Diagnosis and management of bronchopulmonary dysplasia

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease in infants and is associated with increased mortality, respiratory morbidity, neurodevelopmental impairment, and increased healthcare costs. In parallel with advances made in the field of neonatal intensive care, the phenotype of BPD has evolved from a fibrocystic disease affecting late preterm infants to one of impaired parenchymal development and dysregulated vascular growth predominantly affecting infants born before 29 weeks' gestational age. BPD has been shown to have significant lifelong consequences. Adults with BPD have been found to have abnormal lung function tests, reduced exercise tolerance, and may be at increased risk for developing chronic obstructive pulmonary disease. Evidence shows that BPD occurs secondary to genetic-environmental interactions in an immature lung. In this review, we evaluate the various clinical definitions, imaging modalities, and biomarker data that are helpful in making an early diagnosis of BPD. In addition, we evaluate recent evidence about the prevention and treatment of BPD. We discuss the invasive and non-invasive ventilation strategies and pharmacological agents used in the early, evolving, and established phases of BPD.

Introduction

Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity,[1] affecting up to 45% of infants born at <29 weeks' gestational age.[2] Although advances in care have led to improved survival, BPD incidence has remained static or even increased.[3] BPD is not merely a lung disease, but a systemic condition with lifelong implications for adult health and quality of life.[4 5] The healthcare costs associated with BPD are substantial[6] and extend beyond the initial hospitalization.[7] BPD lacks an objective definition for accurate prediction of future mortality and morbidity.[8] The development of an optimal definition is challenging, given the complex multifactorial nature and variable clinical presentation of the disease.[9] Frequently used definitions of BPD from the National Institutes of Health (2001[10] and 2018[11]) rely on the subjective need for various respiratory support modalities to identify and categorize severity of disease. This approach has important limitations. In this review, we appraise alternative models that could improve diagnostic accuracy and identify specific patterns of disease. Emerging approaches to diagnosis—proteomic, metabolomic, and microbiomic—are included in the review. We focus on existing interventions to prevent or mitigate the severity of BPD, and evaluate the evidence and recommendations made based on the US Preventive Services Task Force grading (supplementary files: table 1).[12]

Sources and selection criteria

We searched the PubMed, Embase, and Cochrane databases for the dates 1967 to September 2020 for articles published in peer reviewed journals within the past two decades. Search terms included "bronchopulmonary dysplasia", "chronic lung disease of prematurity", "definition of bronchopulmonary dysplasia", "bronchopulmonary dysplasia and pulmonary hypertension", "bronchopulmonary dysplasia biomarkers", "bronchopulmonary dysplasia and postnatal steroids", "bronchopulmonary dysplasia and oxygen", "less invasive surfactant and bronchopulmonary dysplasia", "bronchopulmonary dysplasia and mechanical ventilation", "bronchopulmonary dysplasia and imaging", "bronchopulmonary dysplasia and lung function testing", "bronchopulmonary dysplasia and diuretics", "bronchopulmonary dysplasia and bronchodilators", and "bronchopulmonary dysplasia guidelines". We chose to focus on the results of randomized controlled trials (RCTs) and systematic reviews with an emphasis on results published after 2010. We included results of well designed retrospective studies, and prioritized

those that included at least 150 participants born before 29 weeks' gestational age. Animal studies were included to ascertain biological plausibility. We included consensus statements and clinical guidelines published in peer reviewed journals. We also searched the website www.clinicaltrials.gov using the terms "bronchopulmonary dysplasia" and "chronic lung disease of prematurity" to identify potential therapies currently undergoing investigation. We excluded articles not published in English and those that were not peer reviewed.

Why is an accurate diagnosis of BPD important?

The BPD phenotype has evolved, so that the emphysematous, fibrotic disease first described in 1967[13] is less commonly seen in contemporary clinical practice. A "new" pattern, characterized by alveolar simplification and pulmonary vascular dysregulation with functional impairment,[14] has become the predominant BPD phenotype encountered in neonatal intensive care units (NICUs). Rapid progress has been made in understanding the inciting, modulating, and mitigating factors that lead either to long term respiratory morbidity owing to lung repair, or healing and recovery (fig 1). Exposure to inflammation,[15] placental vascular disease,[16] hormonal deficiencies,[17] genetics,[18] and epigenetics[19] influence the relative vulnerability or resilience of the respiratory system prior to preterm birth. Events occurring in the postnatal period such as late onset infection with bacterial or viral agents[20] can also have an adverse effect on short and long term outcomes. Variations in clinical care, including use of supplemental oxygen,[21] positive pressure,[22] medications,[23] and nutrients,[24] provoke responses modulated by genetic and epigenetic influences. Infants with BPD show substantial heterogeneity in clinical presentation and long term outcomes.[25-27] The manner and precision with which BPD is defined have far-reaching consequences for translational and clinical research.[8] For the clinician, an accurate diagnosis of BPD helps inform the use of specific respiratory support strategies and medications.

Evaluation of the NIH 2018 criteria

Early definitions of BPD relied on measures consistent with impairment of gas exchange in addition to radiographic abnormalities and clinical symptoms persisting for >28 days[28] (fig 2). In 1988, a single center retrospective study showed that continued use of supplemental oxygen at 36 weeks' post menstrual age (PMA) was more closely associated with abnormal pulmonary findings (as per the criteria listed in the study) upon long term follow-up in infants of <32 weeks' gestational age than earlier diagnostic models.[29] This observation was incorporated in the Shennan 1988 definition, which is frequently used in clinical research.[30] The NIH 2001 definition[10] diagnoses BPD if supplemental oxygen has been required for at least 28 days. The severity of disease is graded "mild", "moderate", or "severe" at 36 weeks' PMA, or discharge for infants born at <32 weeks, or day of life (DOL) 56 for infants >32 weeks' gestational age, according to the need for respiratory support.[10]

Studies that compare the NIH 2001 criteria[10] with the 28 days[28] and the Shennan 1988 definitions[29] are summarized in table 1.[31-33] The incidence of

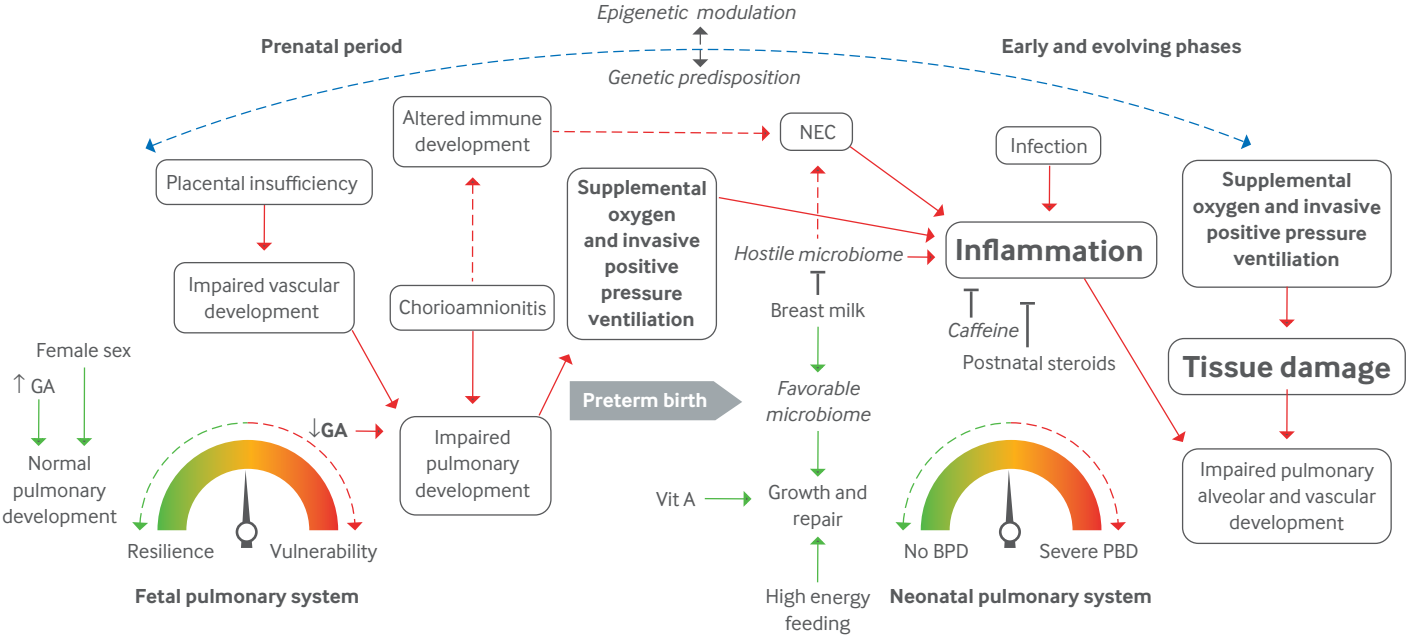

Fig 1 | A summary of the inciting, protective, and modulating factors that influence the development of BPD. Prenatal factors that lead to impaired lung development have an impact on the postnatal course, increasing the likelihood of exposure to invasive mechanical ventilation and supraphysiological oxygen. Exposure to inflammation in utero also alters immune development and may predispose to a dysregulated prolonged response to relatively minor stimuli. Responses to injurious and protective influences are modulated by genetic and epigenetic mechanisms. BPD=bronchopulmonary dysplasia; GA=gestational age, NEC=necrotizing enterocolitis; Vit A=vitamin A

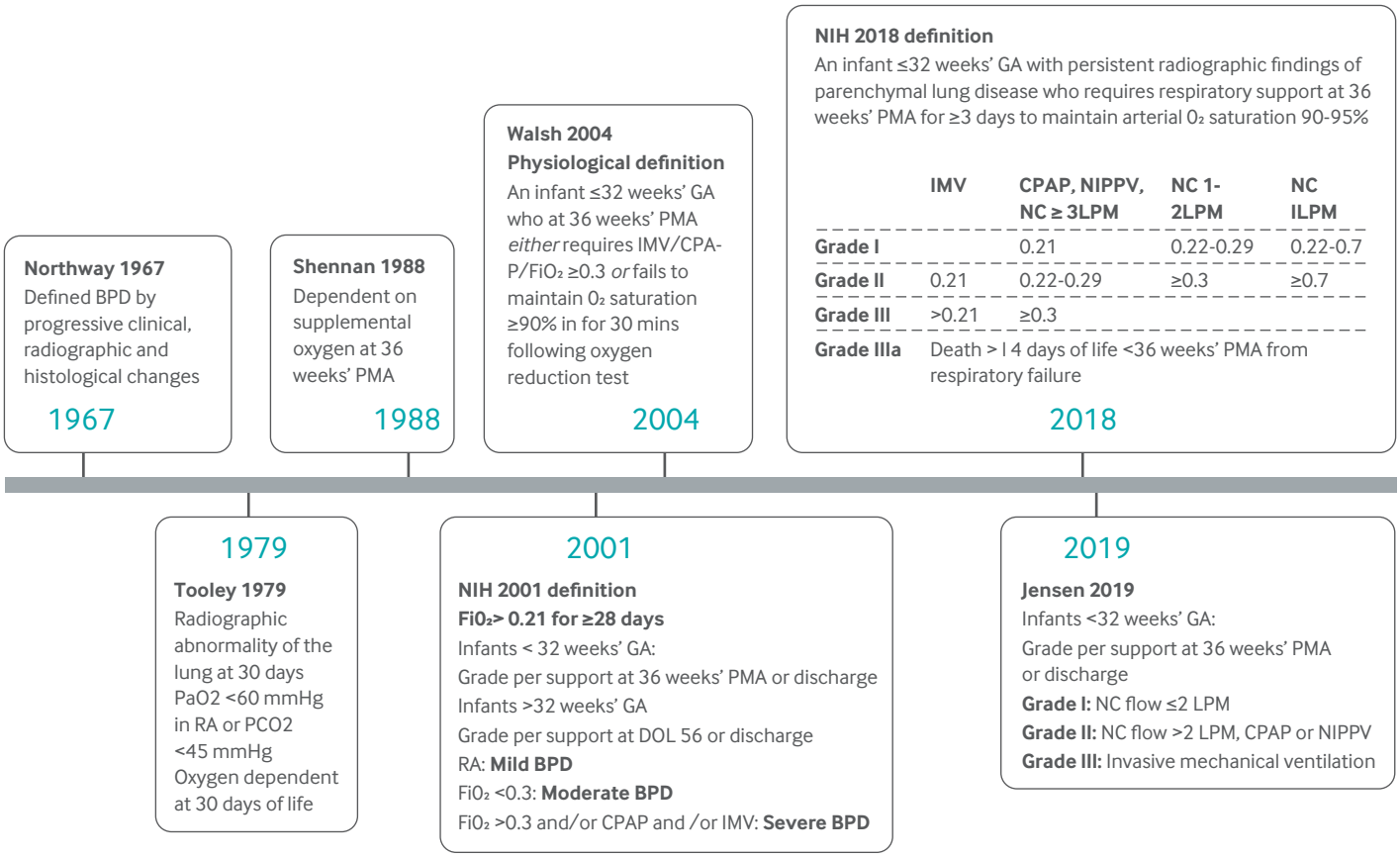

Fig 2 | Evolution in complexity of proposed definitions of BPD over time. BPD=bronchopulmonary dysplasia; GA=gestational age; IMV=invasive mechanical ventilation; CPAP=continuous positive airway pressure; FiO_2=fraction of inspired oxygen; NIPPV=nasal intermittent positive pressure ventilation; NC=nasal cannula; LPM=liters per minute; PMA=post menstrual age; RA=room air

mortality, growth failure, and neurodevelopmental impairment (NDI) was increased with statistical significance in infants with severe BPD.[31] Other studies have linked severe BPD to NDI, indicating meaningful prognostic information.[34] The 28 days definition increases the sensitivity, but decreases

Table 1 | Studies comparing different BPD definitions in the post-surfactant era

Reference	Study population	Definition used	Incidence	Relative predictive value for use of pulmonary medications and hospital readmission
31	4866 infants ‹32 weeks' GA, ‹1000 g birth weight Born 1995-1999 Follow-up information for 3848 infants available	Oxygen for 28 days[28]	77%	Sens ++++ Spec +
		Shennan[29]	44%	Sens +++ Spec +++
		NIH 2001[10]	77%	Sens ++++ Spec +
		Mild	31%	Risk insignificant
		Moderate	30%	Risk 1.5-2× that of no BPD
		Severe	16%	Risk at least 2× that of no BPD
32	765 infants 23+0 to 28+6 weeks' GA prospectively enrolled in a multicenter research cohort	Shennan *% unclassifiable*	41% *2.9%*	NA
		Physiological *% unclassifiable*	32% *16%*	
		NIH 2001 *% unclassifiable*	58.6% *2.1%*	
		Mild	19.5%	
		Moderate	11.6%	
		Severe	27.5%	
33	247 infants ≤ 30 weeks admitted to a level IV neonatal intensive care unit 2013-2015	Shennan	39%	NA
		NIH 2001	71%	
		Mild	17%	
		Moderate	44%	
		Severe	49%	

BPD=bronchopulmonary dysplasia; GA=gestational age; Sens=sensitivity; Spec=specificity; NA=not applicable; ++++ indicates value ›80%, +++ value 50-60%, + value less than 25%.

specificity, of adverse outcome prediction in mild BPD, compared with Shennan 1988.[30 31]

Comparing NIH 2001, physiological, and Shennan 1988 definitions showed considerable barriers to their use in current clinical practice.[32] Around 2-16% of infants were not classified because of variations in the use of nasal cannula and failure to perform an oxygen reduction test (ORT) (table 1); thus, this makes a strong argument for a new consensus definition to encompass contemporary respiratory strategies.

A workshop sponsored by the National Institute for Child Health and Human Development (NICHD) led to a revised definition (NIH 2018)[11] (fig 2). High flow nasal cannula (HFNC) and severely affected infants who die from respiratory causes prior to 36 weeks' PMA were included in the definition. Supplemental oxygen need for 28 days was removed as it lacks precision in predicting long term outcomes,[31] and is often misinterpreted as need for oxygen on DOL 28.[30] Instead, infants with persistent radiographical evidence of parenchymal lung disease who remained on respiratory support were classified according to the therapy required to maintain oxygen saturation (SpO_2) at 90-95% at 36 weeks' PMA.[11] One major change proposed was that infants would need to be on the stated respiratory support for a minimum of three consecutive days with the intent of minimizing up- or down-classification based on acute clinical events.

Use of the NIH 2018 criteria identified a greater proportion of patients than either the Shennan 1988 or NIH 2001 definitions.[35] Infants who were diagnosed BPD of any grade using the NIH 2018 criteria were more likely to develop other comorbidities than those without BPD (P<0.001) suggesting a high degree of sensitivity in predicting short term outcomes. The ability of the NIH 2018 definition of BPD to predict long term outcomes has not been assessed.

Several limitations remain.[36] Firstly, the decision for respiratory support still lies with the clinician. Decisions about the need for respiratory support are often based on subjective assessment of the infant's work of breathing, frequency of apnea/bradycardic events, ability to take adequate oral feeds, or maintenance of an optimal growth trajectory. At 36 weeks' PMA, preterm infants may still have immature respiratory control that manifests as periodic breathing or apneic events. Diuretics[37] and bronchodilators[38] may influence the need for respiratory support, and their use varies markedly between centers[39] and may influence reporting of BPD. The revised definition also fails to differentiate infants with BPD associated pulmonary hypertension (BPD-PH). The European Pediatric Pulmonary Vascular Disease Network (EPPVDN) recommends an evaluation for any infant of <28 weeks' gestational age with severe respiratory compromise at 36 weeks' PMA, and at discharge in those with established BPD.[40] Transthoracic echocardiography (TTE) can identify infants at risk of BPD-PH as early as DOL 7.[41] TTE screening in a clinical BPD definition may provide more accurate prognostic information, given the increased incidence of adverse outcomes associated with BPD-PH.[25 27] Variation in the mean airway pressure generated by different modes of non-invasive support—for example, HFNC versus nasal intermittent positive pressure ventilation (NIPPV)—could lead to significant phenotypic heterogeneity. The degree of positive pressure required could signify large airway disease such as tracheomalacia,[42] underlying parenchymal disease, or immature respiratory control.

Alternative clinical definitions for BPD

One of the main criticisms leveled at NIH 2018 was the use of semi-quantitative categories and arbitrary thresholds to assign disease severity, rather than the creation of a model based on critical outcomes such as death and NDI.[36] In a retrospective study that tested 18 potential definitions against outcome data obtained from the NICHD Neonatal Research Network,[43] the models tested were found to predict late death or serious respiratory morbidity with a c-statistic ranging from 0.741 to 0.785. A model that defined severity by the support mode at 36 weeks' PMA without reference to oxygen requirement was found to correlate most closely with adverse outcomes, predicting death or serious respiratory morbidity in 81% of study infants. This optimal definition (table 2), referred to as Jensen 2019, was also most effective in the prediction of late death or NDI with a c-statistic of 0.747. Consistent with evidence linking chronic mechanical ventilation to cerebral palsy,[44] the population of infants who remain on invasive mechanical ventilation at 36 weeks' PMA is at particularly high risk for adverse outcomes. The ability of Jensen 2019 to separate infants dependent on invasive versus non-invasive ventilation or nasal cannula with a fraction of inspired oxygen (FiO_2) >0.3 would be of benefit when evaluating the impact of novel therapies designed to mitigate the severity of BPD. These criteria also have the benefit of being easy to apply in clinical practice and in research studies because of the omission of the ORT.

Some important limitations include that these criteria were tested on infants born at gestational age <32 weeks, and most were ≤27 weeks. Jensen 2019 may therefore lack sensitivity and specificity in predicting outcomes in infants born at >27 weeks' gestational age. The choice of 36 weeks as a time point for assessment continues to offer potential for infants to be "up-classified" for needing respiratory support to compensate for impaired control of breathing or difficulties coordinating oral feeding. A retrospective study utilizing data from the Canadian Neonatal Network suggested that allowing for assessment at 40 weeks' PMA may improve the predictive value of a BPD diagnosis.[45] The need for oxygen or respiratory support ≥ nasal cannula 1.5 liters/minute at 36 weeks' PMA was found to have the greatest value in predicting serious respiratory

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Table 2 | Comparison between the predictive value of criteria selected to closely replicate the NICHD definition of BPD[10] and alternative parameters as tested by Jensen et al using a population of 2677 infants ≤32 weeks[43]

	Treatment with the following support at 36 weeks PMA or at discharge, whichever comes first						Predictive accuracy of definition (c-statistic)	
	RA: Mild BPD: ≥ 21% FiO_2 for ≥ 28 days No BPD: no 28 day assessment	NC ≤2LPM FiO_2 <0.3	NC ≤2LPM FiO_2 ≥0.3	NC ≥2LPM	nCPAP NIPPV	IMV	Mortality or serious respiratory morbidity	Mortality or moderate to severe NDI
NIH 2001 definition	Mild BPD	Moderate BPD	Severe BPD				0.741	0.727
Jensen et al alternative definition	No BPD	Grade 1 BPD		Grade 2 BPD		Grade 3 BPD	0.785*	0.747*

Shaded boxes represent criteria selected by Jensen et al to closely match the NICHD definition. Nasal cannula flow ≥2 liters/minute (LPM) was used as a surrogate for CPAP or non-invasive pressure ventilation. *P<0.001 in comparison with NIH 2001 definition, PMA=post-menstrual age; RA=room air; NC=nasal cannula; LPM=liters per minute; FiO_2=fractional inspired oxygen concentration; nCPAP=nasal continuous positive airway pressure; NIPPV=nasal intermittent positive pressure ventilation; IMV= invasive mechanical ventilation; NDI=neurodevelopmental impairment defined as a Bayley Scales of Infant and Toddler Development, 3rd edition, cognitive or motor composite score <85, Gross Motor Function Classification System level greater than or equal to 2, bilateral blindness and/or severe hearing impairment that cannot be corrected with amplification.

morbidity (adjusted odds ratio (AOR) 3.4, 95% confidence interval (95% CI) 1.8 to 6.3). Only 2.5% of infants who did not meet criteria for BPD went on to develop serious respiratory morbidity according to the study definition. The need for supplemental oxygen or respiratory support at 36 weeks' PMA was found to have marginally greater accuracy in predicting serious neurosensory impairment than other "traditional" BPD definitions (AOR 1.7, 95% CI 1.2 to 2.4).[45] When the criteria of supplemental oxygen and/or respiratory support with > 1.5 liters/minute by nasal cannula was applied at different gestational ages, improved ability to predict severe respiratory morbidity was noted at 40 weeks' PMA (AOR 6.4, 95% CI 3.4 to 11.0). The optimal time to apply the criteria for prediction of severe neurosensory morbidity was noted to be at 37 weeks' gestational age (area under the curve or AUC=0.743, AOR 1.8, 95% CI 1.3 to 2.6); however, application of the definition at 40 weeks yielded similar results (AUC=0.74, AOR 1.5, 95% CI 1.0 to 2.1). This is perhaps not surprising, as an evaluation performed later in time is more likely to be predictive of a more distant event. An ORT was not routinely performed, limiting accuracy of the data. One of the greatest difficulties in moving the time point of assessment to 40 weeks is that many infants will have already met criteria for discharge. Those who are breathing room air without support at 36 weeks' PMA are unlikely to require oxygen or support at 40 weeks' PMA. However, infants with a relatively modest oxygen requirement who meet all other prerequisites for discharge may be anomalously classified as BPD, if assessment is delayed for several weeks.

In summary, the NIH 2001 definition of BPD is poorly reflective of current respiratory support strategies[32] with the "mild" category of BPD having limited predictive value for long term morbidity.[31] The NIH 2018 definition[11] is more easily applicable to contemporary neonatal care; however, these criteria have yet to be validated with long term outcomes in a large preterm population. The accuracy in predicting long term outcomes could be improved by moving the assessment from 36 to 40 weeks' PMA.[45] However, this could make obtaining information on infants who are discharged earlier on supplemental oxygen problematic. The evidence based Jensen 2019 definition seems the most promising in providing a relatively simple means of predicting outcomes.[43] Further discussions regarding refinements to clinical definitions should be informed by both the Jensen 2019[43] and the 40 weeks' PMA evidence based definitions.[45]

Physiological measurements in the diagnosis of BPD

A physiological definition for BPD using SpO_2 during an ORT was first described in a single center prospective observational study in 2003, and a refined version applied in a larger multicenter prospective observational study.[46] Infants requiring FiO_2 >0.3 or invasive mechanical ventilation or continuous positive airway pressure (CPAP) to maintain SpO_2 at 90-95% at 35-37 weeks' PMA were classified as having BPD. Infants on nasal cannula 1-2 liters/minute who either required FiO_2 <0.3 at rest to maintain SpO_2 90-96% or were maintaining saturations >96% breathing FiO_2 >0.3 were eligible to undergo an ORT. Those who maintained SpO_2 ≥ 90% breathing FiO_2 0.21 for 30 minutes were then classified as "no BPD."[46] Use of the physiological definition was found to result in a significant decrease in the rate of diagnosis (mean reduction 10%; range 0-44%) and reduced variation in incidence of BPD between institutions.[46] One potential limitation of the physiological definition when compared with the NIH 2001 classification is the binary outcome of "BPD" versus "no BPD." A more nuanced method that evaluates SpO_2 during a stepwise reduction of supplemental oxygen in order to derive the degree of right shift of the oxygen saturation curve, ventilation perfusion ratio (Va/Q), and right-left shunt in preterm infants has been evaluated in a prospective observational study.[47] Right shift, and the magnitude of the right-left shunt was found to increase and Va/Q found to decrease in accordance with BPD severity as per the NIH 2001 definition.[47] Although the "shift test" is non-invasive and can be performed in 25-30 minutes, it does require the use of an oxygen analyzer

and is yet to be validated in a large population of preterm infants. Although the ORT and the "shift test" offer potential as non-invasive objective tests, these may not be easily incorporated in research or clinical care. A prospective cohort study enrolled in the Prematurity and Respiratory Outcome Program showed that 32% of infants met the criteria for "physiological" BPD compared with 58.6% and 40.8% with NIH 2001 or Shennan 1988 definitions, respectively.[32] A recent systematic review found that only 5% of studies conducted between 2010 and 2015 reported "physiological" BPD as an outcome.[30] An observational study revealed significant episodes of periodic breathing in 43.2% of infants who failed the ORT.[48] This finding indicates immature respiratory control may be an important confounding factor limiting the validity of the physiological definition.

Pulmonary function testing has been proposed to gain meaningful information in the diagnosis of BPD and validation of proposed definitions.[49 50] Preterm birth and very low birth weight (VLBW) status have been consistently associated with diminished lung capacity,[51-53] increased airway obstruction,[51-54] impaired gas exchange,[51] and a premature decline in respiratory function.[53 54] Longitudinal assessment by lung function and respiratory questionnaire has played a role in BPD outcomes[55 56]; however, it is limited by the need for specialist equipment and expertise.[50] Serial measures of lung function and assessment of respiratory morbidity should form part of the routine follow-up of infants with BPD.[57]

Radiographical studies in the prediction of BPD

Among imaging modalities, plain chest radiography and computed tomography scanning remain the most extensively studied in BPD.[58] Several different radiographic abnormalities have been associated with continued oxygen requirement at 36 weeks' PMA, including chronic pulmonary edema[59] and a "bubbly" cystic appearance.[59 60] A scoring system applied to radiographs on DOL 7 was found to correlate better with BPD diagnosis at DOL 28 than certain readily available clinical data.[61] A pattern of interstitial pneumonitis noted on DOL 7 was independently associated with the combined outcome of death before 36 weeks' PMA or BPD (odds ratio [OR] 4.0, 95% CI 1.1 to 14.4).[62] Measurement of the chest radiograph thoracic area (CRTA) has potential as a quantitative predictor of altered pulmonary mechanics.[63 64] Elevated CRTA obtained from radiographs in the first 48 hours of life and decreased functional residual capacity (FRC) on DOL 3 was associated with BPD in intubated preterm infants.[63] Increased CRTA and decreased FRC were indicative of gas trapping with low functional lung volumes. Reduced FRC had strong predictive value for the development of moderate to severe BPD. Increased CRTA measurements in preterm infants already meeting the criteria for BPD have been associated with impaired oxygenation.[64] Using CRTA in combination with functional measurements may potentially be of use in the prediction of BPD.

Despite considerable drawbacks, computed tomography is recognized as the optimal method to obtain detailed pulmonary images. Several qualitative,[65] semi-quantitative,[66] and quantitative[67] scoring systems have been proposed to predict the severity of long term respiratory outcome in BPD.[58] Most scoring systems involve rating of the degree of peri-bronchial wall thickening, areas of decreased attenuation, and the presence and severity of bullae and bronchiectasis. Computed tomography scoring systems correlate with a range of adverse physiological and clinical outcomes including duration of oxygen therapy,[66] desaturation events during sleep,[67] incidence of wheezing,[65] likelihood of hospital admission,[65] clinical severity scores,[66 68] and progressive decline in forced expiratory volume inone second (FEV_1) in patients who have had BPD.[53] Although computed tomography findings were more specific for BPD than those of plain radiographs,[66 68] the considerable exposure to radiation, increased cost of the procedure, and need for either patient cooperation or deep sedation has limited the use of computed tomography. The European Respiratory Society (ERS) guidelines recommend follow-up imaging with ionizing radiation only in the most severely affected patients.[57]

In contrast, ultrasound does not require exposure to ionizing radiation and can be performed at the patient's bedside. An ultrasound scoring system involving evaluation of three different areas of the lung with a semi-quantitative score has shown some potential for predicting moderate to severe BPD.[69] Lung ultrasound showed that failure of scores to improve with diuretic therapy was associated with worse respiratory outcome.[70] If validated in a larger population, it could be useful in informing treatment as well as prognosis.

Ultra-short echo time (UTE) MRI has begun to emerge as an exciting new technique in respiratory imaging.[71] MRI with UTE may provide a similar degree of information to computed tomography in preterm infants, without the disadvantages of exposure to ionizing radiation or deep sedation.[72] Both structural and functional evaluation is possible, offering insight into the impact of cystic pulmonary lesions[73] and tracheomalacia[74] on respiratory mechanics. An MRI protocol identified an association between increased T2 and decreased T1 relaxation times to predict BPD with an AUC of 0.8.[75] Functional MRI could play a key role in defining specific phenotypes and may eventually replace chest computed tomography as the high resolution modality of choice for BPD.

Biomarker based approaches

The identification of various biomarkers[76] or genomic, proteomic, metabolomic,[77] or microbiomic[78 79] signatures specific for BPD holds considerable promise as a strategy to develop a comprehensive, objective definition (table 3). It is already accepted that susceptibility to BPD is in part determined by genetic inheritance[18] and the contribution of epigenetic mechanisms is also likely

to be considerable.[19 89] Among the advantages of biomarker and "omic" diagnostic strategies are the ability to identify markers of risk versus those of resilience at an early stage, and the potential to limit exposure to interventions with documented side effects. These measures could also offer a means by which to evaluate different disease phenotypes within the BPD population, and they remain an important focus for continued research.

Management—early and evolving BPD

Use of supplemental oxygen

Strategies that prevent BPD by interventions in the delivery room have strong potential to influence long term outcomes.[90] Use of FiO_2 0.21 for resuscitation of term infants is associated with improved outcomes,[91] but for preterm infants, outcomes are uncertain.[92] Data from a meta-analysis of RCTs that analyzed 251 and 253 infants who were enrolled in eight studies (six masked, two unmasked) in the lower and higher oxygen groups, however, have shown no advantage to initiation of resuscitation with FiO_2 0.3 versus 0.6 in preventing BPD (RR 0.88, 95% CI, 0.68 to1.14),[93] despite biological plausibility.[94] Differences in methodology could have an important influence as, for example, mortality was found to be significantly lower in the low oxygen group in masked RCTs where oxygen was titrated by a researcher (RR 0.46, 95% CI, 0.23 to 0.92, P=0.03) and significantly higher in unmasked trials where oxygen was adjusted by the clinical team (RR 1.94 (1.02 to 3.68), P=0.04).[93] At present, the only clear recommendation, based on an individual patient analysis of eight RCTs, is to initiate continuous monitoring of SpO_2 promptly after birth and to titrate supplemental oxygen to achieve a SpO_2 measurement of >80% by 5 minutes of life given the association between hypoxia at this time point and increased mortality.[95]

Data from the Neonatal Oxygenation Prospective Meta-analysis collaborative study showed that use of the lower target range (85-89%) was associated with increased risk for mortality prior to discharge (RR 1.17, 95% CI 1.04 to 1.31, P=0.01).[96] Use of the higher saturation target (91-95%) was not found to be associated with an increased incidence of "physiological" BPD.[96] A systematic review and meta-analysis of five RCTs failed to show an impact of either a low or high saturation target on the incidence of BPD.[97] Therefore, we recommend the use of saturation targets within the range 90-95% for infants requiring supplemental oxygen.

Early respiratory support and surfactant administration

Use of sustained inflations at birth in preterm neonates requiring delivery room resuscitation does not reduce the risk of BPD.[98] Administration of exogenous surfactant has not shown a reduction in the incidence of BPD.[99] Pooled results of three major RCTs comparing early CPAP with prophylactic surfactant administration[100-102] found only marginal improvements in the incidence of BPD.[103] Meta-analyses data have shown no advantage of early InSURE technique over initiation of CPAP.[104] Minimally invasive surfactant treatment (MIST) and LISA techniques employ either a semi-rigid catheter or flexible feeding tube to deliver surfactant during spontaneous breathing, usually on nasal CPAP (nCPAP).[105] The largest multicenter RCT that compared the outcomes of infants with extremely low birth weight receiving LISA with those receiving endotracheal surfactant did not find a significant reduction in BPD (67.3% infants survived without BPD versus 58.7% in the control group, with an absolute risk reduction of 8.6% [95% CI, -5.0% to 21.9%; P=0.20] in BPD.[106] In another study,[107] the greatest benefit of survival without BPD was in infants 26+0 to 28+6 weeks' gestational age. A systematic review of RCTs including 5598 infants in 30 studies showed that LISA may have significant benefit in reducing the composite outcome of death or BPD at 36 weeks' PMA (OR 0.49; 95% credible interval [CrI], 0.30 to 0.79) and CPAP alone (OR 0.58; 95% CrI 0.35 to 0.93).[108] Few adverse effects have been reported with LISA, most being bradycardia during instillation of surfactant that can often be addressed by transiently pausing instillation and continuing over a slower time frame.[105] A cohort study indicated that LISA is associated with a substantial increase in spontaneous intestinal perforation (SIP), most marked in infants of <26 weeks' GA (LISA 10.0 *v* ETT 7.4%, P=0.029).[109] This finding warrants further evaluation in a larger prospective RCT.

RCT and meta-analyses data support the early initiation of CPAP in the delivery room for those at risk of BPD.[101-104] Meta-analyses data revealed a small but significant reduction in the outcome of BPD for infants who were initially supported with CPAP compared with those who were intubated and given surfactant,[103] and a follow-up study[101] revealed an association between CPAP use and reduced respiratory morbidity.[56] The beneficial effect of nCPAP on long term respiratory outcomes may be underestimated owing to 33-50% of the infants randomized to nCPAP eventually requiring intubation and invasive mechanical ventilation.[100] The likelihood of CPAP failure is highest in the most immature infants,[110] and has been associated with increased risk of BPD.[111] Among strategies that reduce the failure rate of nCPAP in infants of extremely low birth weight, aside from early use of caffeine, most are based on a physiological rationale rather than high quality RCT data.[44] Various strategies can be used to generate CPAP—ventilator driven CPAP, use of a flow driver, and "bubble CPAP."[112] Evidence to suggest superiority of any one CPAP modality over another is limited. Meta-analysis data have shown reduced failure rates of bubble CPAP compared with ventilator or flow driver regulated CPAP (RR 0.75, 95% CI 0.57 to 0.98); however, use of bubble CPAP was not associated with reduced risk for BPD.[113]

NIPPV involves brief elevations of pressure above a baseline of nCPAP support and promotes respiratory stability by recruiting and stabilizing collapsed

Table 3 | A summary of selected biomarkers associated with BPD and/or BPD-PH

Marker category	Specimen	Pattern conferring increased risk for BPD or BPD-PH
Growth factors/vascular integrity markers/nitric oxide pathway markers[12 80 81]	Cord blood	Elevated: endostatin; decreased: Ang1, PlGF Elevated: VEGF, PDGF-BB, *BMP-10*, *FGF-19*, *HGF*[82]
	Blood	Decreased: *L-arginine*, Ang1, *FGF-18*, *PDGF-AA*[82] Increased: Ang 2, nitrites
	TA	Decreased: VEGF; elevated: VEGF receptor
Cytokines and pro-inflammatory molecules[12 80 81 83]	Blood	Elevated: IL-1β, IL-6, IL-8, E-selectin, IFNγ, GCSF Decreased: IL-17, RANTES, TNF-β, soluble L-selectin, *MCP*-1
	TA	Elevated: IL-6, IL-8, NF-κB, MCP-1, MCP-2, MCP-3, IL-1β:ILRA ratio
Epithelial or fibrotic markers[12 80 81]	TA	Elevated: MMP-8, MMP-9/TIMP-1, TGFβ Decreased: TIMP-2, MMP-2, NGAL
	Blood	Elevated: TGFβ, KL-6, MMP/TIMP-1
Oxidant injury markers[77]	TA	Elevated: elastase, myeloperoxidase, xanthine oxidase, catalase, total sulfhydryls, epithelial lining carbonyls, 3-chlorotyrosine, malondialdehyde
Proteomic signatures[77]	TA	Increased: surfactant protein-A2, annexin-3, calcium and integrin binding protein-1, Decreased: leukocyte elastase inhibitor, calcyphosine
Metabolomic signatures[77]	Amniotic fluid	Increased: leucinic acid, byproducts of fatty acid oxidation Decreased: DHEAs, s-adenosylmethionine
	Cord blood	Increased: oxylipins, PGE1, PGE2, PGF2a, 9- and 13-HOTE, 9- and 13-HODE, and 9- and 13-KODE[84] Decreased: *sphingomyelins*, *phospholipids*[84]
	TA	Increased: byproducts of fatty acid oxidation and estrogen and testosterone synthesis[85] histidine, glutamic acid, citrulline, glycine and isoleucine, acyl carnitines (fatty acid oxidation), sphingolipids, sphingomyelin C18:1 and C22:3, lysophosphatidylcholine[86] Volatile organic compounds detected by "electronic nose"[87]
Microbiomic patterns[77]	TA	Increased: *Enterobacteriae*, *Ureaplasma*, *Staphylococcus* Decreased: *Lactobacillus*
Gene expression patterns[77 88]	Blood	Increased: inflammatory response genes, CD44, phosphorus oxygen lyase activity, connective tissue mast cells Decreased: T cell receptor related activation genes
Epigenetic markers[77]	TA	Elevated: miR-34a Decreased: miR-876-3p, miR-378b, miR-20a-50, +miR-20b-5p, miR-1254, miR-1252-5p
	Blood	Elevated: miR-219

Ang=angiopoietin; BMP=bone morphogenic protein; DHEAs=dehydroepiandrosterone sulfate; FGF=fibroblast growth factor; GCSF=granulocyte colony stimulating factor; HGF=hepatocyte growth factor; HOTE/HODE/KODE=oxooctadecadienoic acids resulting from fatty acid oxidation; IFN=interferon; IL=interleukin; KL-6=Krebs von den Lungen-6; MCP=monocyte chemoattractant protein; miR=microRNA; MMP=matrix metalloproteinase; NF-κB=nuclear factor kappa B; NGAL=neutrophil gelatinase-associated lipocalin; PDGF=platelet derived growth factor; PGE=prostaglandin; PlGF=placental derived growth factor; RANTES=regulated upon activation normal T cell expressed and presumably secreted; TA=tracheal aspirate; TIMP=tissue inhibitor of matrix metalloproteinase; TNF=tumor necrosis factor; VEGF=vascular endothelial growth factor.

alveoli.[114] Elevations in pressure can be either synchronized with the infant's own efforts (SNIPPV) or unsynchronized. When compared with NCPAP, systematic reviews have shown that early use of NIPPV is associated with reduced need for intubation in preterm infants.[115 116] However, this effect was not significantly associated with reduced risk for BPD.[117]

Invasive mechanical ventilation

If invasive mechanical ventilation cannot be avoided, the use of volume targeted ventilation (VTV) strategies should be strongly considered.[118] A meta-analysis of 20 RCTs and quasi-randomized trials revealed that VTV was associated with reduced risk for the combined outcome of death or BPD at 36 weeks (RR 0.73, 95% CI 0.59 to 0.89, number needed to treat (NNT) 8, 95% CI, 5 to 20).[119]

Primary use of high frequency ventilation (HFOV) in several RCTs was not consistently shown to decrease BPD.[120] Primary use of HFOV was not associated with any significant improvement in lung function when evaluated between 16 and 19 years of age.[121] No strong recommendations can therefore be made regarding use of elective HFOV in preterm infants at risk of BPD.

The requirement for invasive ventilation at DOL 7 has been shown consistently to be associated with increased risk for BPD.[122 123] A single center retrospective study has shown that for infants of extremely low birth weight and <28 weeks' gestational age, extubation after DOL 8 is associated with a significantly increased hazard of developing BPD, compared with extubation between DOL 1 and 3 (hazard ratio (HR)16.9, 95% CI 10.5 to 27.1, P<0.001) and DOL 4-8 (HR 10.0, 95% CI, 6.1 to 16.3; P<0.001).[123] A similar reduction in the combined outcome of BPD and death was not affected by need for reintubation.[123] The inflammatory response in the first few days of life is possibly different and less persistent, compared with later postnatal ages, and could potentially account for the improved pulmonary outcome.[15 124] A large multicenter retrospective study has shown that the total number of days of positive pressure delivered via an endotracheal tube is more predictive of adverse long term pulmonary outcomes than the number of courses of invasive mechanical ventilation.[125] Earlier extubation was associated with reduced supplemental oxygen requirement at 36 weeks' PMA and shorter length of hospital stay in another retrospective study where the need for reintubation was also not shown to influence either mortality or incidence of BPD.[126] However, another recent retrospective study showed a significant association between recommencement of invasive mechanical ventilation and the composite outcome of BPD or death.[127] The relation between reintubation and death or moderate to severe BPD was strongest when invasive mechanical ventilation was

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Table 4 | A summary of the effects of systemic glucocorticoid treatment

Study description	Time on respiratory support	BPD at 36 weeks	Death or BPD at 36 weeks' PMA	Home oxygen	Cerebral palsy	Cerebral palsy or death	Late onset sepsis	SIP
Meta-analysis of RCTs using dexamethasone in preterm infants <8 days of life[135]	Failure to extubate at 7 days 0.71 (0.64-0.84)	0.71 (0.62-0.85)	0.87 (0.80-0.94)	0.78 (0.48-1.26)	1.75 (1.20-2.55)	1.17 (1.00-1.37)	1.02 (0.91-1.15)	RD 0.03 (0.01-0.05)
GRADE: Moderate to high	6 RCTs, n=703	16 RCTs, n=2584	16 RCTs, n=2581	3 RCTs, n=691	7 RCTs, n=921	7 RCTs, n=921	14 RCTs, n=2821	9 RCTs, n=1936
Meta-analysis of RCTs using dexamethasone in preterm infants >7 days[136]	Failure to extubate by day 7 of Rx 0.65 (0.59-0.72)	0.77 (0.67-0.88)	0.77 (0.70-0.86)	0.71 (0.54-0.94)	1.16 (0.82-1.64)	0.95 (0.78-1.15)	1.14 (0.97-1.34)	1.60 (0.28-9.31)
GRADE: Moderate to high	15 RCTs, n=761	11 RCTs, n=580	11 RCTs, n=580	7 RCTs, n=611	16 RCTs, n=919	16 RCTs, n=919	18 RCTs, n=1349	3 RCTs, n=159
Single patient analysis of RCTs using low dose hydrocortisone in the first week of life Preterm infants mean GA 25.2 to 26.9 weeks[137] GRADE: High	No significant difference in number of days' ventilation. Extubation prior to 10 days of life. 2.07 (1.42 -3.02 P=0.002). 1 RCT[138] n=522	0.73 (0.54-0.98 P=0.038) 4 RCTs n=982	Survival without BPD 1.45 (1.11-1.90 P=0.007) ≥26 weeks 1.52 (1.07-2.17) Chorio 2.01 (1.19-3.39 P=0.009) 4 RCTs n=982	0.92 (0.64-1.33) 4 RCTs n=982	0.95 (0.56-1.60) 4 RCTs n=709 (came for follow-up)	N/R	1.34 (1.02-1.75) >26 weeks 1.14 (0.78-1.65) P=0.5 Chorio 1.91 (1.18-3.08 P=0.009) 4 RCTs n=982	2.5 (1.33-4.69 P=0.004) No Indo 1.52 (0.73-3.15 P=0.26) 4 RCTs n=982
RCT of hydrocortisone 72.5 mg/kg/22 days in PT infants dependent on MV at 7-14 days[139] GRADE: High	Failure to extubate by day 7 of Rx 0.34 (0.21-0.54, P<0.001)	1.24 (0.82-1.86)	0.87 (0.54-1.38)	NR	NR	NR	0.80 (0.61-1.05)	RD −2.5 (-6.8-1.5)

Data shown as odds ratio (95% confidence interval). BPD=bronchopulmonary dysplasia; chorio=chorioamnionitis; GA=gestational age; indo=indomethacin. MV=mechanical ventilation; NR=not recorded; PMA=postmenstrual age; PT=preterm; RD=risk difference; RCTs=randomized controlled trials; Rx=treatment; SIP=spontaneous intestinal perforation. GRADE classification, as per Guyatt et al.[140x]

recommenced within 48 hours of the first extubation attempt, a finding that maintained significance even when adjusted for total duration of invasive mechanical ventilation (OR 12.76, 95% CI, 1.38 to 117.62).[127] Interestingly, reintubation was not found to be associated with increased risk for moderate to severe BPD alone (OR 1.09, 95% CI, 0.38 to 3.15).

In summary, current evidence continues to support the need for proactive weaning of invasive mechanical ventilation during the first week of life and consideration for a trial of extubation in infants who tolerate weaning to low settings, even if long term success is not guaranteed.[126]

Caffeine

Early initiation of caffeine therapy, within the first three days of life, has a significant impact in reducing BPD[128 129] and associated long term neurological morbidity.[130] An RCT showed that initiation of caffeine within 10 days of life significantly reduced the incidence of BPD (AOR 0.63, 96% CI 0.53 to 0.76, P<0.001).[90] Lung function studies performed on children aged 11 who had overcome BPD and were enrolled in the same study revealed a significant improvement in expiratory flow in those who received caffeine (FEV_1: mean Z score; -1.0 versus 1.53; mean difference, 0.54, 95% CI, 0.14 to 0.94, P=0.008).[131] Subgroup analysis of a trial,[132] together with other studies[133 134] indicated that the greatest benefit was obtained by infants who receive caffeine within the first three days of life. Questions remain regarding the optimal dosage and timing of caffeine initiation to prevent or mitigate BPD. An RCT is under way to compare the effect of earlier (2 hours of life) with later (12 hours of life) initiation of caffeine (NCT03086473).

Postnatal steroids

The use of postnatal steroids for the prevention and mitigation of BPD remains a controversial topic (table 4). Early use of dexamethasone has been consistently associated with reduced duration of mechanical ventilation and a reduction in the outcome of BPD; this is at the cost of increased risk of NDI and cerebral palsy.[135] Use of dexamethasone is therefore strongly discouraged in the first week of life. After the first week of life, treatment with postnatal glucocorticoids may reduce the incidence of NDI in infants at high risk for poor pulmonary outcomes.[141] Administration of a low dose course of dexamethasone (0.89 mg/kg over 10 days) to infants on mechanical ventilation after one week of life was found to be associated with increased likelihood of extubation at the end of treatment (OR 11.2, 95% CI 3.2 to 39.0) but not with reduced BPD.[142] Follow-up did not find any adverse consequences or improvements in neurodevelopmental outcome.[143] Postnatal dexamethasone should therefore continue to be reserved for the infants at highest risk of developing BPD who remain dependent on mechanical ventilation beyond 21 days of life.[144]

An individual patient meta-analysis of four RCTs (table 4)[138 145-147] showed treatment with low dose hydrocortisone to be associated with a significant

increase in survival without BPD (OR 1.45, 95% CI, 1.11 to 1.90, P=0.007) and a decrease in the outcome of BPD (OR 0.73, 95% CI, 0.54 to 0.98, P=0.38). Subgroup analysis showed that BPD-free survival was enhanced in infants exposed to chorioamnionitis but failed to reach significance for infants with gestational age <26 weeks. An RCT that evaluated the later use of hydrocortisone at a higher dose in infants who remained dependent on mechanical ventilation did not show any improvement in the outcome of BPD.[139] In contrast with the early use of dexamethasone, early low dose hydrocortisone has not been associated with increased risk of neurosensory impairment.[148] In summary, treatment with low dose hydrocortisone in the first week of life, but not a later or higher dose, is associated with a small but significant improvement in the diagnosis of BPD, especially in infants exposed to chorioamnionitis.[137 149] Long term pulmonary benefits resulting from a reduction in the outcome of BPD are yet to be determined.

Regarding early inhaled budesonide, in an RCT with 437 infants given budesonide versus 417 given a placebo, in reducing the outcome of BPD (RR 0.74, 95% CI 0.60 to 0.91, P=0.004), the composite outcome of death or BPD was partially offset by a non-statistically significant trend towards increased mortality in the intervention group (RR 1.24, 95% CI 0.91 to 1.69, P=0.17).[150] The 2 year outcomes of the study revealed that the early trend towards increased mortality in the intervention group reached significance (RR 1.37, 95% CI, 1.01 to1.86, P=0.04)[151] For this reason, early use of inhaled budesonide is not recommended to prevent BPD.

Diuretic therapy

Chronic, mild pulmonary edema was included in the initial description of the "New BPD" phenotype and both loop and thiazide diuretics continue to be commonly used in preterm infants with evolving and established BPD.[152 153] Diuretic use is more common in extremely preterm infants who are on higher levels of respiratory support[154 155] and the relation between initiation of therapy and improvement in respiratory status has been inconsistent.[154 156] Although a significant association between increased duration of furosemide exposure and reduced incidence of BPD was noted in a large multicenter retrospective cohort study,[155] given the study design, it is not possible to infer causality. As furosemide therapy is linked with multiple adverse consequences,[157] including reduced weight gain, electrolyte losses, nephrocalcinosis,[158] and metabolic bone disease[159]; diuretics should be used judiciously in preterm infants with treatment limited to those that show clinical improvement.

Inhaled bronchodilators

The phenotype of BPD is associated with hypertrophy of the smooth muscle surrounding the airways and inflammation.[160] The fixed and reversible component to airway hyper-reactivity in preterm infants may be more pronounced in those with BPD, as noted by consistently reduced spirometry values.[49] A systematic review and meta-analysis measuring bronchial hyper-responsiveness (BHR) in adults and children born preterm with and without BPD revealed that the risk of BHR was increased in participants with BPD for both methacholine challenge (OR 2.59, 95% CI, 1.50 to 4.50) and exercise challenge (OR 5.13, 95% CI, 1.82 to 14.47). To date there is no evidence linking inhaled steroids and bronchodilators with either reduction in BPD or mortality.[161] The ERS advises the use of bronchodilators only in infants with severe BPD who have asthma-like symptoms (dry cough/wheezing), exercise induced symptoms, frequent hospital admissions, and show reversibility on testing.[57]

Nutritional strategies

The ability to maintain lung growth and repair is dependent on adequate postnatal nutrition. A retrospective cohort study revealed that both lower energy intake during the first four weeks of life and increased fluid intake were significantly associated with BPD.[162] Relative fluid restriction, early introduction of enteral feedings, and optimization of parenteral nutrition components should be strongly considered. An RCT revealed a significant reduction in BPD in infants given donor milk relative to the formula supplemented group (15% versus 28%, P=0.048).[163] Exclusive feeding with fresh maternal breast milk was significantly associated with a decrease in BPD (OR 0.40, 95% CI, 0.27 to 0.67, P<0.001).[164] Maintenance of an exclusive human milk diet, ideally the use of fresh maternal breast milk, is recommended in the management of infants with early and evolving BPD.

Management—established BPD

If there is concern for BPD-PH,[165] SpO_2 targets are usually ~95% (ranging from 92% to 98%).[12] Additional agents may be required, but description of the management of BPD-PH is beyond the scope of this review.

Ventilator management for the subset of infants with severe BPD is especially challenging, with limited high quality data available to guide the clinician.[166] The two major phenotypes of severe BPD are predominantly atelectatic or cystic.[166 167] In the former type, higher positive end expiratory pressures (PEEP), up to 12 cm H_2O may be required, with tidal volumes of 4-7 mL/kg. In the cystic type, moderate PEEPs of 4-8 cm H_2O with higher tidal volumes of 10-12 mL/kg are required to provide optimal oxygenation and ventilation.[166 167] For infants still requiring invasive ventilation at 90-100 days of life, with >5-7 failed attempts at extubation, a tracheostomy should be considered.[168] Tracheostomy has been associated with improved growth and development.[169] Information about long term ventilation in babies with established BPD are available,[170 171] although beyond the scope of this review. In patients with established oxygen dependent BPD, the use of prednisolone was successful in weaning

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supplemental oxygen.[172] Diuretics are continued, as in the early and evolving phases of BPD.[12] More evidence based data are required to guide diuretic therapy in established BPD.[173] Use of beta-agonists, with or without anticholinergics, may be employed in infants with BHR.[12]

Recommendations for initiation and weaning home oxygen support are shown in table 5.[167 174] Infants often receive chronic diuretic therapy despite scarce data to support this practice or guidelines to discontinue them, post-discharge from the NICU.[175] A subset of patients will continue to receive inhaled steroids and bronchodilator therapy post discharge.[175]

Guidelines for management of BPD

Table 6 summarizes recommendations for the clinical management of infants with early, evolving, and established BPD. Many of these recommendations are our own, based on evidence from the literature; however, we have included several recommendations by the ERS.[57] The recommendation to target SpO_2 for infants discharged on supplemental oxygen is in agreement with guidance issued from the American Academy of Pediatrics (AAP) Committee of the Fetus and Newborn (COFN) and ERS.[188 189] The ERS and AAP COFN advocate early use of CPAP in respiratory distress syndrome, early administration of caffeine, and selective administration of surfactant.[189 190] For invasive mechanical ventilation, a volume targeted approach is recommended.[189] ERS and AAP COFN guidelines differ in the technique recommended for surfactant delivery. Current ERS guidelines advocate less invasive surfactant administration (LISA) whereby surfactant is delivered during spontaneous breathing via a semi-rigid catheter or a feeding tube placed in the airway. In contrast, the AAP COFN guidelines recommend consideration for delivery using the intubation surfactant administration and rapid extubation technique (InSURE). AAP COFN guidelines, however, do not reflect some of the more recent evidence emerging regarding the potential advantages of LISA that have emerged in the past seven years.[104]

The American Thoracic Society (ATS), American Heart Association (AHA), and EPPVDN recommend that infants with established BPD should undergo screening for BPD-PH.[40 191] The lack of an international consensus guideline on the diagnosis of BPD is a major obstacle to progress in clinical research and should be an important focus for future collaboration.[30]

Emerging treatments

As research continues to highlight the critical role played by intrauterine exposures in the development of BPD and BPD-PH, interventions that occur in the antenatal period may have the potential to offer protection. Maternal smoking is an important risk factor for persistent respiratory disease in preterm infants.[192] RCT evidence shows that antenatal vitamin C supplementation is associated with improved pulmonary function tests and reduced incidence of wheezing during infancy in newborns whose mothers smoked tobacco during pregnancy.[193] No evidence suggests that antenatal vitamin C supplementation is of benefit in preventing BPD.

Intrauterine infection and inflammation have also been strongly implicated in the development of BPD.[15] A phase I placebo controlled RCT of N-acetylcysteine

Table 5 | Home supplemental oxygen therapy for established BPD: initiation and weaning

Criteria for home use of oxygen: initiation	
Postmenstrual age at least 36 weeks	
Medical problems	Absence of apnea; stabilized or regressed ROP
Growth	Weight gain of at least 20 g/day
Immunization	Completed as appropriate for postnatal age; received first dose of RSV prophylaxis, if appropriate
Flow rate	Stable for at least 1 week on flow rate of 1-2 L/min FiO_2 1.0, and maintaining saturations ≥92%
Home monitoring	Availability of continuous SpO_2 monitoring and downloading data capability
Home environment	Adequate caregiver teaching and home supplies
Criteria for home oxygen use: weaning	
Follow-up	Every 4 weeks, or sooner, if needed
Weaning process	Wean flow 1/4 to 1/8 LPM or 0.25 to 0.1 LPM Increase flow if SpO_2 <93% Target SpO_2 ≥92-96% Consider a slower wean if BPD-PH is present Consider not weaning if growth is inadequate Wean to room air when awake, first, then:
	Overnight oximetry test If SpO_2 >90% for 98% time of the study, wean to room air. Can consider weaning to room air if SpO_2 >90% for 96% time of the study with no low saturation values and absence of artifacts, except when other co-morbidities exist (BPD-PH, inadequate growth) Repeat oximetry in room air
	Overnight polysomnography Discontinue O_2 if there is less than 20 minutes SpO_2 <92%, no continuous desaturation <92% for more than 5 minutes or only infrequent desaturations of 4% causing arousal without evidence of obstruction
	Stable in room air Keep O_2 cylinder and pulse oximeter at home for use as needed for at least 3 months to allow for acute deteriorations, eg, URIs

Adapted from refs [167 174-176] BPD-PH=bronchopulmonary dysplasia-pulmonary hypertension; LPM=liters per minute; ROP=retinopathy of prematurity; RSV=respiratory syncytial virus; URI=upper respiratory tract infections.

Table 6 | Management of BPD according to phase (early, evolving, and established)

Therapeutic intervention	Current status	Evidence level	Recommendation level
Early phase (up to 1 postnatal week)			
Oxygen supplementation	Resuscitation:		
	Titrate supplemental oxygen to obtain preductal oxygen saturation >80% by 5 minutes of life[93]	I	B
	Maintain oxygen saturations 90-95%[96]	I	A
Ventilatory strategy	Trial of CPAP for spontaneously breathing infants	I	A
	Consider surfactant administration if FiO_2 remains consistently >0.4 on PEEP +6 cm H_2O	I	B
	Use InSURE/LISA technique to administer surfactant	I	B
	Consider volume targeted ventilation strategies: TV 4-6 mL/kg[119]	I	A
	Use short inspiratory times (0.3-0.4 s),[177] rapid rates (40-60 per min) and low PIP on pressure control settings (14-20 cm H_2O), moderate PEEP (4-6 cm H_2O)[178] PaO_2: 40-60 mm Hg; $PaCO_2$:45-55 mm Hg[179]	III	B
	Trial of extubation to NIPPV/SNIPPV prior to 7 days in infants who tolerate weaning to minimal settings[180]	II-2	B
Methylxanthines	Administration of caffeine within first 3 days of life decreases BPD[128 132]	I	A
Intratracheal administration of budesonide and surfactant	Associated with an increase in BPD free survival (NNT 4.1 [95% CI 2.8 to 7.8])[181] 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[182] Dose: 5000 IU given intramuscularly 3 times a week for 4 weeks	I	A
Low dose hydrocortisone	Low dose hydrocortisone (total dose 8.5 mg over 10 days) is associated with increased BPD free survival Increased risk of late onset sepsis in infants <26 weeks[137] Increased risk of SIP in infants who receive indomethacin[137]	I	C
Fluids	Restrictive fluid intake may decrease BPD[183]	II-2	B
Nutrition	Exclusive human milk feeding reduces the risk for BPD[163]	I	A
	Provide increased energy intake[162]	II-2	A
Evolving BPD (> 1 postnatal week to 36 weeks' PMA)			
Dexamethasone	Low dose dexamethasone (0.89 mg/kg over 10 days) facilitates extubation but does not reduce BPD[142]	I	C
	High dose dexamethasone (0.5 mg/kg-1 mg/kg) reduces BPD but may increase the risk of NDI and CP[184] Greatest global benefit is for infants with risk of BPD >66%—ie, those who remain intubated at 3-4 weeks postnatal age[141 185]	I	C
Ventilatory strategy	Avoid endotracheal tube ventilation, encourage non-invasive support strategies (NIPPV, SNIPPV, nCPAP)[180]	I	A
	Blood gas targets: pH 7.25-7.35; PaO_2 50-70 mm Hg; PCO_2 50-60 mm Hg[179] No advantage to allowing higher CO_2 limit[186]	I	A
Diuretics	May improve respiratory mechanics and facilitate weaning of support. Do not prevent BPD. Continue use only if clear response demonstrated[37]	I	B
Nutrition	Same as for early phase	I	A
Methylxanthines	Same as for early phase	I	A
Established phase (>36 weeks' PMA)			
Echocardiographic screening for BPD PH	25% of infants with moderate or severe BPD have echocardiographic evidence of pulmonary hypertension[40]	III	A
Bronchodilators	May improve symptoms in subpopulations of affected infants[57]	II-3	B
Inhaled steroids	Later use may improve symptoms in subpopulations of infants[57]	III	B
Diuretics	Chronic therapy as for the evolving phase[37]	I	B
	Consider allowing infant to outgrow dose[57]	III	B
Nutrition	Same as for early and evolving phase. Avoid excessive weight gain	II-2	A
Immunization	Prophylaxis against RSV and influenza decreases re-hospitalization and morbidity RSV prophylaxis is cost effective[187]	I	A

Adapted from Bhandari et al[12] BPD=bronchopulmonary dysplasia; CP=cerebral palsy; FiO_2=fraction of inspired oxygen; InSURE=intubation, surfactant administration, extubation; IVH=intraventricular hemorrhage; LISA=less invasive surfactant administration; nCPAP=nasal continuous positive airway pressure; NDI=neurodevelopmental impairment; NIPPV=nasal intermittent positive pressure ventilation; PEEP=positive end expiratory pressure; PIP=peak inspiratory pressure; RSV=respiratory syncytial virus; SNIPPV=synchronized NIPPV; SIP=spontaneous intestinal perforation; TV=tidal volume.

administration in women presenting in preterm labor with confirmed intrauterine infection or inflammation showed a dramatic reduction in the incidence of BPD in infants born to mothers in the treatment group (RR 0.1, 95% CI, 0.01 to 0.73). Data from a larger scale RCT are required before this approach is incorporated into clinical practice.

Use of exogenous surfactant as a medium to deliver budesonide directly to the airspaces has shown promise in reducing the outcome of BPD.[181 194] In an RCT, the effects of a preparation of 0.25 mg/kg budesonide combined with 100 mg/kg surfactant (Survanta, Abbott Laboratories, Abbott Park, IL) was compared with 100 mg/kg surfactant alone, in a group of 265 intubated VLBW infants.[181] The primary outcome of death or BPD was significantly reduced in the interventional group (42% versus 66%, RR 0.58, 95 % CI 0.44 to 0.77, P<0.001, NNT 4.1). The incidence of BPD was reduced in the intervention group (29% versus 50%, RR 0.70, 95% CI 0.58 to 0.86, P<0.001) without significant increase in mortality. A meta-analysis[195] reported a 43% reduction in the risk for BPD in the intervention group (RR 0.57, 95% CI, 0.43 to 0.76, NNT 5) with a decrease in the combined outcome of BPD or death (RR 0.60, 95% CI, 0.49 to 0.74, NNT 3). The budesonide

in babies trial (NCT04545866) has been designed to evaluate the pulmonary and neurodevelopmental outcomes of infants of 22-28^{+6} gestational age who receive a combination of 0.25 mg/kg budesonide and 2.5 mL/kg surfactant with those who had 2.5 mL/kg surfactant alone. This trial is currently recruiting and likely to report in 5-6 years' time.

Deficiencies in insulin-like growth factor 1 (IGF-1) have been shown to be linked to the pathogenesis of BPD.[196] A phase II clinical trial designed to evaluate the safety and efficacy of recombinant human IGF-1 complexed with its binding protein (rhIGF-1/rhIGFBP-3) in the prevention of retinopathy of prematurity noted a statistically significant decrease in the incidence of BPD in the 61 infants who received the treatment (21.3% treated versus 44.9% standard care; P=0.04).[197] This effect was even more pronounced in the 24 infants in whom IGF-1 levels in the target range were reached (4.8% treated versus 44.9% standard care; P=0.02).[197] A large placebo controlled RCT designed to evaluate the benefit of rhIGF-1/rhIGFBP-3 is ongoing (NCT03253263) and likely to report in 5-6 years' time.

Mesenchymal stem cell (MSC) based therapies have shown great potential for the management of a range of different neonatal conditions including BPD.[198] Findings from a phase II RCT investigating the effect of intratracheal administration of MSCs to preterm infants of 23-28 weeks' gestational age showed a reduction in the incidence of severe BPD in a subgroup of infants born at 23-24 weeks' gestational age (19% treatment group [3/16] versus 53% placebo group [8/15]).[199] A larger multicenter phase II trial focusing on the use of intratracheally delivered MSCs in infants of 23-25 weeks' gestational age is under way (NCT03392467). A clinical trial evaluating the safety of intravenously administered bone marrow MSC derived extracellular vesicles in preterm infants of 23-26 weeks' gestational age is also in progress (NCT03857841).

Conclusions

BPD is a complex multifactorial lung condition that is also associated with other pathologies that affect preterm infants such as NDI and growth failure. The lack of an objective definition of BPD poses a significant challenge to the evaluation of new treatments.[200] The Shennan 1988 definition[29] remains the most consistently used criterion to define BPD in clinical studies.[30] The NIH 2001 outcome of severe BPD, known to be associated with significantly increased morbidity and mortality,[31] is frequently not reported. The NIH 2018 definition is yet to be validated in a large neonatal population. As work continues in the development of more objective criteria defined by biomarkers or "omic" technology, the consistent use of clinical definitions with the potential to differentiate subjects with the highest risk for mortality and morbidity should remain a strong consideration. Despite advances in the understanding of the pathogenesis of BPD, relatively few of the treatments available are supported by high quality evidence. Novel therapies to prevent or mitigate the severity of BPD therefore have the potential to transform healthcare outcomes for a growing population of survivors of prematurity.

QUESTIONS FOR FUTURE RESEARCH

- How accurate is the 2018 NHLBI definition of BPD in predicting long term mortality and morbidity?
- How can biomarkers and "omic" approaches be best utilized for the early prediction of BPD and definition of specific phenotypes?
- Is the use of intratracheal budesonide associated with improved long term pulmonary outcome? Are there any risks of NDI?
- What is the utility of LISA in reducing the incidence of BPD and improving long term outcomes? Could there be added benefit to combining LISA with intratracheal budesonide?
- How can we optimize the management of infants with severe BPD and BPD-PH?

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Supplemental Table 1. Levels of Evidence and Recommendations for Clinical Use Based on the Guidelines Developed by the US Preventive Services Task Force