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Recent Advances in the Management of Bronchopulmonary Dysplasia

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Abstract

Purpose of review Bronchopulmonary dysplasia (BPD) remains a very common complication of extreme prematurity and has significant adverse long-term consequences. Specific treatments to prevent the development of BPD or to treat established BPD are very limited. We have reviewed recent advances in the management of preterm-born infants at risk of developing BPD and in those with established BPD as well as potential future emerging treatment options.

Recent findings Strategies to prevent iatrogenic lung trauma, such as non-invasive respiratory support and administration of exogeneous surfactant in a less invasive manner have now become embedded in clinical practice, but further studies are ongoing with the POLAR and SURFSUP trials aiming to refine these interventions. Strategies, other than postnatal systemic corticosteroids, to suppress lung inflammation have also been evaluated. However, both the early use of azithromycin and administration of endotracheal budesonide mixed with exogenous surfactant have not shown benefits for survival without development of BPD. Later in life, survivors of BPD at school-age show significant improvement in lung function with combined inhaled corticosteroids and long-acting beta$_2$ adrenoreceptor agonists, but therapeutic options to improve long term lung function are urgently required.

Summary Further detailed understanding of the underlying mechanisms for the development of BPD are required so targeted treatments can be developed.

Keywords Preterm · Bronchopulmonary dysplasia · Chronic lung disease of prematurity · Lung

Introduction

Bronchopulmonary dysplasia (BPD), also called chronic lung disease of prematurity (CLD), is a very common complication of extreme prematurity. Since BPD was originally described by Northway et al. [1] almost 60 years ago, advances in perinatal care have led to significant changes in its presentation, clinical course and management of preterm-born infants. Since then, various definitions of BPD have been promoted, none ideal due to the nature of the underlying disease process. The most recent definition promoted by the National Institute of Child Health and Development National Research Network is, as with most previous definitions, based on supplemental oxygen requirement and respiratory support at 36 weeks' postmenstrual age (PMA) [2]. This definition assessed at 36 weeks' post-menstrual age defines Grade 1 as nasal cannula supplemental oxygen with a flow of≤2 L/minute; Grade 2 as nasal cannula supplemental oxygen with flow of>2 L/minute or a requirement for non-invasive positive airway pressure; and Grade 3 as need for invasive mechanical ventilation regardless of need for supplemental oxygen [2]. Although this definition is being increasingly used, its use is inconsistent across centres, leading to difficulties in comparing BPD rates between regions and countries.

Although advances in perinatal care have significantly increased survival, rates of BPD have remained largely unchanged or, indeed, increased in many regions, especially for the most immature infants [3, 4].

Research has been devoted to developing evidence-based strategies which optimise postnatal management of BPD, however, due to its complex and multifactorial nature,

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prevention and treatment of BPD is extremely challenging and cannot be achieved with a single intervention [5]. Risk factors associated with development of BPD following preterm birth include antenatal factors such as intrauterine growth restriction, chorioamnionitis, maternal smoking and pregnancy-induced hypertension, as well as postnatal factors including mechanical ventilation, sepsis, patent ductus arteriosus and hyperoxia; all contributing to pulmonary inflammation during the early stages of development of BPD [6].

Increasingly, it is recognised that there are likely to be several different phenotypes of BPD. Such phenotypes could possibly involve the interstitium, parenchyma, pulmonary vasculature, peripheral and central airways. Arguably differentiating these subgroups, each with different underlying pathophysiological mechanisms or endotypes, could lead to development of more targeted therapies [7–9].

In this review, we describe historical and current management as well as recent and emerging advances in the management of preterm-born infants at risk of developing BPD and those with established BPD both on the neonatal unit and beyond. Antenatal management or strategies to prevent preterm birth or interventions such as antenatal maternal corticosteroid administration to prevent respiratory disease after birth are not addressed. Table 1 summarises historical, current and possible future treatments for BPD.

Prevention and early management of patients at risk of BPD

Delivery room management

A significant proportion of extreme and very preterm-born infants require respiratory support with positive airway pressure and supplemental oxygen. Historically, endotracheal intubation and positive pressure mechanical ventilation has been used. However, due to its association with volu-/barotrauma and subsequent increased risk of developing BPD, non-invasive ventilation (NIV) has become the method of choice to decrease volu-/barotrauma [5]. During initial stabilisation in the delivery room at birth, continuous positive airway pressure (CPAP) is a feasible and effective alternative to more invasive tracheal intubation and mechanical ventilation even for the most extremely preterm- born infants if they are breathing spontaneously [14]. The use of early NIV reduces risk of composite outcome of death or development of BPD and duration of invasive ventilation when compared with immediate tracheal intubation and exogenous surfactant administration in extremely preterm-born infants, with decreased risk of developing a pneumothorax or other significant adverse events [5, 14].

The POLAR clinical trial (*Positive end-expiratory pressure levels during resuscitation of preterm infants at birth*; Clinicaltrials.gov NCT04372953) is an international, multi-centre, randomised controlled trial comparing the effect of positive end-expiratory pressure (PEEP) dynamically adjusted for clinical need, with a static PEEP of 5–6 cmH_2O during stabilisation at birth of extremely preterm-born infants to assess if survival without development of BPD improves. The results should inform the airway management of extreme preterm infants in the delivery room to prevent subsequent lung injury.

Lung protective respiratory support

Whilst CPAP is the most extensively studied mode of ventilation in preterm-born infants, other newer modes of NIV have become available for use in this population. Nasal intermittent positive pressure ventilation (NIPPV) has been shown to be more effective than CPAP in preventing respiratory failure in the first few days of life in preterm-born infants with respiratory distress. However, convincing reductions in subsequent rates of developing BPD have not been shown [40].

High flow nasal cannula (HFNC) is the most recently introduced method of NIV. It has potential advantages over CPAP including reduced nasal trauma, greater infant comfort, ease of use for staff, and, therefore, has quickly become established in neonatal care [41]. However, as a primary method for respiratory support, HFNC is not recommended for infants born at < 28 weeks' gestation. Evidence from large international, multi-centre randomised controlled trials showed that HFNC is inferior to CPAP as a tool for early respiratory support to prevent treatment failure [42].

For infants who require invasive mechanical ventilation, research has been undertaken to study the effect of different ventilation strategies such as volume guarantee and neurally adjusted ventilatory assist (NAVA), on the development of BPD and strategies to reduce lung damage. Barotrauma has been identified as the major contributor of lung inflammation in preterm infants, and the benefit of volume targeted ventilation over pressure targeted ventilation is now well recognised [15].

Surfactant administration

Exogenous surfactant is routinely used to treat preterm-born infants with respiratory distress syndrome (RDS) and is associated with improved outcomes including decreased death rates [43]. Traditionally, exogenous surfactant has been administered via an endotracheal tube to already intubated and mechanically ventilated infants, or infants were briefly intubated and ventilated specifically for administration of

Table 1 Historical, current and future treatments for BPD

Treatment	Mechanism	Stage	Key evidence
Historical treatments			
Prolonged mechanical ventilation	Supportive	Prevention, Established BPD	Now minimized due to iatrogenic lung injury (barotrauma, volutrauma)
Early (< 7 days) postnatal dexamethasone	Anti-inflammatory	Prevention	Reduced BPD incidence but high risk of neurodevelopmental impairment [10]
Diuretics	Reduce pulmonary oedema	Established BPD	Short-term improvement, no proven long-term benefit [11]
Vitamin A	Alveolar development, epithelial integrity	Prevention	Not universally adopted due to intramuscular administration [12]; enteral supplementation not efficacious [13]
Current treatments			
Non-invasive ventilation	Avoid mechanical ventilation	Prevention	(Early) NIV reduces BPD incidence [5, 14]
Lung protective ventilation strategies	Minimize barotrauma	Prevention	Volume-targeted ventilation reduces BPD incidence [15]
Surfactant therapy	Surfactant deficiency	Prevention	Lower incidence of BPD when intubation is avoided for surfactant administration [16]
Early low dose hydrocortisone	Anti-inflammatory	Prevention	Increased survival without BPD (PREMILOC trial) [17]
Later hydrocortisone	Anti-inflammatory	Prevention	No significant improvement in survival without BPD [18]
Later (> 7 days) dexamethasone	Anti-inflammatory	Prevention	Improved odds of survival without BPD [19]
Early inhaled corticosteroids	Local anti-inflammatory	Prevention	Borderline reduction in composite death or BPD (NEUROSIS trial) [20]
Intratracheal budesonide with surfactant	Local anti-inflammatory	Prevention	No effect on survival without BPD (PLUSS trial) [21]
Caffeine	Apnoea prevention, neuro-respiratory stimulation	Prevention	Widely used, reduces BPD and improves neurodevelopment (CAP trial) [22]
Azithromycin	*Ureaplasma* and pulmonary inflammation	Prevention	Mixed evidence but recent AZTEC trial did not show benefit [23]
Early ibuprofen for PDA	Induce PDA closure to reduce pulmonary over circulation	Prevention	Not superior to expectant management for composite death or BPD [24]
Inhaled nitric oxide	Vascular remodelling	Prevention	No significant effect on mortality or BPD, may benefit specific subgroups [25]
Family involvement in care	Reduce infant stress, improve stability	Prevention	Associated with lower BPD rates in some programs [26]
RSV prevention	Reduce RSV infections	Prevention	Palivizumab and nirsevimab reduce lower respiratory tract infections and hospitalizations due to RSV [27–29] Maternal RSV vaccination
Home oxygen therapy	Maintain adequate oxygen saturation, supportive	Established BPD	Improves growth and reduces pulmonary hypertension risk
Inhaled corticosteroids	Local anti-inflammatory	Established BPD	Modest improvement in FEV1 (PICSI trial) [30]
Inhaled corticosteroids + long-acting beta 2 receptor agonist	Local anti-inflammatory and bronchodilator	Established BPD	Significant improvement in FEV1 (RHiNO trial) [31]
Future treatments			
Extended CPAP	Promote lung growth via mechanical stretch	Prevention	Larger functional residual capacity [32, 33]
IL-1RA	Targeted pulmonary inflammation, fibrosis	Prevention	Early phase development, preclinical and small pilot studies only [34]
Recombinant human IGF-1/IGFBP-3	Vascular, alveolar development	Prevention	Phase II trials show promise in reducing severe BPD [35, 36]
Mesenchymal stem cells	regenerative	Established BPD	Preclinical, translational studies ongoing [37–39]

exogenous surfactant (INSURE). With the increasing introduction of NIV, alternative methods for surfactant administration have been explored. In Less Invasive Surfactant Administration (LISA) or Minimally Invasive Surfactant Therapy (MIST), exogenous surfactant is administered using a thin catheter which is inserted into the trachea using direct laryngoscopy, whilst the infant is supported by NIV. Such delivery avoids tracheal intubation, thus avoiding the associated risk of lung injury and associated risk of developing BPD [16].

Whilst LISA has now widely been adopted, it involves direct laryngoscopy. Therefore, alternative methods which negate the use of direct laryngoscopy have been explored. Nebulised exogeneous surfactant administration has been reported as being as effective as bolus intratracheal instillation in improving oxygenation in surfactant deficient animals [44]. However, trials in preterm infants to date have not demonstrated significant efficacy for improving short- or long-term outcomes, including the development of BPD [45].

The ongoing SURFSUP trial (*Surfactant administration by supraglottic airway*; ANZCTR trial ID ACTRN12620001184965) is an international, randomised controlled trial studying the safety and efficacy of early administration of surfactant via a supraglottic airway compared with administration via LISA/MIST in preterm infants < 1250 g to prevent development of BPD. Supraglottic airways are increasingly used in neonatal resuscitation and are a safe, reliable method for providing a temporary secure airway. The results of the SURFSUP study could potentially introduce supraglottic airways as the preferred method for exogenous surfactant administration in non-ventilated patients, altogether avoiding the need for direct laryngoscopy.

Corticosteroids

Pulmonary inflammation is an important contributing factor to the development of BPD; therefore, corticosteroids have been used with the aim to suppress the pulmonary inflammatory response. The PREMILOC study (*Early low-dose hydrocortisone to improve survival without BPD in extremely preterm infants)* was a large multi-centre, randomised, placebo-controlled trial conducted in France, assessing the effect of early low dose hydrocortisone on rates of survival without development of BPD in infants born between 24 + 0 and 27 + 6 weeks' gestation [17]. Results showed significant increase in survival without development of BPD in the treated group when compared with the placebo group, without increased severe adverse outcomes including gastrointestinal perforation.

Both later use of hydrocortisone and early use of dexamethasone are not recommended, whilst later use of dexamethasone may be beneficial [10, 19, 46].

Alternative delivery of glucocorticoids has also been investigated. The effect of early inhaled budesonide on BPD in extremely preterm infants was studied in the NEUROSIS trial (*The neonatal European study of inhaled steroids, 2015*), a large international, randomised trial that recruited 863 extremely preterm-born infants [20]. Trial participants received either budesonide or placebo (hydrofluoroalkane propellant) administered with a metered-dose inhaler via a spacer connected to the ventilator circuit. Treatment was started within 24 h of age and continued until the patients reached 32 weeks' gestation or no longer required positive pressure respiratory support and supplemental oxygen. A borderline reduction in the composite outcome of death or development of BPD at 36 weeks' gestation was noted in the budesonide group when compared to the placebo group (95% CI 0.75–1.0, $p = 0.05$). However, inhaled budesonide was associated with increased mortality, which was unexplained. A Cochrane review noted no significant effect on the incidence of BPD, but, equally, did not identify increased mortality, for inhaled budesonide in VLBW infants commenced within the first 2 weeks of life [47]. Follow up of infants recruited to the NEUROSIS trial did not find differences for neurodevelopment, hospital readmission rates or use of pulmonary medications at 18–22 months of age, despite the decreased rates of BPD at 36 weeks' gestation [48].

An initial pilot study demonstrated feasibility, potential benefits and safety of intratracheal administration of budesonide combined with exogenous surfactant when compared with exogenous surfactant alone in ventilated very low birthweight infants with severe RDS [49]. Further larger trials have since been undertaken. The recently published PLUSS (*Preventing Lung disease Using Surfactant and Steroid*) trial was an international, double-blind, randomised controlled trial which recruited 1059 extremely preterm-born infants who were mechanically ventilated or received NIV and a clinical decision had been made to treat with exogenous surfactant within the first 48 h of life [21]. Infants were randomised to receive intratracheal budesonide (0.25 mg/kg) mixed with exogenous surfactant or to receive exogenous surfactant only. The primary outcome of survival without BPD assessed at 36 weeks corrected gestational age was no different between the two groups (adjusted risk difference, 2.7% [95% CI, −2.1% to 7.4%]).

Other interventions

Caffeine

A common condition in preterm-born infants which might necessitate intubation and mechanical ventilation is apnoea of prematurity. Caffeine is the standard treatment for this condition. Although the mechanism of action for caffeine is not fully understood, it is successfully used in combination with NIV to reduce the need for invasive ventilation [50]. The Caffeine for Apnoea of Prematurity (CAP) trial [22] was an international multi-centre, randomised, placebo-controlled trial which demonstrated beneficial effects of caffeine on infants with a birth weight of 500-1250 g. Short-term benefits included shorter duration of mechanical ventilation,

positive airway pressure and supplemental oxygen. Greater benefits were seen in infants who commenced their caffeine early (<3 days of age). Long term benefits of caffeine use during the first 10 days of life included decreased risk of death and survival without neurodevelopmental disability at a corrected age of 18–21 months, together with reduced rates of developing BPD [51, 52]. Early use of caffeine has become established in the management of extremely preterm born infants [52].

Azithromycin

Data from several meta-analyses have shown that pulmonary colonisation with *Ureaplasma* spp. at birth is associated with an increased subsequent risk of development of BPD in preterm-born infants [53]. Due to their antibiotic properties against *Ureaplasma* spp. and anti-inflammatory activities with particular potency in the lungs, the efficacy of macrolide antibiotics in preventing the development of BPD has been assessed in multiple randomised controlled trials and systematic reviews although previous studies were largely single centre based thus lacking adequate statistical power. The recently published AZTEC trial (*Azithromycin therapy for prevention of chronic lung disease of prematurity*) was an adequately powered, multicentre, double-blinded, randomised placebo-controlled trial which assessed the effect of an early (commencing within the first 72 h of life) 10-day course of azithromycin on survival without development of BPD [23]. 796 infants born<30 weeks' gestation, who received at least 2 h of NIV or invasive ventilation within the first 72 h of life, were included. The results of this study showed no difference between the intervention and placebo groups for the composite outcome of survival without development of moderate/severe BPD at 36 weeks' gestation nor for rates of BPD, death, and number of days of respiratory support, therefore, did not provide evidence to support the use of early azithromycin in early life.

Prevention of respiratory syncytial virus (RSV) infection

Immunisation schedules are comprehensive in most countries but infection with RSV is an important cause of hospitalisation in infants, especially those with established BPD. Since 1998, palivizumab has been used as RSV prophylaxis in infants with BPD and has significantly reduced RSV hospitalisation in these patients. This humanised mouse immunoglobulin monoclonal antibody is administered monthly during the winter period via intramuscular injection [27]. Recently, both maternal vaccination against RSV (from 28 to 32 weeks' gestation of pregnancy) and nirsevimab, a monoclonal antibody with extended half-life administered as a single intramuscular injection before the RSV season have been introduced in many countries. Nirsevimab has shown to reduce lower respiratory tract infections and hospitalisation due to RSV in healthy preterm born (≥29 weeks) and term infants throughout the RSV season [28, 29]. In addition, it is important to follow the comprehensive national immunisation schedules.

Follow-up and later management of patients with BPD

Guidelines for follow-up

Once discharged from the neonatal unit there is significant variation in the follow-up that is provided for infants with established BPD. Whilst domiciliary oxygen programs excel in many high-income countries, at least for the first year or two of life, follow up of BPD graduates discharged home breathing air is very variable, despite it being well established that interdisciplinary follow up is associated with better neurodevelopmental outcomes and less rehospitalisation [54]. However, clear guidance for optimal follow up is currently lacking. Both the European Respiratory Society (ERS) [55] and the American Thoracic Society (ATS) [56] have published guidelines for the outpatient management of established BPD, although these were based largely on expert opinion due to the severe lack of evidence-based studies. Whilst the ERS guideline recommends monitoring with lung function, the ATS guideline does not comment on this. On the other hand, the ATS guideline recommends polysomnography, video fluoroscopic swallow study and airway endoscopy in specific preterm-born patient groups, which were not addressed by the ERS guideline. Both guidelines recommend imaging for subgroups only. Regarding treatment options, there is more consistency with both the European and American guidelines not recommending the routine use of bronchodilators nor inhaled corticosteroids but suggesting a trial of inhaler treatment with monitoring of the effects in symptomatic patients. They both advise against the use of diuretics and to wean these off on any patient discharged on these drugs. The ERS guideline suggests using a 90–95% saturation target when discharged on supplemental oxygen, individual advice regarding daycare attendance and highlights in the text that exposure to smoking should be discouraged. For a summary of both guidelines see Table 2.

Although no single diagnostic test or medication is indicated for every patient with BPD, it is important that standardised multidisciplinary follow-up is provided from discharge from the neonatal unit, throughout childhood and into adulthood. Appropriate treatment of lung function deficits and respiratory symptoms is imperative as those with

Table 2 Summary of ERS [55] and ATS [56] guidelines on outpatient management of children with BPD

	ERS 2020	ATS 2021
Investigations		
Imaging	Subgroup only	Subgroup only
Lung function	Recommended	
Polysomnography		Subgroup
Video fluoroscopic swallow study		Subgroup
Airway endoscopy		If unexplained symptoms
Management		
Bronchodilators	Optional for subgroup	Trial in subgroup
Inhaled corticosteroids	Trial in subgroup	Trial in subgroup
Diuretics	Natural weaning	Discontinuation in a judicious manner
Supplemental oxygen	Saturation target 90–95%	
Daycare attendance	Individual advice	

Table 3 Spirometry phenotypes in PLD [59]

Phenotype	FEV_1	FEV_1/FVC ratio	Bronchodilator response
POLD—reversible	<LLN	<LLN	≥10%
POLD—fixed	<LLN	<LLN	<10%
pPRISm	<LLN	≥LLN	
pDysanapsis	≥LLN	<LLN	

FEV_1 forced expiratory volume in one second, *FVC* forced vital capacity, *LLN* lower limit of normal, *POLD* prematurity-associated obstructive lung disease, *pPRISm* prematurity-associated preserved ratio of impaired spirometry, *pDysanapsis* prematurity-associated dysanapsis of prematurity

BPD are at significant risk for early onset chronic obstructive pulmonary disease (COPD) in adult life [55–57].

Prematurity-associated lung disease (PLD)

Increasingly it is recognised that risk factors other than BPD, including intrauterine growth restriction and gestational age, significantly contribute to development of lung disease in childhood and beyond. To encompass additional risk factors to BPD, the concept of prematurity-associated lung disease or PLD has been developed [58]. To extend this concept, several specific phenotypes of PLD were recently reported by Cousins et al. [59]. They reported spirometry results and early/current life factors of 739 children (544 born preterm, 108 of these with BPD, and 195 born at term) and described their phenotypes based on forced expiratory volume in one second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio: prematurity-associated obstructive lung disease which is bronchodilator responsive (POLD-reversible), prematurity-associated obstructive lung disease which is not bronchodilator responsive (POLD-fixed), prematurity-associated preserved ratio of impaired spirometry (pPRISm), and prematurity-associated dysanapsis (pDysanapsis). See Table 3 for lung function parameters for each phenotype. It is likely that each phenotype has specific underlying mechanisms e.g. the POLD group has increased fractional expired nitric oxide (FE_{NO}) but the other phenotypes do not, thus will permit development of specific targeted interventions.

Treatment of PLD

Evidence regarding treatment of children with PLD remains limited. The preterm inhaled corticosteroid intervention (PICSI) trial randomised 170 preterm born (≤32 weeks' gestation at birth) children aged 6 to 12 years to either inhaled corticosteroid (fluticasone propionate) or placebo for 12 weeks. The study showed modest improvement for FEV_1 (0.30 z scores, equalling to a 4% change) and FEV_1/FVC ratio in the treatment group compared to placebo [30]. The respiratory health outcomes in neonates (RHiNO) study randomised 53 preterm-born children (≤34 weeks' gestation at birth) at 7 to 12 years of age to a 12-week treatment period with inhaled corticosteroid alone (fluticasone propionate), inhaled corticosteroid (fluticasone propionate) with long-acting $beta_2$ receptor agonist (salmeterol) or placebo. In the inhaled corticosteroid group, they reported a non-significant 7.7% improvement in FEV_1 when compared with the placebo group. However, the improvement was 14.1% for FEV_1 in the combined inhaled corticosteroid and long acting $beta_2$ adrenoreceptor agonist group [31]. The effect of monotherapy with long-acting $beta_2$ agonist has not been evaluated due to safety concerns in both adults and children [60]. Interestingly, both trials reported a reduction in FE_{NO} values in the treatment arms including corticosteroids, suggesting that inflammation may play a role in a subgroup of children with PLD [30, 31, 60]. The RHiNO trial studied exercise capacity but did not show an improvement despite a reduced post-exercise bronchodilator response in the treatment groups [31]. Until additional evidence becomes available, it would be reasonable to trial combined inhaled corticosteroid and long acting $beta_2$ adrenoceptor agonist for 12 weeks then to assess if any improvement has occurred.

Future management options for patients with BPD

Evaluation of current strategies

At present there is no specific individual treatment available for patients with developing BPD or for established BPD, although many strategies, such as the use of NIV instead of invasive ventilation, to prevent or reduce iatrogenic trauma to immature lungs resulting in BPD are used in clinical practice. The use of NIV has become the standard, but it is good practice to evaluate the effectiveness of these interventions in reducing rates of BPD. In a retrospective data analysis of 2487 extremely low birth weight infants, Taha et al. [61]reported that BPD or death was significantly higher in the infants who had been managed on only HFNC when compared with those managed only on CPAP. Rates were also higher in those receiving HFNC with or without CPAP, when compared to the CPAP only group. Longer period on respiratory support, more need for supplemental oxygen, more postnatal corticosteroid use, longer time to reach full oral feeds and longer hospitalisation were noted in those infants supported with HFNC or HFNC and CPAP when compared to those managed only on CPAP [61]. This association between the use of HFNC and greater likelihood of developing BPD was confirmed more recently in the retrospective cross-sectional study by Legge et al. who included 3258 infants born between 24 and 28 weeks' gestation [3]. HFNC is a form of NIV and, therefore, aimed to prevent invasive ventilation and its associated risk of BPD, but it may not be optimal for the most immature preterm-born infants.

CPAP could promote lung growth via mechanical stretch, therefore, Lam et al. [32] hypothesised that an extended period on CPAP would result in larger lung volumes, presumably also improved lung growth. Fifty infants born at≤32 weeks' gestation who were stable and ready for weaning from CPAP were randomised to either an additional two weeks on CPAP (extended CPAP group) or to discontinuation of their CPAP (usual care group). They noted that the extended CPAP group had significantly larger functional residual capacity at the end of the additional two weeks on CPAP, and it remained higher at discharge when compared to the usual care group [32]. The same group performed a similar randomised controlled trial assessing the effect of two weeks extended CPAP versus usual care on lung growth, but with longer follow up [33]. Longer term assessments have shown improved alveolar volume, lung diffusion capacity and forced expiratory flow were significantly increased at 6 months corrected age in the extended CPAP group when compared to those who did not receive the additional two weeks of CPAP. These encouraging data suggest that extended use of CPAP could be a strategy to support lung growth and future lung function, but further studies are needed especially to assess if such an intervention increases lung volume alone or in parallel, as desired, improves lung growth including alveolar development.

Emerging treatments

There are several emerging treatment options targeting the underlying mechanisms underpinning the development of BPD on the horizon, all at different stages of development. Some are described below.

Recombinant human interleukin 1 receptor antagonist

Interleukin 1 (IL-1) is a potent pro-inflammatory cytokine that binds to its receptor to mediate the inflammatory processes leading to BPD. By binding to the IL-1 receptor, interleukin 1 receptor antagonist (IL-1RA) competitively inhibits the pro-inflammatory actions of IL-1. Anakinra, recombinant human IL-1RA, has been studied in animal models. It has been safely used in humans, including in infants and children, for other inflammatory pathologies. Therefore, it has the potential for treating pulmonary inflammation associated with the development of BPD. A phase I/IIa safety and feasibility dose-escalation clinical trial recruiting 24 extremely preterm infants to receive anakinra intravenously over the first 21 days of life is planned (clinicaltrials.gov NCT05280340) [34].

Recombinant human insulin-like growth factor 1/ recombinant insulin-like growth factor binding protein 3

Insulin-like growth factor 1 (IGF-1) is an important foetal growth factor, with effects on various organs. Until 30 weeks of pregnancy, IGF-1 is largely provided through the placenta, explaining the low levels of IGF-1 measured in extreme preterm-born infants. From 30 weeks gestation onwards the foetal liver produces IGF-1 in response to stimulation by growth hormone. However, there is a significant time lag before extremely preterm-born infants start producing IGF-1. IGF-1 promotes alveologenesis and IGF-1 reduces lung fibrosis by inhibiting transforming growth factor beta. It has been reported that plasma IGF-1 levels are lower in infants who develop BPD than in those who do not [35].

It is therefore hypothesised that IGF-1 replacement therapy may promote lung growth after preterm birth. Animal models of BPD that have been administered mecasermin rinfabate, a combination of recombinant human IGF-1 (rhIGF-1) with recombinant insulin-like growth factor binding protein 3 (rhIGFBP-3), have shown improved lung structure and function [35]. In a phase IIa clinical trial assessing the safety and

efficacy of rhIGF-1/rhIGFBP-3 for the prevention of retinopathy of prematurity (ROP) in infants born before 28 weeks' gestation, a significant decrease in severe BPD was noted but severity of ROP was not reduced [36]. To further investigate the efficacy and safety of rhIGF-1/rhIGFBP-3 in preventing BPD in extremely premature infants, a phase IIb trial is currently ongoing (clinicaltrials.gov NCT03253263).

Stem cell therapy

Stem cell-based therapy has emerged as a potential treatment to prevent the development of BPD. Stem cells are undifferentiated cells that can differentiate into many different cell types. They are characterised by their ability for self-renewal, organogenesis, and for maintenance, repair and regeneration of tissues [37]. Mesenchymal stem cells (MSCs), which are derived from the mesoderm, can modulate the immune response, do not induce cell rejection, and are relatively easily isolated from various tissues including bone marrow, peripheral blood, placenta, and umbilical cord. MSCs isolated from the umbilical cord have more potent anti-inflammatory and immunomodulatory properties compared to these harvested from other tissues [37, 38].

MSCs have been identified as a potential treatment for developing BPD [38, 62]. MSC therapy reduces pulmonary fibrosis and oedema, improves lung function and reduces lung inflammation in animal models of BPD. Animal studies have also shown that MSC therapy has better results when umbilical cord blood derived MSCs are administered early, in high dose and directly into the trachea [38, 39].

Phase I human clinical trials have shown that MSC treatment is both safe and feasible in preterm-born infants. Phase II clinical trials have been conducted to assess the effectiveness of MSC therapy in preterm-born infants [37–39]. A double-blind randomised, placebo-controlled trial involving 66 infants born at 23 to 28 weeks of gestation receiving MSCs or placebo did not show significant reduction in death or severe/moderate BPD with MSC administration. However, in infants born at 23 and 24 weeks' gestation, they reported significant reduction in severe BPD in the treated group when compared with the placebo group [39]. Further studies to establish optimal dosing and timing of treatment, assess short- and long-term safety as well as efficacy in adequately powered studies are required before this treatment becomes established in clinical practice.

Conclusion

Management of BPD remains challenging because of its multifactorial aetiology. No specific treatment for BPD is currently available. Strategies to prevent iatrogenic pulmonary injury, such as early use of NIV with less invasive administration of surfactant, have become embedded in clinical practice, with further refinements planned in clinical trials. Emerging treatments are now targeting the underlying mechanisms associated with the development of BPD with several showing promise.

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References

1. Northway WH, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease bronchopulmonary dysplasiNorthway WH, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease bronchopulmonary dysplasia. N Engl J Med. 1967;276(7):357–68. https://doi.org/10.1056/NEJM196702162760701.
2. Jensen EA, Dysart K, Gantz MG, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants an evidence-based approach. Am J Respir Crit Care Med. 2019;200:751–9.
3. Legge N, Popat H, Fitzgerald D. Improved survival at the cost of more chronic lung disease? Current management and outcomes in extremely preterm infants born in New South Wales and the Australian Capital Territory: 2010–2020. World J Pediatr. 2024;20:230–8.

4. Bancalari EJD. Bronchopulmonary dysplasia: 50 years after the original description. Neonatology. 2019;4:384–91.
5. Jensen EA. Prevention of bronchopulmonary dysplasia: a summary of evidence-based strategies. NeoReviews. 2019;20(4):e189-201.
6. Morrow LA, Wagner BD, Ingram DA, Poindexter BB, Schibler K, Cotten CM, Dagle J, Sontag MK, Mourani PM, Abman SH. Antenatal determinants of bronchopulmonary dysplasia and late respiratory disease in preterm infants. Am J Respir Crit Care Med. 2017;196:364–74.
7. Nuthakki S, Ahmad K, Johnson G, Cuevas Guaman M. Bronchopulmonary dysplasia: ongoing challenges from definitions to clinical care. J Clin Med. 2023. https://doi.org/10.3390/jcm12113864.
8. Gilfillan M, Bhandari V. Pulmonary phenotypes of bronchopulmonary dysplasia in the preterm infant. Semin Perinatol. 2023;47(6):151810. https://doi.org/10.1016/j.semperi.2023.151810
9. Wu KY, Jensen EA, White AM, Wang Y, Biko DM, Nilan K, Fraga MV, Mercer-Rosa L, Zhang H, Kirpalani H. Characterization of disease phenotype in very preterm infants with severe ronchopulmonary dysplasia. Am J Respir Crit Care Med. 2020;201:1398–406.
10. Doyle L, Cheong J, Ehrenkranz R, Halliday H (2017) Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants (Review). Cochrane Database Syst Rev. 2017. https://doi.org/10.1002/14651858.CD001145.pub4.
11. Stewart A, Brion LP. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Cochrane Database Syst Rev. 2011;2011(9):CD001453. https://doi.org/10.1002/14651858.cd001453.pub2.
12. Ding Y, Chen Z, Lu Y. Vitamin A supplementation prevents the bronchopulmonary dysplasia in premature infants. MedicDing Y, Chen Z, Lu Y. Vitamin A supplementation prevents the bronchopulmonary dysplasia in premature infants. Medicine. 2021;100(3):e23101. https://doi.org/10.1097/MD.0000000000023101.
13. Rakshasbhuvankar AA, Simmer K, Patole SK, Stoecklin B, Nathan EA, Clarke MW, Pillow JJ. Enteral vitamin A for reducing severity of bronchopulmonary dysplasia: a randomized trial. Pediatrics. 2021;147(1):e2020009985. https://doi.org/10.1542/peds.2020-009985.
14. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358:700–8.
15. Klingenberg C, Wheeler KI, Mccallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in neonates. Cochrane Database Syst Rev. 2017. https://doi.org/10.1002/14651858.CD003666.pub4.
16. Göpel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet. 2011;378:1627–61.
17. Baud O, Maury L, Lebail F, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet. 2016;387:1827–36.
18. Watterberg KL, Walsh MC, Li L, Chawla S, D'Angio CT, Goldberg RN, Hintz SR, Epi MS. Hydrocortisone to improve survival without bronchopulmonary dysplasia. New Engl J Med. 2022;12:1121–31.
19. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants (Review). Cochrane Database of Syst Rev. 2017;10(10):CD001145. https://doi.org/10.1002/14651858.CD001145.pub4.
20. Bassler D, Plavka R, Shinwell ES, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med. 2015;373:1497–506.
21. Manley BJ, Kamlin COF, Donath SM, et al. Intratracheal budesonide mixed with surfactant for extremely preterm infants: the PLUSS randomized clinical trial. JAMA. 2024;332(22):1889–99. https://doi.org/10.1001/jama.2024.17380.
22. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354 (20):2112-2121.
23. Lowe J, Gillespie D, Aboklaish A, et al. Azithromycin therapy for prevention of chronic lung disease of prematurity (AZTEC): a multicentre, double-blind, randomised, placebo-controlled trial. Lancet Respir Med. 2024;12:608–18.
24. Potsiurko S, Dobryanskyy D, Sekretar L, Salabay Z. Randomized noninferiority trial of expectant management versus early treatment of patent ductus arteriosus in preterm infants. Am J Perinatol. 2024;6:730–8.
25. Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2017. https://doi.org/10.1002/14651858.CD000509.pub5.
26. O'Brien K, Robson K, Bracht M, et al. Effectiveness of family integrated care in neonatal intensive care units on infant and parent outcomes: a multicentre, multinational, cluster-randomised controlled trial. Lancet Child Adolesc Health. 2018;2:245–54.
27. American Academy of Pediatrics. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134(2):e620–38. https://doi.org/10.1542/peds.2014-1666.
28. Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med. 2020;383:415–25.
29. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med. 2022;386:837–46.
30. Urs RC, Evans DJ, Bradshaw TK, Gibbons JTD, Smith EF, Foong RE, Wilson AC, Simpson SJ. Inhaled corticosteroids to improve lung function in children (aged 6–12 years) who were born very preterm (PICSI): a randomised, double-blind, placebo-controlled trial. Lancet Child Adolesc Health. 2023;7:567–76.
31. Goulden N, Cousins M, Hart K, Jenkins A, Willetts G, Yendle L, Doull I, Williams EM, Hoare Z, Kotecha S. Inhaled corticosteroids alone and in combination with long-acting β2 receptor agonists to treat reduced lung function in preterm-born children: a randomized clinical trial. JAMA Pediatr. 2022;176:133–41.
32. Lam R, Schilling D, Scottoline B, Platteau A, Niederhausen M, Lund KC, Schelonka RL, MacDonald KD, McEvoy CT. The effect of extended continuous positive airway pressure on changes in lung volumes in stable premature infants: a randomized controlled trial. J Pediatr. 2020;217:66-72.e1.
33. McEvoy CT, MacDonald KD, Go MA, et al. Extended continuous positive airway pressure in preterm infants increases lung growth at 6 months. Am J Respir Crit Care Med. 2025;211:610–8.
34. Green EA, Metz D, Galinsky R, et al. Anakinra Pilot– a clinical trial to demonstrate safety, feasibility and pharmacokinetics of interleukin 1 receptor antagonist in preterm infants. Front Immunol. 2022;27:13:1022104. https://doi.org/10.3389/fimmu.2022.1022104.
35. Kramer BW, Abman S, Daly M, Jobe AH, Niklas V. Insulin-like growth factor-1 replacement therapy after extremely premature birth: an opportunity to optimize lifelong lung health by preserving the natural sequence of lung development. Paediatr Respir Rev. 2023;48:24–9.
36. Ley D, Hallberg B, Hansen-Pupp I, et al. rhIGF-1/rhIGFBP-3 in preterm infants: a phase 2 randomized controlled trial. J Pediatr. 2019;206:56-65.e8.

37. Tang E, Zaidi M, Lim WH, Govindasamy V, Then KY, Then KL, Das AK, Cheong SK. Headway and the remaining hurdles of mesenchymal stem cells therapy for bronchopulmonary dysplasia. Clin Respir J. 2022;16:629–45.
38. Marega M, El-Merhie N, Gökyildirim MY, Orth V, Bellusci S, Chao CM. Stem/progenitor cells and related therapy in bronchopulmonary dysplasia. Int J Mol Sci. 2023;24(13):11229. https://doi.org/10.3390/ijms241311229
39. Ahn SY, Chang YS, Lee MH, Sung SI, Lee BS, Kim KS, Kim AR, Park WS. Stem cells for bronchopulmonary dysplasia in preterm infants: a randomized controlled phase II trial. Stem Cells Transl Med. 2021;10:1129–37.
40. Lemyre B, Laughon M, Bose C, Pg D. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants (Review). Cochrane Database Syst Rev. 2016;12(12):CD005384. https://doi.org/10.1002/14651858.CD005384.pub2.
41. Roberts CT, Hodgson KA. Nasal high flow treatment in preterm infants. Matern Health NeonatolRoberts CT, Hodgson KA. Nasal high flow treatment in preterm infants. Matern Health Neonatol Perinatol. 2017;3:15 https://doi.org/10.1186/s40748-017-0056-y.
42. Roberts CT, Owen LS, Manley BJ, et al. Nasal high flow therapy for primary respiratory support in preterm infants. N Engl J Med. 2017;375:1142–51.
43. Seger N, Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome (Review). Cochrane Database Syst Rev. 2009. https://doi.org/10.1002/14651858.CD007836.
44. Wagner MH. Endotracheal surfactant atomization: an alternative to bolus instillation?. Crit Care Med. 2000;28(7):2540–4.
45. Nancarrow L. Neonatal respiratory outcomes following nebulised surfactant administration: a literature Nancarrow L. Neonatal respiratory outcomes following nebulised surfactant administration: a literature review. J Neonatal Nurs. 2025;31(2):101618.
46. Watterberg KL, Walsh MC, Li L, et al. Hydrocortisone to improve survival without bronchopulmonary dysplasia. N Engl J Med. 2022;386:1121–31.
47. Shah S, Ohlsson A, Halliday H, Shah V. Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants (Review). Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD002057.pub4.www.cochranelibrary.com.
48. Bassler D, Shinwell ES, Hallman M, et al. Long-term effects of inhaled budesonide for bronchopulmonary dysplasia. N Engl J Med. 2018;378:148–57.
49. Yeh TF, Lin HC, Chang CH, Wu TS, Su BH, Li TC, Pyati S. Early intratracheal instillation of budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants: a pilot study. Pediatrics. 2008;121:e1310–8.
50. Vliegenthart R, Miedema M, Hutten GJ, Van Kaam AH, Onland W. High versus standard dose caffeine for apnoea: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2018;103:F523–9.
51. Davis PG, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, Sinha S, Tin W. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. J Pediatr. 2010;156(3):382–7. https://doi.org/10.1016/j.jpeds.2009.09.069.
52. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med. 2007;19:1893–902.
53. Lowe J, Watkins WJ, Edwards MO, Spiller OB, Jacqz-Aigrain E, Kotecha SJ, Kotecha S. Association between pulmonary ureaplasma colonization and bronchopulmonary dysplasia in preterm infants: updated systematic review and meta-analysis. Pediatr Infect Dis J. 2014;33:697–702.
54. Shepherd EG, Knupp AM, Welty SE, Susey KM, Gardner WP, Gest AL. An interdisciplinary bronchopulmonary dysplasia program is associated with improved neurodevelopmental outcomes and fewer rehospitalizations. J Perinatol. 2012;32:33–8.
55. Duijts L, van Meel ER, Moschino L, et al. European respiratory society guideline on long-term management of children with bronchopulmonary dysplasia. Eur Respir J. 2020. https://doi.org/10.1183/13993003.00788-2019.
56. Cristea AI, Baker CD, Allen J, et al. Outpatient respiratory management of infants, children, and adolescents with postprematurity respiratory disease an official American thoracic society clinical practice guideline. Am J Respir Crit Care Med. 2021;204:E115–33.
57. Gibbons JTD, Course CW, Evans EE, Kotecha S, Kotecha SJ, Simpson SJ. Increasing airway obstruction through life following bronchopulmonary dysplasia: a meta-analysis. ERJ Open Res. 2023. https://doi.org/10.1183/23120541.00046-2023.
58. Kotecha S, Doull I, Wild J, Bush A. Prematurtiy-associated lung disease: looking beyond bronchopulmonary dysplasia. Lancet Respir Med. 2022. https://doi.org/10.1183/13993003.01766-2021.
59. Cousins M, Hart K, Kotecha SJ, Henderson AJ, Watkins WJ, Bush A, Kotecha S. Characterising airway obstructive, dysanaptic and PRISm phenotypes of prematurity-associated lung disease. Paediatr Lung Dis. https://doi.org/10.1136/thoraxjnl-2022-219301.
60. Course CW, Kotecha SJ, Kotecha S. Evolving treatment for prematurity-associated lung disease. Transl Pediatr. 2024;13(1):1–5. https://doi.org/10.21037/tp-23-505.
61. Taha DK, Kornhauser M, Greenspan JS, Dysart KC, Aghai ZH. High flow nasal cannula use is associated with increased morbidity and length of hospitalization in extremely low birth weight infants. J Pediatr. 2016;173:50-55.e1.
62. Popova AP, Bozyk PD, Bentley JK, Linn MJ, Goldsmith AM, Schumacher RE, Weiner GM, FilbrunPopova AP, Bozyk PD, Bentley JK, Linn MJ, Goldsmith AM, Schumacher RE, Weiner GM, Filbrun AG, Hershenson MB. Isolation of tracheal aspirate mesenchymal stromal cells predicts bronchopulmonary dysplasia. Pediatrics. 2010;126(5):e1127–33. https://doi.org/10.1542/peds.2009-3445.