respiratory support and de-escalation of medications	Fluids: 120–140mL/kg/day Energy: 110–120kcal/kg/day Protein: 2.5–4g/kg/day
III: Pro-growth	Comfortable work of breathing Tolerates therapies well Developmental progress Weight-for-length trend improves Consistent linear growth	Respiratory requirements stable Corticosteroid and sedation requirements minimal to none PH well controlled	Fluids: 110–130mL/kg/day Energy: 70–120kcal/kg/day Protein: 2.5–3g/kg/day

**Notes:** Data from Miller AN, Curtiss J, Taylor SN, Backes CH, Kielt MJ. A review and guide to nutritional care of the infant with established bronchopulmonary dysplasia. *J Perinatol.* 2023;43(3):402–410. doi:10.1038/s41372-022-01578-0.<sup>124</sup>

**Abbreviations:** BPD, bronchopulmonary dysplasia; FiO<sub>2</sub>, fraction of inspired oxygen; BPD-PH, BPD associated pulmonary hypertension; mL, milliliters; Kg, kilogram; Kcal, kilocalories; FBM, fortified breast milk; MCT, medium chain triglycerides; g, grams.





**Figure 1** Multiple exposures during the prenatal and postnatal periods contribute to the development of BPD. Stimuli encountered in the prenatal and early postnatal period appear to have the strongest influence in determining long-term pulmonary outcome. These exposures and their potential for generating inflammatory responses and altered lung development are outlined in the top part of the figure. The lower boxes summarize key strategies needed to prevent and manage early, evolving and established BPD in a system-based manner.

**Abbreviations:** BPD, bronchopulmonary dysplasia; wks, weeks; GA, gestational age; GDM, gestational diabetes mellitus; RDS, respiratory distress syndrome; hsPDA, hemodynamically significant patent ductus arteriosus; IMV, invasive mechanical ventilation; DOL, day of life; wks, weeks; PMA, postmenstrual age; LISA, less invasive surfactant administration; InSurE, Intubate; surfactant; extubate; NRS, non-invasive respiratory support; CPAP, continuous positive airways pressure; NIPPV, nasal intermittent positive pressure ventilation; HFOV, high frequency oscillatory ventilation; TV, tidal volume; Ti, inspiratory time; PEEP, positive end expiratory pressure; RR, respiratory rate; PNS, postnatal steroids; Wt, weight; abx, antibiotics; OMM, own mother's milk.

on ventilator support 43.4% versus 0%.<sup>298</sup> There were no statistically significant differences in survival post-lung transplant when comparing the BPD group to the group with other diagnoses nor was there a difference when comparing pre-SE and post-SE BPD patients.<sup>298</sup> While an extreme option, lung transplant could be considered for patients with progressive, life-limiting lung disease secondary to BPD.

## Conclusions

BPD is a complex multifactorial lung injury syndrome that has proven to be extremely challenging to diagnose, prevent and manage. Current strategies used for the prevention and management of BPD, summarized in Figure 1, have shown efficacy in preventing and mitigating the extent of lung injury. The impact of these treatments has not, however, been sufficient to keep pace with improvements in survival. Novel treatments are needed to address the needs of a growing population of peri-viable infants. In the meantime, QI frameworks need to be leveraged for optimal delivery of existing therapeutic strategies. Continued investigation, identification and action are required to urgently address racial and socio-economic disparities in respiratory outcomes. Finally, collaboration between basic scientists, clinical investigators, and clinicians in a range of subspecialties is necessary to close gaps in knowledge and optimize outcomes for patients at all stages of life.

## Disclosure

The authors report no conflicts of interest in this work.

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