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Bronchopulmonary dysplasia

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A.H.J. consults occasionally for Chiesi Farmaceutici about BPD and surfactant. S.H.A. has served as a consultant for Takeda Pharmaceuticals. R.H.S. is a consultant for Takeda Pharmaceutical Company and for Actelion Pharmaceutical Ltd. The remaining authors declare no competing interests.

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Abstract

In the absence of effective interventions to prevent preterm births, improved survival of infants who are born at the biological limits of viability has relied on advances in perinatal care over the past 50 years. Except for extremely preterm infants with suboptimal perinatal care or major antenatal events that cause severe respiratory failure at birth, most extremely preterm infants now survive, but they often develop chronic lung dysfunction termed bronchopulmonary dysplasia (BPD; also known as chronic lung disease). Despite major efforts to minimize injurious but often life-saving postnatal interventions (such as oxygen, mechanical ventilation and corticosteroids), BPD remains the most frequent complication of extreme preterm birth. BPD is now recognized as the result of an aberrant reparative response to both antenatal injury and repetitive postnatal injury to the developing lungs. Consequently, lung development is markedly impaired, which leads to persistent airway and pulmonary vascular disease that can affect adult lung function. Greater insights into the pathobiology of BPD will provide a better understanding of disease mechanisms and lung repair and regeneration, which will enable the discovery of novel therapeutic targets. In parallel, clinical and translational studies that improve the classification of disease phenotypes and enable early identification of at-risk preterm infants should improve trial design and individualized care to enhance outcomes in preterm infants.

In 1967, Northway, Rosen and Porter described a new lung disease in preterm infants who had hyaline membrane disease (now known as respiratory distress syndrome (RDS; see BOX 1 for a description of neonatal terms), which at that time was a highly lethal condition that resulted from using mechanical ventilation without positive end-expiratory pressure and high levels of supplemental oxygen in an attempt to save these infants¹. In that era, survival was rare despite a relatively mild degree of prematurity (mean gestational age, 34 weeks), but many preterm infants had a slow and prolonged recovery from airway and lung parenchymal injury. The authors termed this new syndrome bronchopulmonary dysplasia (BPD; also known as chronic lung disease) on the basis of airway histopathological features.

The characteristics of BPD have evolved over the past 50 years, as most preterm infants now survive with the use of antenatal corticosteroids, advanced neonatal care techniques, effective respiratory support devices and surfactant treatments². A current perspective regarding the initiation, progression and variable extent of lung repair of the most extremely preterm infants who are at highest risk of BPD³ is shown in FIG. 1. In the framework of the Developmental Origins of Adult Diseases concept, trans-generational and pre-conception factors interact with pregnancy exposures to modulate the risk of BPD, and gestational age at birth is the greatest single predictor of BPD. It is essential to recognize that no infant born very preterm is 'normal', because of many factors, including abnormalities of pregnancy that result in preterm birth, and the fact that health problems in a preterm newborn are more severe the earlier the birth⁴. The remarkable plasticity of the lung development programme to support very early gestational lung maturation is crucial for the survival of extremely-low-birth-weight (ELBW; <1,000 g) infants. However, the structurally very immature lungs of these infants are easily injured by the routine care required to ensure their survival. Remarkably, lung development can proceed after preterm birth despite ongoing lung injury from supplemental oxygen and mechanical ventilation and/or lung stretch. BPD is the clinical expression of this mixture of lung developmental plasticity, injury and repair that

ultimately results in a remarkable ability of the lungs of surviving infants to remodel until perhaps 20 years of age⁵.

In this Primer, we discuss the different definitions of BPD, ongoing controversy about the optimal time point and method for determining whether BPD exists, and how this variability might affect assessment of disease prevalence. Furthermore, we review advances in neonatal care, such as non-invasive ventilation and alternative strategies for surfactant administration, which are improving outcomes in preterm infants with BPD. Last, we examine various key issues that require further research to improve our understanding of disease pathobiology and enable development of better interventions that may enhance short-term and long-term outcomes.

Epidemiology

Prevalence

Premature birth (<37 weeks gestational age) is common and affects 6–14% of pregnancies, depending on the country^{6,7}. Generally, premature infants are classified on the basis of gestational age (extremely preterm infants or extremely low gestational age newborns (ELGANs) are <28 weeks gestation; very preterm infants are 28 to <32 weeks gestation, moderate preterm infants are 32 to <34 weeks, and late preterm infants are 34 to <37 weeks) or birth weight (ELBW infants are <1,000 g, very-low-birth-weight (VLBW) infants are <1,500 g, and low-birth-weight (LBW) infants are <2,500 g). BPD incidence increases as gestational age and weight at birth decreases. BPD remains the most common complication associated with prematurity and is increasing in prevalence, most likely due to the increased survival of ELGANs^{8,9}. Almost 50,000 ELGANs are born each year in the USA, and ~35% (18,000) of these children develop BPD. The incidence of BPD varies widely between centres (~20–75%), even after adjusting for potential risk factors¹⁰. Data from major cohort studies (such as ELGAN, Canadian Neonatal Network, Korean Neonatal Network, Vermont–Oxford Network and Swiss Neonatal Network, as well as studies in China, Taiwan and India) demonstrate a BPD prevalence of 11–50%, a wide range that is due to differences in gestational age or birth weight criteria for a BPD diagnosis^{11–17}.

Marked variations in neonatal outcomes between countries have been identified in a large, multicentre, multinational cohort of 58,004 very preterm and VLBW infants from Australia, New Zealand, Canada, Israel, Japan, Spain, Sweden, Switzerland and the UK¹⁸. For example, Japan had the lowest mortality but the highest rate of treatment for retinopathy of prematurity, whereas Spain had the highest mortality but a comparatively lower prevalence of BPD. These variations could be the result of differences in population coverage, organization of perinatal health-care delivery, population characteristics, case definitions, ascertainment, data quality and reliability, and care processes, and highlight the need for international multicentre clinical trials and international benchmarking and quality improvement activities.

Risk factors

The strongest risk factors for BPD are prematurity and low birth weight^{19–25}. Almost 80% of infants who are born at 22–24 weeks of gestation are diagnosed with BPD²⁶, whereas only 20% of infants born at 28 weeks of gestation develop BPD. Among infants with BPD, 95% are VLBW²⁷. Other perinatal risk factors include intrauterine growth restriction (IUGR)¹³, male sex^{13,20,23} and, inconsistently, chorioamnionitis²⁸, race or ethnicity^{13,20,23}, and smoking^{29,30}. Genetic risk factors may also contribute to the development of BPD, as indicated by twin studies^{31,32}, and there is an ongoing search for genetic markers for BPD^{33–37}.

Early respiratory patterns of premature infants provide insight into risk factors for BPD. An early study suggested that peak inspiratory ventilator pressure and requirement for assisted ventilation on day 4 of life are early predictors of BPD³⁸. Subsequent studies found that three patterns of lung disease generally emerge in the first 2 weeks of life^{39–45} (FIG. 2). In the first pattern, infants have fairly minimal lung disease and progressively recover. In the second pattern, early persistent pulmonary deterioration (EPPD), substantial and prolonged respiratory support is required from birth. In the third pattern, an initial improvement in lung disease in the first week of life is followed by a respiratory decompensation termed pulmonary deterioration, which often requires mechanical ventilation and an increase in supplemental oxygen. Risk factors that may be associated with pulmonary deterioration include late surfactant deficiency⁴⁶, sepsis, increased levels of inflammatory proteins (such as RANTES)⁴⁷ and patent ductus arteriosus^{40,43}. Almost 50% of infants with pulmonary deterioration and almost 70% of infants with EPPD develop BPD⁴⁸.

The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network developed an online, publicly available risk estimator (<https://neonatal.rti.org/index.cfm>) that accurately estimates the risk of developing BPD by postnatal day⁴⁹. Investigators identified risk factors for BPD, and the competing outcome of death, among gestational age, birth weight, ethnicity and sex, ventilatory support (ranging from no support (breathing room air without positive airway pressure) to high frequency ventilation) and fraction of inspired oxygen (FiO₂), on postnatal days 1, 3, 7, 14, 21 and 28 in 3,636 infants born at 23–30 weeks of gestation. The BPD prediction tool is internally and externally validated. The models predict the correct level of BPD or the occurrence of death in >80% of cases and have the highest area under the curve (AUC) among current BPD risk predictors⁵⁰. This tool is used to provide counselling to families and to quantify risk for determining patient inclusion in early phase therapeutic trials. Interestingly, systemic inflammation occurs early in the neonatal period and precedes clinical symptoms in infants with BPD⁵¹. This finding suggests that a therapeutic window of opportunity exists during the early phase of BPD.

Mechanisms/pathophysiology

Lung development and surfactant

Normal lung development.—Respiration after birth is entirely dependent on the architecture of the peripheral lung saccules and alveoli. The close interface between alveolar

epithelial cells and endothelial cells of the pulmonary microvasculature enables efficient exchange of oxygen and carbon dioxide (FIG. 3). Lung formation begins between week 3 and week 6 of gestation. Subsets of endodermal cells from the anterior foregut form the initial tracheal and pulmonary lung buds that invade the splanchnic mesenchyme. Branching morphogenesis⁵² forms the conducting airways and peripheral acinar buds that will ultimately form the alveoli after birth (FIG. 4). Complex paracrine interactions among various mesenchymal cells, including pericytes, smooth muscle cells, endothelial cells and various types of fibroblasts, and respiratory epithelial cells and endothelial progenitor cells are involved in the formation of the pulmonary parenchyma^{53–55}. Acinar structures dilate later in gestation, creating the peripheral saccules (the primitive gas exchange portion of the lung) and alveoli that will accommodate postnatal adaptation to breathing. During morphogenesis, the lung is transformed from a solid gland-like tissue to an expanded open alveolar structure in which gas exchange can occur (FIG. 5). During the last trimester (28–40 weeks of gestation), peripheral saccules undergo a process of septation that further divides the airspaces, creating and increasing the number of alveoli and thereby increasing the surface area for gas exchange. Peripheral lung epithelial cells mature into alveolar type 1 (AT1) cells and AT2 cells, the latter producing pulmonary surfactant (FIG. 3). Thus, preterm infants at the edge of viability (22–23 weeks of gestation) begin ventilation at the canalicular–saccular stage of lung formation, well before morphogenesis and alveolar differentiation are completed.

Pulmonary surfactant.—Pulmonary surfactant is a complex mixture of phospholipids, primarily phosphatidylcholine, and the surfactant proteins SP-A, SP-B, SP-C and SP-D, which together define the physical structure, function and metabolism of surfactant in the alveolus (FIG. 3). Synthesis of surfactant lipids and proteins depends on the differentiation of AT2 cells, which occurs fairly late in gestation. Consequently, a lack of pulmonary surfactant as a result of incomplete differentiation of AT2 cells causes RDS in preterm infants⁵⁶. Assisted ventilation, continuous airway pressure and supplemental oxygen can initially support ventilation after birth. Furthermore, administration of exogenous pulmonary surfactant has greatly facilitated the transition to air breathing, decreasing the requirement for oxygen and assisted ventilation and thereby improving survival but secondarily increasing the number of infants at risk of BPD.

In conclusion, postnatal adaptation of the preterm lungs to breathing at birth is challenged by initial lung injury owing to surfactant deficiency, exposure to increased oxygen, mechanical ventilation, inadequate nutrition, infection and inflammation, which together provide considerable hurdles to normal pulmonary growth and repair and result in a loss of alveolar surface area (FIG. 5) that has lifelong consequences.

Pathophysiology of acute lung injury

BPD is a clinical syndrome of lung injury that disrupts alveolarization and microvascular development. The anatomical changes in BPD result in abnormal gas exchange and lung mechanics. However, of note, the pathological features of BPD are based on only a few reports that primarily describe necropsy specimens⁵⁷. In fact, most patients with BPD survive, and imaging studies reveal that they probably have a very heterogeneous pathology

throughout the lungs, including regions of decreased alveolarization, cystic emphysema, fibrosis and variable airway injury⁵⁸. This complex injury results primarily from damage to the very preterm lungs by multiple antenatal and postnatal exposures, each of which may disrupt specific developmental pathways and promote injury (FIG. 1).

An extensive review of publications over an 18 month period (January 2015 to June 2017) identified 60 genes in transgenic mouse models that result in altered mouse lung development with characteristics of BPD⁵⁹. Inflammation is the common pathway that leads to a BPD phenotype. Supplemental oxygen, positive pressure ventilation and postnatal sepsis, which all cause lung inflammation, are clinically associated with BPD. In animal models, supplemental oxygen alone or positive pressure ventilation alone cause a BPD phenotype (that is, decreased alveolarization and microvascular injury)⁶⁰. The most frequently used animal models are term mice or rats that are exposed to supplemental oxygen or preterm sheep or primates that are injured by excessive oxygen and/or ventilation or stretch⁶¹. Numerous studies have shown that blockers of inflammatory mediators, receptors and signalling pathways improve the BPD phenotype in mice, rats and rabbits⁵⁹.

Unfortunately, proinflammatory cascades are complex and redundant. Although inflammatory responses in preterm lungs may differ from those in term or adult lungs⁶², limited clinical attempts to block oxidants with antioxidants and to block inflammation with inflammatory modulators have been uniformly unsuccessful in treating BPD in infants^{63,64}, with the exception of postnatal corticosteroids. Corticosteroids decrease the incidence of BPD when given soon after birth and prevent the progression of lung injury to BPD when given in the first weeks of life⁶⁵. For example, the potent general anti-inflammatory drug dexamethasone can decrease BPD incidence in preterm infants, although not without complications. However, anti-inflammatory treatments that target specific inflammatory mediators have been ineffective to date⁶⁰.

A striking difference between animal models and very preterm infants who develop BPD is that infants are exposed multiple times to factors that alter lung development, such as preterm birth and its associated pathologies, pre-eclampsia, antenatal steroids, infection and/or inflammation, maternal smoking, antenatal and postnatal nutrition, genetic background, sex and ethnicity³⁰. Each of these factors changes the response of the preterm lungs to injury. Of note, the infants who are at highest risk of BPD are extremely premature — for example, an infant born at 24 weeks of gestation is born 4 months early (~65% of normal gestation length) and therefore has structurally under-developed lungs (FIG. 4) that are often able to support gas exchange but are easily injured. The progression of lung injury to BPD in infants is not the same as the progression that occurs in acute lung injury in adults, as the primary insults (supplemental oxygen and ventilation-mediated injury) in preterm infants can continuously injure the lungs, often for months, depending on the nature of respiratory support and related ventilator strategies (see below). Although these extremely preterm infants can frequently still develop fairly normal lungs, the risk of life-long respiratory and cardiovascular impairment remains high. Insufficient knowledge of the interactions of lung development, injury and repair pathways hampers the development of effective treatments.

Further confounding the epidemiology and pathophysiology of BPD are very preterm infants who initially have almost normal lung function but cannot tolerate modest initial oxygen and ventilation and progress to early respiratory death or severe BPD³⁹. The converse are infants with early severe respiratory failure who respond poorly to surfactant treatment and require very high supplemental oxygen and ventilation pressure, although lung function returns to normal over weeks. These extreme respiratory function patterns indicate that some very premature lungs are particularly sensitive to injury and do not heal, whereas others are quite resilient, with resistance to injury and with effective healing. These differences in injury and repair patterns probably result from multiple lung dysmaturity phenotypes that are caused by antenatal exposures, early postnatal exposures and different genetic backgrounds.

Perturbed lung development in BPD

Chorioamnionitis and inflammation.—Inflammation is the common pathway that initiates the lung injury that can progress to BPD. Neonatal respiratory support at delivery can easily injure the premature lung during the transition from fluid-filled lungs to air breathing⁶⁶. Subsequent ventilatory support and oxygen exposure can amplify injury. Some injury may be unavoidable, even with gentle assisted ventilation and surfactant treatment in infants <30 weeks gestational age. Subsequent inflammation from sepsis or necrotizing enterocolitis can increase the risk of developing BPD. These post natal inflammatory exposures are often preceded by two antenatal exposures that are potent effectors of delayed lung development and lung injury. More than 50% of pregnancies that result in very preterm births (<28 weeks gestational age) have histological evidence of chorioamnionitis⁶⁷ — inflammation of the fetal membranes, maternal decidua and, often, the amniotic fluid — which may be the proximal cause of the preterm labour. Concurrently, in ~90% of pregnancies that are at risk of preterm delivery, maternal antenatal corticosteroid treatment is prescribed to treat RDS and decrease infant mortality⁶⁸. In the complex context of prematurity and BPD, these exposures confound simple interpretations of the causality of BPD.

Chorioamnionitis simply indicates an intrauterine exposure to inflammation, most often associated with *Ureaplasma* sp., but multiple vaginal commensals and pathogens have also been identified⁶⁷. Chorioamnionitis-associated deliveries may also have ‘sterile’ inflammation. In clinical practice, the identity of the multiple microorganisms, the duration of fetal exposure and the location of the infection (decidua, amniotic fluid or fetus) are usually unknown. Studies in multiple animal models have demonstrated that fetal breathing exposes the fetal lung to infection and/or inflammation in amniotic fluid and causes lung inflammation and often a fetal inflammatory response⁶⁹. Low-grade lung inflammation induces lung maturation in experimental models. In clinical practice, histologically-confirmed chorioamnionitis is associated with decreased RDS incidence⁷⁰, whereas the presence of *Ureaplasma* sp. in cord blood is associated with increased incidence of BPD but no change in the incidence of RDS⁷¹. In another clinical series, increased severity of BPD correlated with increased severity of chorioamnionitis⁷². However, a summary meta-analysis of 59 studies could not definitively associate chorioamnionitis with increased BPD risk²⁸, perhaps reflecting issues with standardizing the diagnoses of chorioamnionitis and the complex interactions of multiple perinatal risk factors.

Most very preterm fetuses exposed to chorioamnionitis are also exposed to antenatal corticosteroids, which in animal models suppress the inflammation associated with chorioamnionitis, cause an arrest of alveolarization and also induce greater lung maturation than either exposure alone⁷³. Tolerance or preconditioning (modulation of the response to a fetal or neonatal exposure by a previous fetal exposure) is a possible reason why single fetal or neonatal exposures in animal models poorly replicate outcomes in preterm infants. Depending on timing and the exposure, a second similar or different exposure can result in a blunted or exaggerated lung injury response. In fetal sheep, an intra-amniotic injection of endotoxin causes fetal lung inflammation. However, prior chronic exposure of pregnant ewes to live *Ureaplasma* sp. completely blocks the fetal lung response to endotoxins⁷⁴. Similarly, fetal exposure to intra-amniotic lipopolysaccharide (LPS) can protect the newborn from hypotension from intravascular LPS administration⁷⁵. Very preterm infants are exposed to multiple potent antenatal and postnatal inflammatory modulators that modify injury and repair pathways, which is expressed as the clinical variability and severity of BPD.

Alterations of the lung microbiome have been recognized in multiple respiratory disorders. It is conceivable that, similar to chorioamnionitis, alterations in the lung microbiome prime the developing lung to injury⁷⁶. The increasing evidence linking the microbiome in preterm infants to BPD has been analysed in a systematic review⁷⁷, which reported substantial heterogeneity in the six included studies. Microbial dysbiosis may be associated with BPD progression and severity. Most of these infants were born by caesarean section and were exposed to postnatal antibiotics. Novel insights into systems biology based on ‘omics’ approaches may enable the temporal analysis of the fetal and neonatal lung and gut microbiomes in preterm infants, and ultimately permit manipulation to correct dysbiosis and restore a ‘healthy’ microbial environment.

Vascular abnormalities.—Pulmonary hypertension and related pulmonary vascular disease (PVD) have long been recognized as strong contributors to poor survival in preterm infants with BPD¹. A diagnosis of pulmonary hypertension that persists beyond the first few months of life has been associated consistently with mortality rates as high as 40–50%, ranging from a report in 1980 (REF.⁷⁸) to a study in 2007 (REFS^{79,80}). Prospective studies have provided echocardiographic evidence of pulmonary hypertension in 14–25% of preterm infants at 36 weeks post-menstrual age (PMA), with pulmonary hypertension especially prevalent (29–58%) in infants with severe BPD^{81–83}. Thus, despite major advances in perinatal and neonatal intensive care unit (NICU) care with improved survival and changes in the nature of BPD over the decades, pulmonary hypertension continues to be a prominent clinical challenge in the pathobiology and outcomes of infants with BPD.

There has been growing awareness in the past decade that pulmonary hypertension in premature infants encompasses several PVD phenotypes (BOX 2), including the fairly high incidence of sustained elevation of pulmonary vascular resistance (PVR) after birth that can cause profound hypoxaemia due to extrapulmonary right-to-left shunting across the foramen ovale and/or ductus arteriosus (persistent pulmonary hypertension of the newborn (PPHN)) with a slow adaptation or ‘delayed vascular transition’^{75,84–86}. Although more often considered in near-term or term infants with hypoxaemia at birth, PPHN also occurs in preterm infants and is negatively associated with gestational age (FIG. 6a). Severe

parenchymal lung disease can contribute to elevated PVR; however, abnormalities of the pulmonary vasculature can also contribute to high PVR, especially in the setting of antenatal stresses, such as oligohydramnios and prolonged premature rupture of membranes^{84–87}. Importantly, echocardiography-confirmed delayed pulmonary vascular transition⁸⁶ and early pulmonary hypertension⁸⁸ are associated with a higher risk of the subsequent development of BPD, late pulmonary hypertension and higher mortality^{86,88}. Experimental studies support epidemiological findings that adverse intrauterine stimuli are sufficient to impair vascular growth and induce longstanding and severe pulmonary hypertension independent of postnatal factors, such as hyperoxia and ventilator-induced injury⁸⁹.

In addition to the important effect of pulmonary hypertension, preclinical and clinical studies suggest that early disruption of lung vascular growth and function can impair growth of the distal airspace (the ‘vascular hypothesis’ of BPD)^{90–93}. Furthermore, strong clinical studies have shown that abnormal placental vascular structure and placental hypoperfusion on histopathology are strikingly associated with neonatal outcomes of IUGR and susceptibility to subsequent development of BPD and pulmonary hypertension^{94,95}. Prospective studies have shown that antenatal factors assessed on the first day of life^{30,96}, cord blood biomarkers of impaired angiogenesis^{97–99} and early echocardiography findings of pulmonary hypertension shortly after birth are strongly linked to the risk of BPD, pulmonary hypertension, prolonged NICU hospitalization and late respiratory outcomes in childhood^{83,100} (FIG. 6b–d). Thus, antenatal determinants not only cause abnormalities of short-term respiratory function, as reflected by NICU course, but early injury in utero causes sustained disruption of lung and pulmonary vascular structure throughout infancy, reflecting the adverse effect of fetal programming^{89,101} (FIG. 1). Antenatal stresses, including chorioamnionitis and pre-eclampsia (with or without IUGR), in preterm neonates contribute to BPD risk^{102–104}, although data from animal models of mechanisms linking antenatal stress to BPD pathogenesis and late cardiorespiratory outcomes are limited.

Diagnosis, screening and prevention

Diagnosis

BPD was first described in moderately preterm infants in an era when supplemental oxygen was the primary therapy for severe RDS¹ and mortality was >50%. Since then, the definition of BPD has evolved (TABLE 1), in large part because of the improved survival of extremely preterm infants and the new modalities used to support them (BOX 1).

Current challenges in defining BPD.—For most diseases, diagnosis is an end in itself. For preterm infants, a diagnosis of BPD is more akin to a functional lung assessment at the time a preterm infant is expected to transition out of hospital (similar to how forced expiratory volume in 1 second (FEV1) is used in conditions such as cystic fibrosis)¹⁰⁵. More than 30 years after BPD was defined by Shennan et al.¹⁰⁶, how well a BPD diagnosis can predict pulmonary outcomes in infancy and childhood, and how those long-term pulmonary outcomes should be defined, remain primary research and clinical questions¹⁰⁷.

The populations at risk and respiratory treatment strategies have also evolved since publication of the 2001 National Heart, Lung, and Blood Institute (NHLBI) workshop

report¹⁰⁸. The number and survival of the smallest and most preterm infants has increased, and some NICUs now routinely care for babies born at 22 weeks of gestation^{24,26}. Respiratory care practices have also changed, as recently documented by the Prematurity and Respiratory Outcomes Program (PROP) cohort of 765 surviving infants of <29 weeks of gestation¹⁰⁹. In the PROP cohort, 359 infants (47%) were treated with nasal cannula flow at 36 weeks PMA, including 95 infants (12%) on flow with room air. This creates new problems for BPD classification, as it is not possible to differentiate whether flow is needed for control of breathing or for lung parenchymal injury. Data capture outside a rigorous research environment is also challenging. In the database maintained by the National Perinatal Registry of the Netherlands, only 67% of preterm infants were correctly categorized according to the NHLBI workshop definition¹¹⁰, owing predominantly to a false-negative diagnosis rate of 31%, including 9% with severe BPD. A bedside analysis of the ‘shift’ of the oxyhaemoglobin dissociation curve (accomplished through simultaneous measurement of FiO₂ and peripheral saturation at a single time point) was proposed as an objective test for the presence and severity of BPD^{111,112}. This measurement would provide more accurate assessment of oxygen need than the Walsh ‘physiological test’, but would be difficult to accomplish in most infants outside a research protocol. A retrospective analysis of infants from the NICHD Neonatal Research Network has led to a proposal to modify the 2018 NICHD definition³ to a severity scale that is based on the use of positive pressure at 36 weeks PMA instead of supplemental oxygen. Infants were classified as no BPD (no support), grade 1 (nasal cannula ≤ 2 l/min), grade 2 (nasal cannula >2 l/min or non-invasive positive airway pressure), or grade 3 (invasive mechanical ventilation). These criteria predicted death or serious respiratory morbidity at 18–26 months corrected age in 81% of infants in the study¹¹³.

Although BPD is a ‘yes/no’ diagnosis at 36 weeks PMA, the term has become shorthand for the presence of respiratory morbidity in a preterm infant before and after discharge from hospital. It is increasingly recognized that defining BPD at 36 weeks PMA by the use of oxygen alone is inadequate. Data from the Canadian Neonatal Network revealed that oxygen use and/or respiratory support is a better indicator of chronic respiratory insufficiency than oxygen alone, and that assessment at term equivalent (40 weeks PMA) increases the predictive value¹⁴. Newer proposed definitions have suggested quantifying oxygenation through assessment of oxygen dissociation curves, or alternatively relying solely on the amount of positive pressure an infant receives at 36 weeks PMA^{112,113}. One of the greatest needs is a definition and severity scale to systematically describe the continuum of disease severity for at least the first year of life. One promising example is the Chronic Lung Disease of Infancy (CLDi) score¹⁰⁷, although, like BPD, it is based on details of clinical management, such as supplemental oxygen, bronchodilators and the need for rehospitalization. More objective measures, such as pulmonary function testing, require sedation and are not yet practical outside the research setting. A challenge for any classification system beyond the birth hospitalization is to account for other environmental confounders, such as smoking and viral infections.

The 2001 NHLBI workshop definition took the important step of including a BPD severity scale¹⁰⁸, and infants with severe BPD were subsequently found to have higher mortality and rates of adverse outcomes after discharge than those with mild or moderate disease¹¹⁴.

However, the definition of severe BPD was overly broad, and combined infants receiving 31% oxygen by low flow nasal cannula with infants on high ventilator settings and receiving drugs for pulmonary hypertension. This issue was partly addressed by the NHLBI 2018 revision, which reserved grade 3 BPD for infants receiving positive pressure or nasal cannula flow >3 l/min in addition to oxygen³. To better refine the approach to defining disease severity for clinical care and research, the BPD Collaboration Group recommended that severe BPD be further subclassified, with infants receiving only nasal cannula oxygen at 36 weeks PMA defined as type 1 severe BPD and infants requiring mechanical ventilation defined as type 2 severe BPD¹¹⁵. The Canadian Neonatal Network added weight to this idea by showing that a more severe BPD diagnosis (that is, at 36 weeks PMA requiring oxygen plus respiratory support versus oxygen only) better predicted serious respiratory morbidity at 18–22 months¹⁴. However, because of the low incidence of type 2 severe BPD in any single centre, long-term outcomes remain poorly understood for this population. In addition, although pulmonary hypertension is a common comorbidity and probably contributes to the pathophysiology of severe BPD, it has not been incorporated in any existing definition¹¹⁶.

The most severe BPD leads to early mortality prior to 36 weeks PMA. Although this outcome was estimated to occur in 3% of the PROP cohort¹¹⁷, these especially high-risk infants have been inconsistently classified using existing definitions. The 2018 NICHD workshop definition proposed a grade 3A BPD for infants with early death between 14 days postnatal age and 36 weeks PMA from persistent parenchymal lung disease and respiratory failure that is not attributable to other neonatal morbidities. Further work and validation of the NICHD BPD risk calculator⁴⁹ is needed to better identify this population of infants as early as possible in their clinical course (ideally before 14 days), as a particularly high-risk group for novel therapies.

Finally, future BPD definitions should provide strong specificity in addition to sensitivity. In the PROP cohort, about 50% of infants with persistent respiratory disease at 1 year of life had no or mild BPD at 36 weeks PMA⁹⁶. Improving predictive value will require better objective measurements and biomarkers of lung injury and BPD and the ability to incorporate antenatal factors, such as IUGR, maternal hypertension, maternal smoking and male sex.

Screening and prevention

Biomarkers.—Prevention of BPD and long-term cardiorespiratory impairment remains elusive, making identification of early predictive BPD biomarkers to guide new therapies a laudable goal. Preterm infants with differing risks of developing BPD have been enrolled in early prevention trials, sometimes with adverse consequences. A prime example is the trials of high-dose dexamethasone, which was later found to be associated with a higher risk of cerebral palsy and intestinal perforation¹¹⁸. BPD is a heterogeneous disease resulting from multiple pathophysiological processes, with varying magnitudes of impairment of alveolar septation, lung fibrosis and abnormal vascular development and remodelling¹¹⁹. Failure to identify subpopulations at highest risk and with distinct mechanisms of disease (endotypes) contributes to exposure to therapies that are unlikely to benefit or may cause harm to individual patients, as well as scepticism about biologically plausible therapies that may

benefit a subset of at-risk infants^{120,121}. Identifying infants at high risk of BPD at birth is possible, as was shown for the PROP cohort⁹⁶. Infants who have a persistent need for respiratory support beyond 10–14 days of age are at the highest risk of a BPD diagnosis at 36 weeks^{96,122}. Although persistent oxygen requirement in the first weeks of life may be a clinical predictor of later BPD, it provides little information about disease endotypes or therapeutic interventions that may benefit individual patients.

A good BPD biomarker should be easily measurable, be affordable, use a reliable assay with high analytical sensitivity and specificity, predict later lung disease or serve as a surrogate for long-term respiratory outcomes, elucidate underlying pathophysiological mechanisms (thereby refining BPD risk by endotypes) and be validated in diverse replication cohorts. A validated BPD biomarker offers the potential to reduce health-care costs and the risks of broadly applying ineffective therapies. Biomarkers may be valuable for earlier diagnosis of BPD, enabling initiation of therapies when they may be more effective or avoidance of therapies and their potential hazards¹¹⁹. A validated biomarker may also facilitate the development of tailored, personalized therapeutic approaches and improve patient endotyping prior to study randomization, thereby enhancing safety and efficacy of randomized controlled trials of novel therapies. Conversely, biomarker testing may increase screening costs and result in fewer infants who are eligible for trials, thus requiring larger multicentre collaborative efforts¹²⁰.

Despite their promise, there are many challenges to identifying BPD biomarkers. An important consideration is the optimal biomarker source or specimen type, which could include DNA, microRNA, amniotic fluid, tracheal aspirate, blood, urine and stool. For example, the levels of IL-1 β , IL-6, CXCL10 and uric acid are substantially higher in tracheal aspirate but not in plasma of patients with moderate and severe BPD than in that of infants with no BPD¹²³. The best approach to normalizing a sample for volume collected or dilution factors in some specimen types, such as tracheal aspirate and urine, must be determined. The optimal timing for measurement of the biomarker and therefore therapeutic intervention (at birth and/or the first hours, days or weeks of life) must also be ascertained. Normal patterns of biomarker expression must be determined across a range of gestational and postnatal ages to identify patterns that predict disease or deviation from normal development. Determining the appropriate control group is a unique challenge for research in the preterm population. Healthy term infants may not represent an appropriate control when biomarker expression changes with developmental maturation. It is not always clear whether the absolute value or a change in biomarker level over time will yield the most predictive signal or whether to apply cut-off values or quartiles for risk stratification. Last, interactions among various biomarkers must be taken into account; for example, the balance of pro-inflammatory and anti-inflammatory cytokines or pro-oxidants and antioxidants may be a better predictor of BPD and later respiratory morbidity than a single biomarker of inflammation or oxidative stress.

Various biomarkers have been studied in association with BPD but have yet to be validated as predictors of important long-term outcomes (see TABLE 2 for a non-exhaustive list of BPD biomarkers). Ideal biomarkers for BPD will target causal pathways that have been implicated in BPD pathogenesis^{120,121}, such as biomarkers of endothelial injury and

dysfunction^{124,125}; growth factors and biomarkers of altered angiogenesis^{6,126–131}; biomarkers of epithelial injury and fibrosis^{132–135}; biomarkers of nitric oxide deficiency or insufficiency^{120,136–140}; biomarkers of oxidative stress, oxidant and antioxidant capacity, and redox status^{141–143}; oxyradical biomarkers^{141–144}; biomarkers of inflammation and host immune responses^{129,145,146}; genomic, epigenomic, metabolomic¹⁴⁷, microbiomic¹⁴⁸, methylomic and transcriptomic biomarkers^{119,149}; lung function measures^{119,150}; MRI of the lungs for measurement of perfusion, blood flow, ventilation, gas exchange, mechanics and early changes in alveolar structure¹¹⁹; and biochemical¹⁵¹ and physiological biomarkers of vascular injury and pulmonary hypertension^{80,82,123,140,152}. A 2013 systematic review identified serum KL6, CC16 and neutrophil gelatinase-associated lipocalin, and end-tidal carbon monoxide (etCO), as performing well in predicting BPD in preterm infants¹⁵³. Identification of early markers of endothelial or vascular injury may lead to mechanistic interventions to support normal vascular and alveolar growth and prevent BPD.

Rare single-gene diseases with a BPD-like phenotype probably occur in preterm infants. In the absence of a high suspicion of such a single-gene pulmonary disease, genomic analysis is unlikely to be useful as a screening biomarker. To date, only a few underpowered genome-wide association studies (GWAS) on BPD have been published^{149,154} (reviewed in REF.³⁷). Very large genomic studies with international or multicentre participation and including multiple ethnicities, antenatal risk factors and careful definition of phenotypes, may provide important clues about pathogenetic pathways and BPD endotypes. Although identification of biomarker-defined BPD endotypes holds promise for a new era of BPD prevention research, none of the biomarkers discussed above have been effectively used. Harnessing the promise of biomarkers will depend on identification and validation of affordable, reproducible, point-of-care or rapid biomarker tests and advances in computational biology and artificial intelligence¹⁵⁵.

Management

Short-term management

In the absence of effective interventions to prevent preterm birth, treatment strategies have focused on reducing exposure to ventilation using an endotracheal tube, to avoid or minimize long-term lung and brain damage in preterm infants (TABLE 3). Of note, some clinical studies have suggested that BPD is an independent risk factor for poor neurodevelopmental outcomes, even in the absence of definite brain injuries, such as intraventricular haemorrhage or hypoxic ischaemic encephalopathy^{156,157}. For example, motor functions, cognitive development and academic progress are worse in preterm infants with BPD than in those without BPD¹⁵⁸, possibly because strategies to protect the lungs might also be neuroprotective.

Avoiding intubation and ventilation.—Attempts to avoid lung injury in extremely preterm infants have led to recommendations to avoid intubation and ventilation in the first minutes of life and a preference for non-invasive respiratory support¹⁵⁹. Besides nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV) and high-flow nasal cannulae have become more popular, but the

efficacy of these respiratory support methods in reducing the rates of BPD has been modest^{160–163}. Exogenous surfactant therapy improves neonatal outcomes, including reducing mortality, air leak and the combined outcome of death or BPD^{164,165}. Traditionally, surfactant has been administered using an endotracheal tube. A number of techniques have been developed for the delivery of surfactant to infants who are managed with NCPAP, including less-invasive surfactant administration (LISA)¹⁶⁶, which uses McGill's forceps to guide a feeding tube between the vocal cords. Alternatively, minimally invasive surfactant therapy (MIST)¹⁶⁷ uses a firmer vascular catheter and does not require forceps. A meta-analysis of six randomized trials in 895 infants showed that surfactant delivered using a thin catheter reduced the composite outcome of death or BPD compared with conventional intubation for surfactant delivery¹⁶⁸. Some NICUs have responded to this evidence enthusiastically and implemented routine administration of surfactant to infants on NCPAP. Others have been more cautious and await the results of ongoing larger randomized controlled trials to determine the place of this therapy in modern neonatal intensive care¹⁶⁹. Alternative approaches to surfactant administration, such as nebulization¹⁷⁰ and administration into the pharynx or via a laryngeal mask airway¹⁷¹, have potential but require further rigorous assessment before general use.

Based on evidence that extremely preterm infants exhibit persistent surfactant dysfunction, late or repeated surfactant administration has been explored. Although the TOLSURF trial showed no difference in survival at 36 weeks between infants without BPD receiving late surfactant administration versus no surfactant, there was a trend toward improvement at 40 weeks (with >20% decrease in the number infants requiring respiratory support at 40 weeks) and a substantial decrease in the number of infants who required home respiratory support during the first year^{172,173}, an issue that is very important for parents because of the level of stress they experience.

Caffeine.—Treatment with respiratory stimulants, such as caffeine, is the best-evaluated treatment for reducing BPD risk. The Caffeine for Apnea of Prematurity (CAP) trial demonstrated that caffeine administration reduces the risk of BPD and shortens the duration of ventilation with an endotracheal tube and exposure to supplemental oxygen¹⁷⁴. Importantly, these short-term benefits are followed by an improvement in cognitive and motor outcomes in infants at 18 months of age¹⁷⁵. Important questions about caffeine remain, including whether a higher dose and prolonged treatment lead to further improvements in important outcomes.

Corticosteroids.—Antenatal steroid therapy represents a major advance in perinatal care, which has resulted in reduced mortality, respiratory distress syndrome, intraventricular haemorrhage and necrotizing enterocolitis, although it does not reduce rates of BPD¹⁷⁶.

Corticosteroids are powerful downregulators of inflammation and have been widely used postnatally to prevent and treat BPD. Concerns about adverse effects of these agents, such as neurodevelopmental impairment, mostly with dexamethasone, in the early 2000s led to recommendations against their use¹⁷⁷. Further evidence has emerged suggesting that the benefits may outweigh the dangers when the risk of BPD is high (>50%)¹⁷⁸. In a small randomized controlled trial, a short course of dexamethasone delivering a lower initial and

total dosage than used previously led to a reduction in the duration of ventilation and was not associated with long-term neurodevelopmental impairment^{179,180}. The current decade has seen the pendulum swing back in favour of the prescription of corticosteroids. A European survey showed that 13.9% of infants born between 24 and 29 weeks of gestation were prescribed postnatal corticosteroids¹⁸¹. However, substantial variation in prescription occurred in practice (3.1–49.4%) across the regions surveyed, which was not explained by neonatal characteristics. The authors suggest that this may reflect different interpretations of the evidence, in particular for infants at highest risk of BPD.

Other attempts to improve the risk/benefit ratio of steroid therapy have involved evaluation of other corticosteroids and routes of administration. Based on extensive studies by Watterberg et al.^{104,182–184}, the PREMILOC study compared the early use of 10 days of hydrocortisone therapy to placebo in 523 infants <28 weeks of gestation¹⁸⁵. Unfortunately, the trial was stopped at 66% of planned recruitment because of financial considerations. The primary outcome, survival without BPD, was higher with hydrocortisone treatment than with placebo (60% versus 51%, $P=0.04$). Follow-up of survivors at 2 years of age revealed no important differences in rates of neurodevelopmental impairment¹⁸⁶. A smaller trial evaluated the effect of hydrocortisone administered for 22 days in 372 infants born <30 weeks of gestation who were ventilator-dependent between day 7 and day 14 of life¹⁸⁷. There were no important differences in rates of death or BPD between the hydrocortisone and placebo groups. The most recent individual patient data (IPD) meta-analysis including four randomized controlled trials (982 infants) suggests that early low-dose hydrocortisone therapy increases survival without BPD in very preterm infants, despite an increased risk of intestinal perforation (when given in association with indomethacin) and late-onset sepsis¹⁸⁸.

Avoidance of systemic administration underpinned the NEuroSIS trial of inhaled budesonide^{189,190}. Although budesonide reduced the rate of BPD, a follow-up study showed no improvement in rate of death or disability and an increased risk of mortality compared with placebo. In a randomized controlled trial of 265 infants weighing <1,500 g who were treated with combination budesonide and surfactant (Survanta) or surfactant alone administered intratracheally, rates of death or BPD were 66% with surfactant alone and 42% with the combination therapy¹⁹¹. Follow-up into infancy revealed no differences in rates of neurodevelopmental impairment. Although promising, uncertainty about the optimal dose persists¹⁹² and this intervention needs to be tested further in larger, multicentre trials.

Inhaled nitric oxide.—Inhaled nitric oxide (iNO) is an effective, widely used treatment for neonatal pulmonary hypertension. Studies in animal models showed that NO is required for normal lung development and that replacement therapy may benefit the injured lung^{193,194}. However, these benefits have not been replicated in human infants. The authors of an IPD meta-analysis that included 14 randomized controlled trials and 3,430 preterm infants suggested that routine use of iNO in this population could not be recommended¹⁹⁵. Observations that the effectiveness of iNO might vary by ethnicity led to an IPD meta-analysis examining this question. A pooled analysis of three randomized controlled trials showed an interaction between ethnicity and the outcome death or BPD. A reduction in rate of this outcome was found in the African American population but not the white or Hispanic

groups¹⁹⁶. This observation may be regarded as hypothesis-generating and an appropriate basis for further prospective randomized controlled trials¹⁹⁷.

Oxygen saturation targeting.—Balancing the risks and benefits of oxygen therapy has been a long-term, unrealized goal of neonatal intensive care. Currently, oxygen administration to preterm infants is titrated to achieve certain oxygen saturation ranges. An IPD meta-analysis of five high-quality randomized controlled trials comparing high (91–95%) and low (85–89%) saturation ranges provides useful guidance for clinicians¹⁹⁸. The higher range was associated with a reduced risk of death and necrotizing enterocolitis but no difference in the primary outcome, the combined rate of death or major disability at a corrected age of 18–24 months. Treatment for retinopathy of prematurity was more common in infants in the high than in the low saturation target group but there was no difference in the rates of blindness. Importantly, there was no important difference in the rates of BPD between the two treatment groups.

Long-term management

Despite advances in early respiratory care to minimize ventilator-induced lung injury from delivery to later times, some preterm infants develop severe chronic respiratory disease and related comorbidities that persist throughout their NICU course and after NICU discharge. Prolonged care needs include tracheostomy with mechanical ventilation, high FiO₂ concentrations and multiple respiratory medications, such as intermittent corticosteroids, bronchodilators, diuretics and other drugs.

Preterm infants who require prolonged respiratory support at 36 weeks corrected age, including the need for tracheostomy and chronic ventilator care, constitute the most severe subgroup of BPD by NIH criteria (defined as type 2 severe BPD; TABLE 1). These infants are at the highest risk of late mortality, poor cardiopulmonary outcomes and extensive comorbidities, including worse somatic growth, neurocognitive problems and developmental delays¹¹⁵. Management is further complicated by the diverse contributors to the underlying lung pathophysiology, including airways, airspace and vascular components that probably define distinct ‘respiratory phenotypes’¹⁹⁹ (BOX 3). Better characterization of key physiological contributions to pathophysiology in individual patients with severe BPD will probably enhance overall management and result in more selective and targeted use of pharmacological agents for therapy.

The goals and challenges in the management of cardiopulmonary dysfunction in the setting of the complex problems associated with severe BPD are strikingly different from those primarily focused on disease prevention and short-term therapies^{115,116,199–201}. Despite some consensus recommendations^{115,200}, striking variations exist in respiratory care, diagnostic evaluations, selection and use of drug therapies, patterns of long-term follow-up and other factors that reflect many differences among centres and among practitioners¹¹⁶. In the absence of data from multicentre randomized controlled trials, current approaches for the long-term management of severe BPD remain primarily based on clinical experience, physiology-based strategies and small case series. Thus, optimal management strategies to enhance long-term outcomes in patients with severe BPD remain uncertain.

In addition to the absence of proven and effective evidence-based strategies to improve outcomes, patients with chronic ventilator-dependent BPD have historically been cared for in acute care settings. Management strategies for chronic disease differ considerably from those for acute respiratory failure, especially regarding approaches to mechanical ventilation²⁰⁰ (FIG. 7). When compared with approaches for acute respiratory failure, neonatologists may have less experience with ventilator management of infants with severe BPD and the different approaches to optimize care. Most importantly, in the setting of chronic complex lung disease, poor communication can exist among providers, subspecialists, nursing staff and families during prolonged hospitalization, which can lead to inconsistent care and adverse outcomes. High staff turnover and infrequent discussions among doctors and bedside staff and between parents and the medical team may contribute to these inconsistencies. Interdisciplinary care teams have the potential to alleviate many of these issues and improve outcomes in these infants. The formation of such teams has been associated with improved survival²⁰², shorter hospitalization and reduced costs²⁰³. The clinical course in infants with severe BPD is complex, with multiple morbidities, including frequent hospitalization throughout childhood, and often with poor continuity of care^{115,199}. As a result, linking in-patient and long-term out-patient care is important for enhancing the continuity of care, understanding the complex clinical course, and anticipating complications due to persistent morbidities and other issues¹¹⁵.

The developing lung has remarkable capacity for remodelling, yet disease of the airways, airspace and vasculature can persist (FIG. 8a). Multiple studies have shown abnormalities in lung function and structure in patients with BPD that persist throughout childhood, adolescence and young adulthood. In addition, several studies have further emphasized that prematurely born young adults with or without a history of BPD are at risk of PVD and abnormal cardiac performance^{204–210}. These multiple reports suggest that there is a high risk of severe respiratory impairment after an apparent ‘honey moon’ period during childhood and highlight the vital importance of early interventions, linking early NICU care with close follow-up in the ambulatory setting over time, and further strengthening collaborations between paediatric and adult subspecialists, especially in the fields of pulmonary medicine and cardiology. More research is clearly needed to determine optimal strategies to improve lung and cardiovascular health across the lifespan in preterm infants with and without severe BPD to ultimately improve quality of life (QOL).

Quality of life

Premature infants with BPD have a longer initial hospitalization than those without BPD²¹¹, and BPD remains a substantial life-long burden. The costs of the disorder are both social and economic and are measured in impaired childhood health and QOL, family stress, economic hardship and increased health-care costs^{212–214}.

Support for parents

Mothers of very preterm infants experience substantially more psychological distress in the first months of life than mothers of full-term infants. This stress may continue for the first few years beyond discharge from the NICU, particularly for parents of the highest-risk

infants²¹⁵. As infants with severe BPD reach term-equivalent gestation, their parents are often asked whether they prefer oxygen and home monitoring or a more prolonged hospital stay. At least half of parents express fear over home oxygen while still in the hospital, although by 3 months, most parents seem to adapt, and prefer this option to facilitate earlier discharge to home²¹⁶. The stress of caring for a baby with severe BPD extends well beyond the first few months of life. In one parental survey, parental perceived health-related QOL of children with severe BPD at 18–36 months corrected age was substantially lower than that of children born at term, and also lower than that of preterm children without BPD²¹⁷. Parents vividly described living in fear of their baby catching a cold, being rehospitalized, or dying from BPD, and considered that they were not provided with enough support and education to meet their needs²¹⁸.

Respiratory outcomes

Up to 50% of children with BPD are rehospitalized during the first 2 years of life^{219,220}. Respiratory viruses, such as respiratory syncytial virus, influenza virus and rhinovirus, frequently precipitate pulmonary exacerbations, increasing the risk of hospitalization in this age group^{221–223}.

Lung function, measured as FEV1, has improved in preterm infants over the past few decades²²⁴. Nevertheless, children born preterm with and without BPD continue to have lower lung function than children born at term^{225,226}. Children with BPD have a higher risk of having asthma-like symptoms during pre-school and school-age years^{199,227–230}. Symptoms of wheezing, cough, airway reactivity and shortness of breath are frequently encountered in this population, along with exercise-induced expiratory flow limitation^{228,231,232}. Impaired postnatal alveolar growth may also occur in children with BPD. A study in young children with BPD found normal alveolar volumes but decreased pulmonary diffusion capacity, consistent with impaired alveolar growth compared with children born at term²³³. However, another study in school-age children born extremely prematurely showed similar alveolar sizes as in term and mildly preterm infants, suggesting the capacity for catch-up alveolar growth²³⁴. Nonetheless, the extremely preterm children in this study had lower FEV1 values than term and mildly preterm children. Although obstructive lung disease is more commonly found in children with BPD than in those without BPD, restrictive lung disease can also be present²³⁵. Factors contributing to chronic lung dysfunction in children with BPD can include non-synchronous increases in lung size and airway calibre (contributing to airflow obstruction), chronic airway inflammation, air trapping and emphysematous changes^{230,236–240} (FIG. 8b).

Several studies have shown a decline in lung function in preterm children as they age^{236,241}. As an association exists between reduced lung function in early life and chronic obstructive pulmonary disease (COPD) in adult life, there is a concern that children with BPD are at increased risk of early-onset COPD²⁴². Environmental exposures, including in utero and postnatal tobacco smoke exposure, may adversely affect lung function in children with BPD³⁰. In addition, genetic^{31,243} and epi-genetic factors²⁹ may influence severity of respiratory symptoms and long-term outcomes in children with BPD. Risk stratification guidelines that include gestational age, lung function, and genetic and environmental factors

are needed to enable identification of preterm children at increased risk of respiratory symptoms and decline during childhood and adult life.

Pulmonary vascular disease

Although numerous studies have addressed the short-term and long-term effects of BPD on respiratory QOL, few if any have accounted for the additive effects of PVD. Although not specific to BPD, QOL surveys of parents of children with pulmonary hypertension who were treated with pulmonary vasodilators have found substantially lower QOL scores and higher parental stress, with scores even worse than those reported in children with cancer or congenital heart disease^{244,245}. Limited data indicate that treatment of BPD-related pulmonary hypertension correlates with improvements in functional status and thus presumably QOL²⁴⁶. Many of these infants are able to wean from vasodilator therapy, although the long-term effect of early PVD remains largely undefined.

There is growing evidence that premature infants with or without BPD who escape the neonatal window without developing clinical PVD have subclinical PVD that persists into adolescence and adulthood (FIG. 9). Echocardiographic markers, such as pulmonary artery acceleration time, indicate the presence of subtle PVD through childhood in preterm infants^{210,247–249}. By adolescence, mild elevations in mean pulmonary artery pressure are detected, which are highest in preterm-born adults with BPD²¹⁰. By right heart catheterization, adults who were born moderately to extremely preterm also have higher mean pulmonary artery pressure than those born at term²⁰⁵. Although most individuals in these studies fell below treatment thresholds, numerous studies now associate subclinical elevations in mean pulmonary artery pressure with increased overall mortality^{250–253}. Finally, right ventricular function is a primary driver of overall function and QOL in preterm-born adults with PVD. Limited evidence demonstrates right ventricular dysfunction in preterm-born adults despite subclinical PVD, and thus potential for persistent impairment in QOL^{205,208}.

Outlook

Since 2005, the prevalence of BPD in preterm infants in the Vermont Oxford Network has dropped from 31% to 28%²⁵⁴. Worldwide, rates of BPD vary from 13% to 32% in the iNEO reference (VLBW infants born weighing <1,500 g at 24+0 to 31+6 weeks gestation and admitted to the contributing neonatal units of participating countries during the period 2007–2010)¹⁸. The prevalence of BPD has shown only a limited change in spite of dramatic changes in practice during the same time period²⁵⁵, including increased use of antenatal corticosteroids for the promotion of lung maturity and increased use of various postnatal interventions, including high-frequency oscillatory ventilation and, paradoxically, the increased use of less-invasive ventilation techniques. This begs the question as to why so many of the current therapeutic initiatives have failed to meaningfully reduce the prevalence of BPD.

Randomized controlled trials have shown minimal decreases in the prevalence of BPD with the use of these interventions, such as elective high-frequency oscillatory ventilation²⁵⁶. Improved outcomes are seen in the use of volume-targeted ventilation compared to pressure-

limited ventilation, but the number of trials is low and the evidence is imprecise²⁵⁷. However, the results regarding less-invasive respiratory support are more promising. Aggressive delivery room intubation, surfactant administration and ongoing assisted ventilation were less effective than stabilization on NCPAP and selective surfactant administration in minimizing BPD²⁵⁸.

Both early use²⁵⁹ and later use²⁶⁰ of corticosteroids substantially decrease the risk of BPD. However, research on corticosteroid use has stalled because of concerns about long-term developmental outcomes in treated infants. In particular, the hope that hydrocortisone would be a safer alternative to high-dose dexamethasone has not fully born fruit. Hydrocortisone may or may not be as effective as dexamethasone, and few trials have demonstrated that it is truly safer. However, the decreasing use of steroids in the past decade, to a baseline of 8% in VLBW infants²⁴, is laudable. Whereas caffeine administration seems to decrease the risk of BPD in various at-risk populations¹⁷⁴, other pharmacological therapies, such as vitamin A, have not found widespread use²⁶¹. The debate about the role of iNO in both the prevention and the treatment of evolving BPD continues, but little evidence exists to support a meaningful impact of this treatment²⁶².

The future of clinical care of BPD will undoubtedly rely on a greater understanding of the ‘clinical phenotype’ of infants with BPD; that is, understanding the contribution of airway disease, parenchymal lung disease and PVD to the respiratory difficulty³. A greater appreciation of the vast difference between the underlying pulmonary vascular pathology of evolving or established BPD and the pathophysiology of prematurity in the newly born preterm infant is essential to the establishment of effective approaches to the care of these infants. Refinements in BPD definitions will clearly help in the identification of infants who are at higher risk of BPD (and thus might benefit from future trials of either available therapies, such as corticosteroids, or novel therapies that are yet to be tested) and give a greater understanding of the extent of improvement (or lack of improvement) that is associated with various interventions. However, existing definitions (such as supplemental oxygen at 36 weeks PMA) predict poor outcome and continue to be useful in clinical practice to decrease the prevalence of BPD in NICUs¹⁴ (see list of priorities in BOX 4).

Perhaps through improved quality of care and by enhancing each of these small benefits, we might see continued improvement in outcomes by reducing the incidence and severity of BPD²⁶³. Top performing neonatal units maintain rates of BPD as low as 20%²⁵⁴. For the future, we will have to look to these incremental improvements, as well as breakthrough therapies, such as mesenchymal stromal cells (MSCs), to truly address this problem.

Emerging treatments

Within less than 10 years from the initial proof of concept studies^{264,265}, promising preclinical data with MSCs²⁶⁶ have led to phase I clinical trials. Two trials have shown that administration of a single intratracheal dose of allogeneic cord blood-derived MSCs in extreme preterm infants during the first week of life is feasible and without severe adverse events attributable to the intervention^{267,268}. Similarly, the successful off-label use of repeated intravenous injections of bone marrow-derived MSCs in two extreme preterm infants with severe and advanced BPD supports the feasibility of this therapy²⁶⁹. Ongoing

phase II trials will indicate whether MSC therapy is safe and effective. Numerous other types of repair cells are being investigated in the clinic²⁷⁰ and in the laboratory for use in BPD therapy. Despite rapid clinical translation, cell-based therapies for regenerative indications are still in their infancy and major knowledge gaps remain. A better understanding of the biology and mechanism of action of MSCs and other repair cell types^{271–273} and the link between resident stem or progenitor cells and disease pathogenesis^{274–277}, together with technological advances, will allow the development of potency assays and manufacturing processes²⁷⁸ to yield superior cell products that may truly curb complications of prematurity and improve outcomes.

Other anti-inflammatory agents, such as IL-1 receptor antagonist (IL-1Ra) or modulators of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome upstream of IL-1 β , seem to be encouraging in preclinical studies (reviewed in REF.²⁷⁹). For example, recombinant human insulin-like growth factor 1 complexed with its binding protein (rhIGF1–rhIGFBP3) was investigated in a phase II trial for the prevention of retinopathy of prematurity in 121 extreme preterm infants²⁸⁰. Although development of retinopathy of prematurity was unaltered, rhIGF1–rhIGFBP3 treatment decreased the occurrence of severe BPD. These results warrant a trial focused on BPD as the primary end point.

Expected benefits of lung research

Technical advances in imaging, transcriptomics, epigenetics and lineage labelling are providing ever more detailed insights into the diverse cell types, including stem or progenitor cells, and the molecular processes by which cells interact to form and regenerate the lung after injury^{53–55,281–283}. Identification of the signalling and transcriptional networks that direct lung formation, repair and function might lead to the identification of pertinent biomarkers and inform clinical strategies to protect the critical progenitor cells and processes on which lung formation and repair depend. These insights will enable development of therapeutics aimed at enhancing normal tissue regeneration while inhibiting the cellular and molecular processes that underlie pathological tissue remodelling and loss of tissue that underlies many chronic lung diseases. In spite of severe lung dysfunction and injury associated with preterm birth, most infants with BPD achieve remarkable recovery of lung structure and function. Understanding the resilience of the neonatal lung will provide further insights that will be highly relevant to the processes of normal and pathological repair associated with chronic lung diseases that are active throughout the lifespan.

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Box 1 |**Neonatal definitions and intensive care interventions****Definitions**

Prematurity: Birth before 37 completed weeks of gestation. This is further subdivided on the basis of gestational age into extremely preterm (<28 weeks of gestation), very preterm (28–32 weeks of gestation) and moderate or late preterm (32–37 weeks of gestation).

Very low birth weight (VLBW): Infants who weigh <1,500 g at birth. Most VLBW infants are born at <30 weeks gestational age.

Extremely low birth weight (ELBW): Infants who weigh <1,000 g at birth. Most ELBW infants are born at <28 weeks gestational age.

Extremely low gestational age newborn: Infants born at <28 weeks gestational age.

Post-menstrual age: A measure of the age of an infant that combines gestational and postnatal age, both in weeks. For example, a 23-week gestational age infant at 9 weeks after birth has a postmenstrual age of 32 weeks.

Hyaline membrane disease: Also known as respiratory distress syndrome, this is the formation of a characteristic translucent membrane in collapsed alveoli, which can result from inadequate pulmonary surfactant production and structural immaturity in the under-developed lungs of preterm infants.

Intrauterine growth restriction (IUGR): Also known as fetal growth restriction, IUGR usually refers to infants whose weight is below the tenth percentile for infants of that gestational age or less than two standard deviations below the average weight for infants of that gestational age.

Persistent pulmonary hypertension of the newborn: Sustained elevation of pulmonary vascular resistance after birth that can cause profound hypoxaemia due to extrapulmonary right-to-left shunting across the foramen ovale and/or ductus arteriosus.

Interventions

Conventional mechanical ventilation: Positive airway pressure through an endotracheal tube. There are multiple ways to provide ventilation. Examples include time cycled, pressure limited; volume targeted; and neurally adjusted ventilatory assist.

Fraction of inspired oxygen (FiO₂): The percentage of oxygen content that is involved in gas exchange in the alveoli. Supplemental oxygen usually has an FiO₂ of <0.5 to avoid oxygen toxicity.

High-frequency jet ventilation: Ventilation through an endotracheal tube, usually with a device that is paired with a conventional mechanical ventilator and provides high rates around a targeted mean airway pressure with active inhalation and passive exhalation.

High-frequency oscillatory ventilation: Ventilation through an endotracheal tube, usually with a device that provides high rates around a mean airway pressure, with active inspiration and expiration.

Nasal continuous positive airway pressure: Continuous distending pressure, usually measured in centimetres of water, through the nasal passage (with a nasal or face mask instead of an endotracheal tube), with blended FiO_2 .

Nasal intermittent positive pressure ventilation: Usually a baseline continuous distending pressure with intermittent higher levels of pressure, which can be synchronized or non-synchronized, with blended FiO_2 .

Inhaled nitric oxide: A selective pulmonary vasodilator that reverses pulmonary vasoconstriction by modulation of vascular muscle tone.

Box 2 |**Pulmonary vascular disease phenotypes of prematurity****Early (first 2 weeks after birth)**

- Persistent pulmonary hypertension of the newborn syndrome: hypoxaemic respiratory failure with extrapulmonary right-to-left shunt
- Delayed vascular transition
- Mild pulmonary hypertension as a biomarker for risk of bronchopulmonary dysplasia or late pulmonary hypertension

Late (weeks to months after birth)

- Sustained need for high levels of respiratory support (fraction of inspired oxygen, ventilation), often with recurrent exacerbations or cyanotic episodes
- Pulmonary hypertension after discharge from neonatal intensive care unit, with persistent respiratory problems (such as intermittent hypoxia and obstructive sleep apnoea), acute viral infections and other symptoms

Chronic (months to years after birth)

- Persistent echocardiographic abnormalities during infancy, childhood and adolescence
- Exercise intolerance during childhood and adolescence
- High normal ('borderline') pulmonary hypertension and abnormal cardiac size and structure in young adults

Box 3 |**Lung pathophysiology of bronchopulmonary dysplasia****Central airways**

- Tracheomalacia
- Subglottic stenosis, cyst
- Granulomas
- Bronchomalacia
- Bronchial stenosis

Small airways

- Structural remodelling
 - Mucus gland hyperplasia
 - Epithelial injury, oedema
 - Smooth muscle cell proliferation
- Bronchoconstriction
- Hyperreactivity

Distal airspace and vasculature

- Decreased alveolarization, vascular growth
- Abnormal vascular remodelling, tone and reactivity
- Impaired lymphatic function and structure

Other

- Control of breathing
- Sleep disordered breathing
- Chest wall stability
- Diaphragmatic function

Box 4 |**Priority topics to advance the understanding and prevention of BPD****Consensus definition of bronchopulmonary dysplasia (BPD)**

- Definition that is based on pathophysiology and not on components of care (such as pressure and oxygen)
- Predict 'long-term' pulmonary and health-care outcomes
- Definition of BPD phenotypes and endotypes
- Useful as a clinical trial end point

Mechanistic understanding of normal lung development, injury and repair and clinical translation

- Capitalize on current cutting-edge single-cell technology and systems biology to understand the molecular pathways and cell-specific interactions in lung development and injury
- Develop and optimize the use of better animal models that integrate the multiple mechanisms that contribute to BPD pathogenesis

Biomarkers

- Capitalize on the parallel development of 'omics' and systems biology to identify preterm infants for targeted early interventions to minimize injury and promote repair
- Development of novel non-invasive technologies for longitudinal assessment of lung function and imaging
- Combine clinical, functional, imaging and biological markers to better guide care and interventions

Effective interventions that meaningfully reduce incidence and severity of BPD

- Cell-based therapies: improve understanding of the biology of repair cells, identify reliable potency assays and fine-tune the manufacturing process
- Identify new therapeutic targets in injury and repair pathways (for example, insulin-like growth factor 1, IL-1 receptor antagonist and modulators of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome)
- Facilitate clinical translation of preclinical research. For example, enhance the rigour of preclinical research in testing promising therapies to accelerate safe and efficient clinical translation

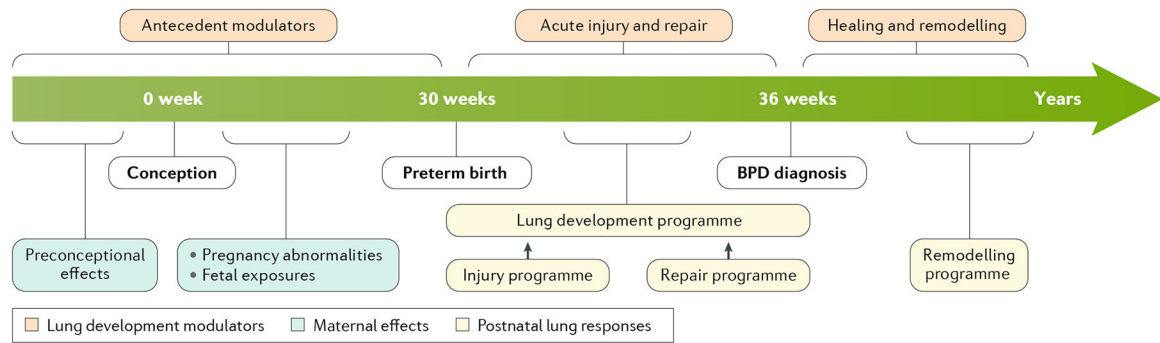


Fig. 1 |. Timeline and stages of BPD.

The timeline indicates variables that may modulate lung development from preconception through fetal development before preterm birth. Acute injury (on the timescale of days and weeks) resulting from neonatal care that is required to ensure survival then progresses to chronic lung injury and, ultimately, repair and remodelling over months and years. The unique aspect of bronchopulmonary dysplasia (BPD) is that it is an injury process that occurs as the premature lung is being injured and must repair as the lung continues to develop and mature. Remodelling of the lungs can occur over years.

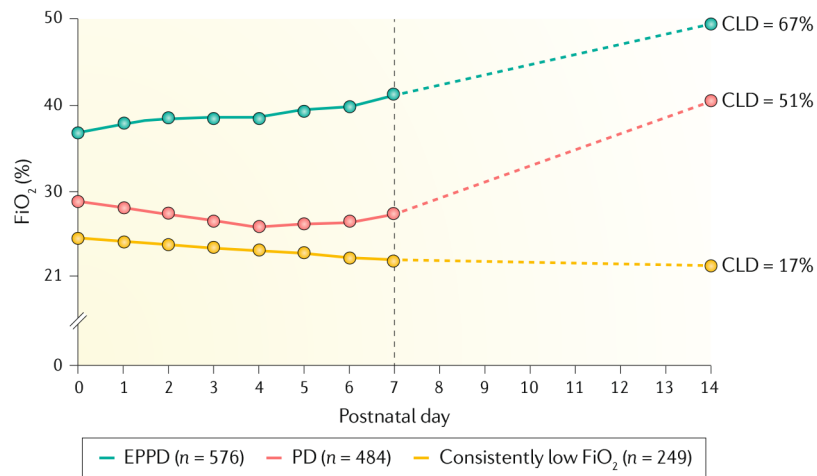


Fig. 2 |. Patterns of lung disease in premature infants.

Median of the mode fraction of inspired oxygen (FiO₂) on postnatal days 0 to 7 and on postnatal day 14, and the frequency of chronic lung disease (CLD) among extremely low gestational age newborns with three patterns of respiratory disease (low FiO₂, pulmonary deterioration (PD) and early persistent pulmonary deterioration (EPPD)) during the first two postnatal weeks. Delineation of the three patterns of disease is useful for early prognostication of bronchopulmonary dysplasia. Some infants have minimal lung disease and recover quickly, whereas others have EPPD, which requires prolonged, substantial respiratory support from birth. In the third pattern, some infants have initial lung disease that resolves in the first week after birth and is followed by respiratory decompensation (PD) that thereafter requires mechanical ventilation and supplemental oxygen. The dashed lines are the presumed FiO₂, as FiO₂ was only obtained on postnatal days 7 and 14. Adapted with permission from REF.⁴⁸, *Pediatrics*, **123**, 1124–1131, Copyright 2009 by the AAP.

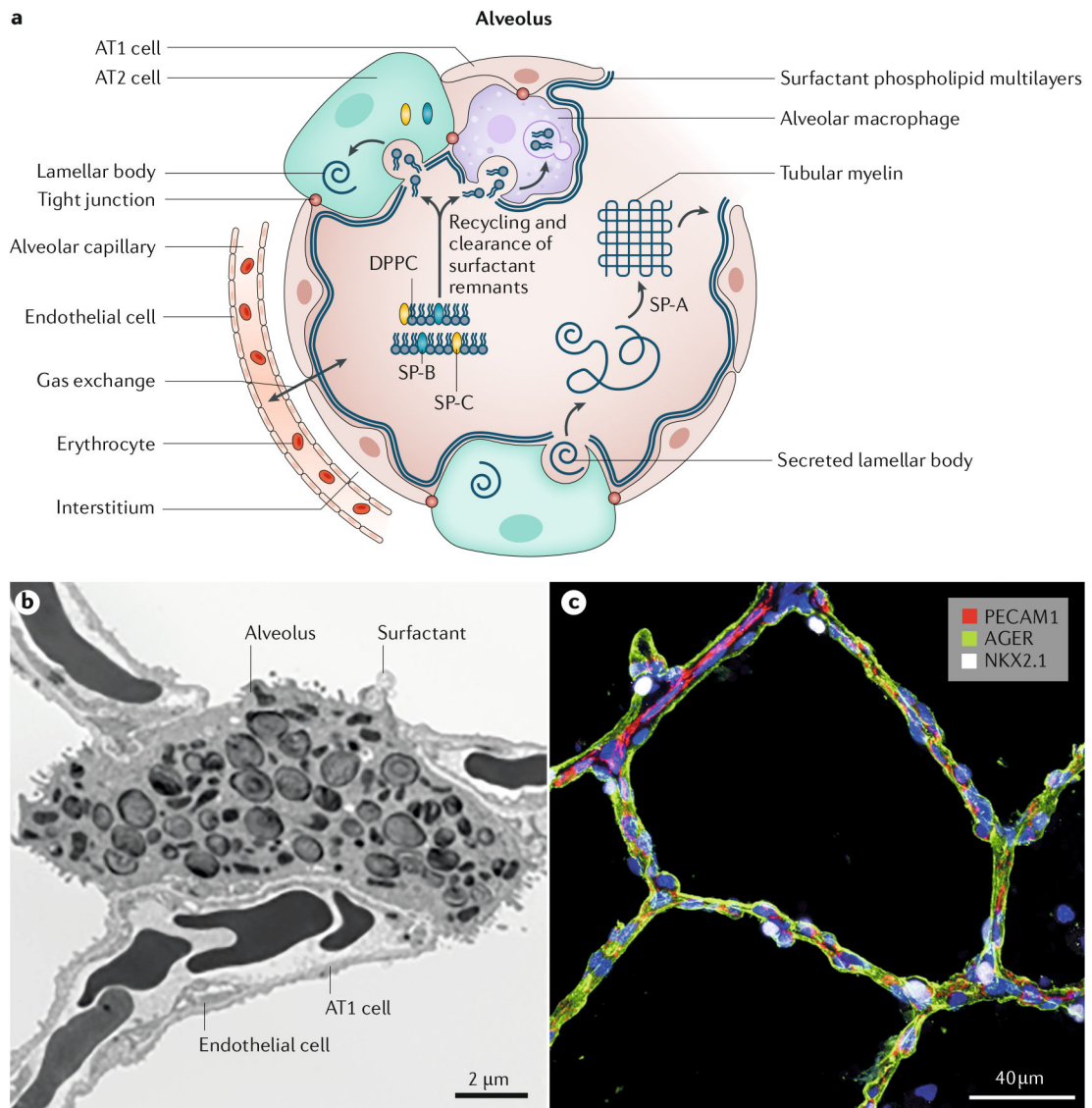


Fig. 3 | Structure of the alveolar gas exchange region.

a | Schematic representation of the alveolar unit. Surfactant lipids (such as dipalmitoylphosphatidylcholine (DPPC)) and proteins (such as SP-B and SP-C) are produced by alveolar type 2 (AT2) cells. Surfactant is secreted onto the alveolar surface to reduce surface tension and prevent atelectasis. After secretion, surfactant lipids interact with SP-A to form tubular myelin, from which a multilayered film of surfactant lipids is produced. The surface-active phospholipids reduce surface tension at the air–liquid interface in the alveolus to prevent alveolar collapse. Surfactant lipids and proteins are recycled or degraded, the latter primarily by alveolar macrophages. Intercellular communication between alveolar epithelial cells and macrophages integrates local inflammatory signals, resulting in upregulated expression of cytokines and chemokines in response to pathogens. **b** | Electron microscopy image revealing the ultrastructure of the alveolus. AT2 cells contain intracellular lamellar bodies that comprise surfactant lipids and proteins. Squamous AT1 cells and endothelial cells form the gas exchange unit. Erythrocytes are seen within the

alveolar capillaries of the pulmonary microvasculature. **c** | Confocal microscopy image of human alveoli from a 4-year-old child. On immunofluorescence imaging, anti-AGER antibody stains the surface of AT1 cells (green), anti-NKX2.1 antibody stains the nuclei of AT2 cells (white) and anti-PECAM1 antibody stains endothelial cells (red) in the microvasculature. Parts **a** and **b** adapted from REF.²⁸⁷, Springer Nature Limited.

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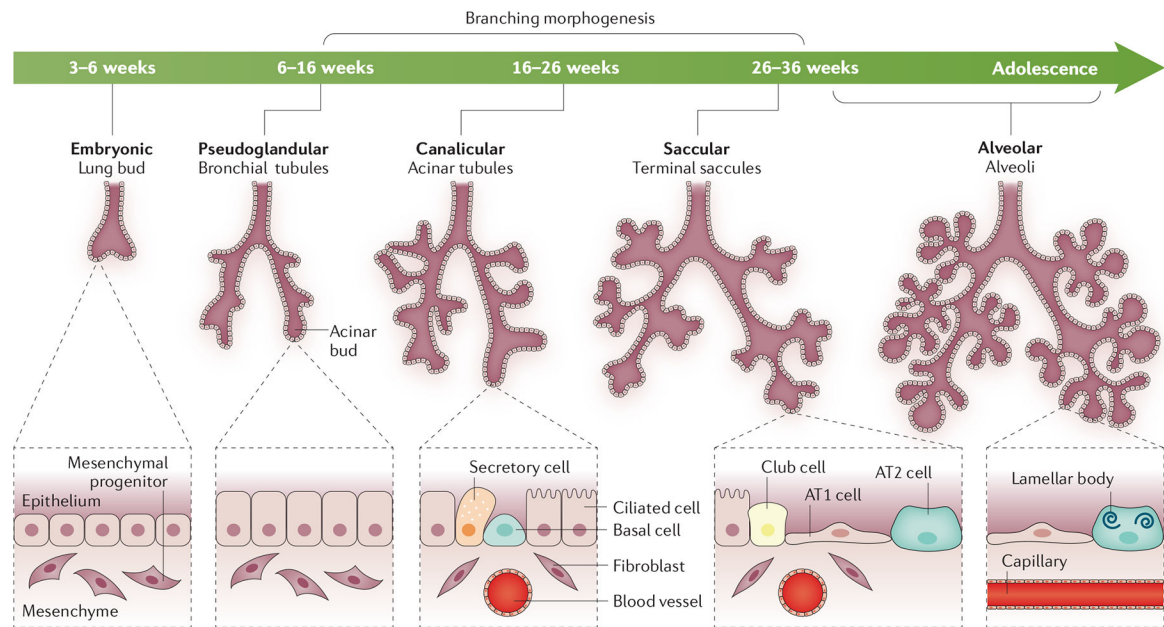


Fig. 4 |. Human lung morphogenesis.

Schematic of the stages of lung formation from the embryonic stage to alveolarization.

Changes in lung structure with advancing gestation are shown. In the embryonic period of lung bud formation, the tracheal primordium forms from the ventral region of the anterior foregut endoderm and separates from the oesophagus. During the pseudoglandular period, the lung buds proliferate and invade the splanchnic mesenchyme in the process of branching morphogenesis to form the airways and peripheral acinar buds, the latter forming the alveoli later in development. During the saccular stage, epithelial cells lining conducting airways differentiate, producing basal, goblet, ciliated and other secretory cells, which are distinct from the epithelial cells lining the peripheral saccules, namely the cuboidal pre-alveolar type 2 (AT2) cells and squamous AT1 cells. In the saccular–alveolar transition, the peripheral saccules further dilate and the surface is increasingly covered by AT1 cells as the gas exchange region expands. AT2 cells differentiate and produce increasing amounts of surfactant lipid and proteins, which are stored in lamellar bodies. Lung growth continues until adolescence. Adapted with permission from REF.²⁸⁸, Oxford University Press.

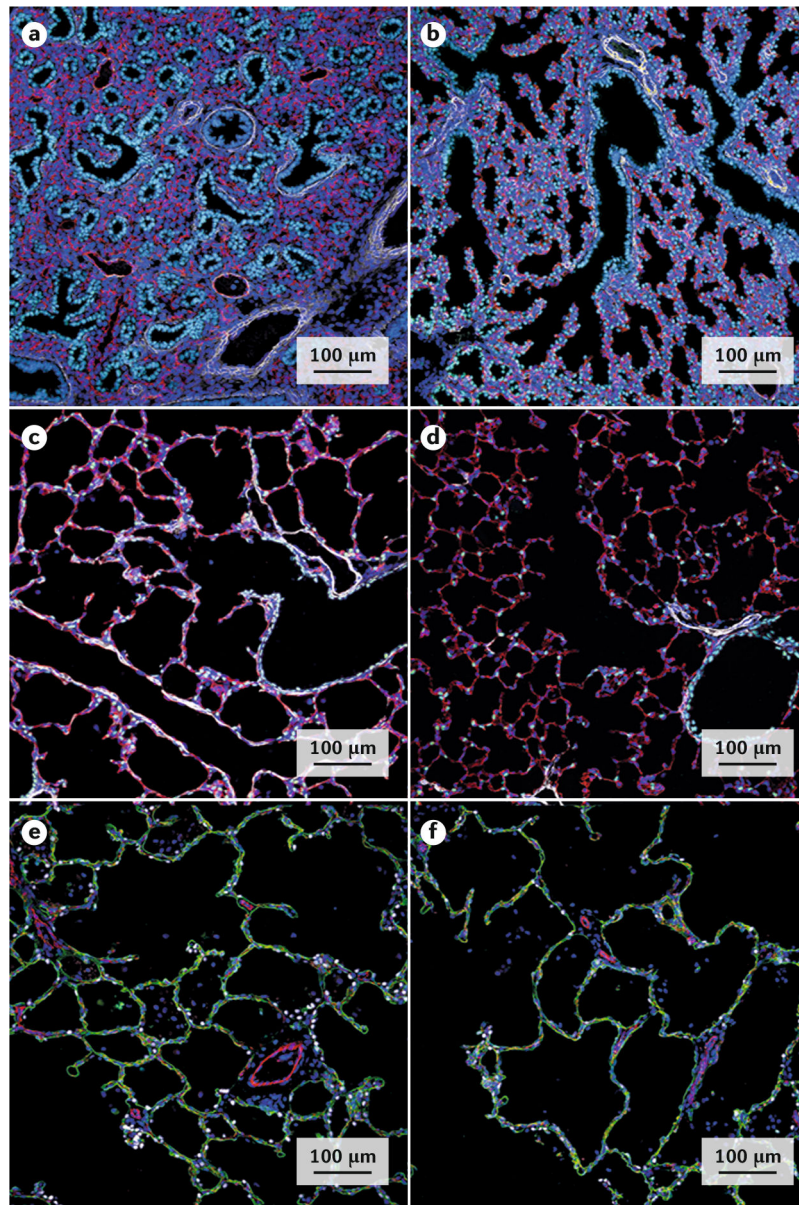


Fig. 5 | Structural changes in the lung during development and in BPD.
a–d | Developmental changes in lung structure revealed by immunofluorescence and confocal microscopy of a mouse lung at the pseudoglandular (embryonic day 16.5 (E16.5); part **a**), canalicular (E18.5; part **b**), saccular (postnatal day 3 (P3); part **c**) and alveolar (P28; part **d**) stages of lung development. The transcription factor NKX2.1 (light blue) is required for lung morphogenesis and is expressed by the epithelial cells lining the trachea, bronchi and peripheral lung tubules. An anti-EMCN antibody stains endothelial cells (red) in the developing microvasculature. An anti-ACTA2 antibody stains smooth muscle cells (white) in pulmonary vessels in the bronchial, submucosal and alveolar regions. Smooth muscle actin (ACTA2) staining is prominent on P3 during active alveolar formation (part **e**) and is less prominent on P28 (part **d**). **e–f** | Simplification of alveolar structure in bronchopulmonary dysplasia (BPD). Confocal microscopy images of a section of the lung of a healthy infant

(part **e**) and that of an infant with BPD (part **f**) at ~3 years of age. Alveolar surfaces are primarily lined by squamous alveolar type 1 (AT1) cells, which are stained with anti-AGER antibodies (green). An anti-PECAM1 antibody stains endothelial cells (red) in pulmonary capillaries. An anti-NKX2.1 antibody selectively stains AT2 cells (white). Alveoli form by septation, creating numerous small saccules in the normal lung (part **e**), whereas the alveoli are enlarged or ‘simplified’ in the lungs of an infant with BPD (part **f**), causing loss of the alveolar–capillary gas exchange surface area.

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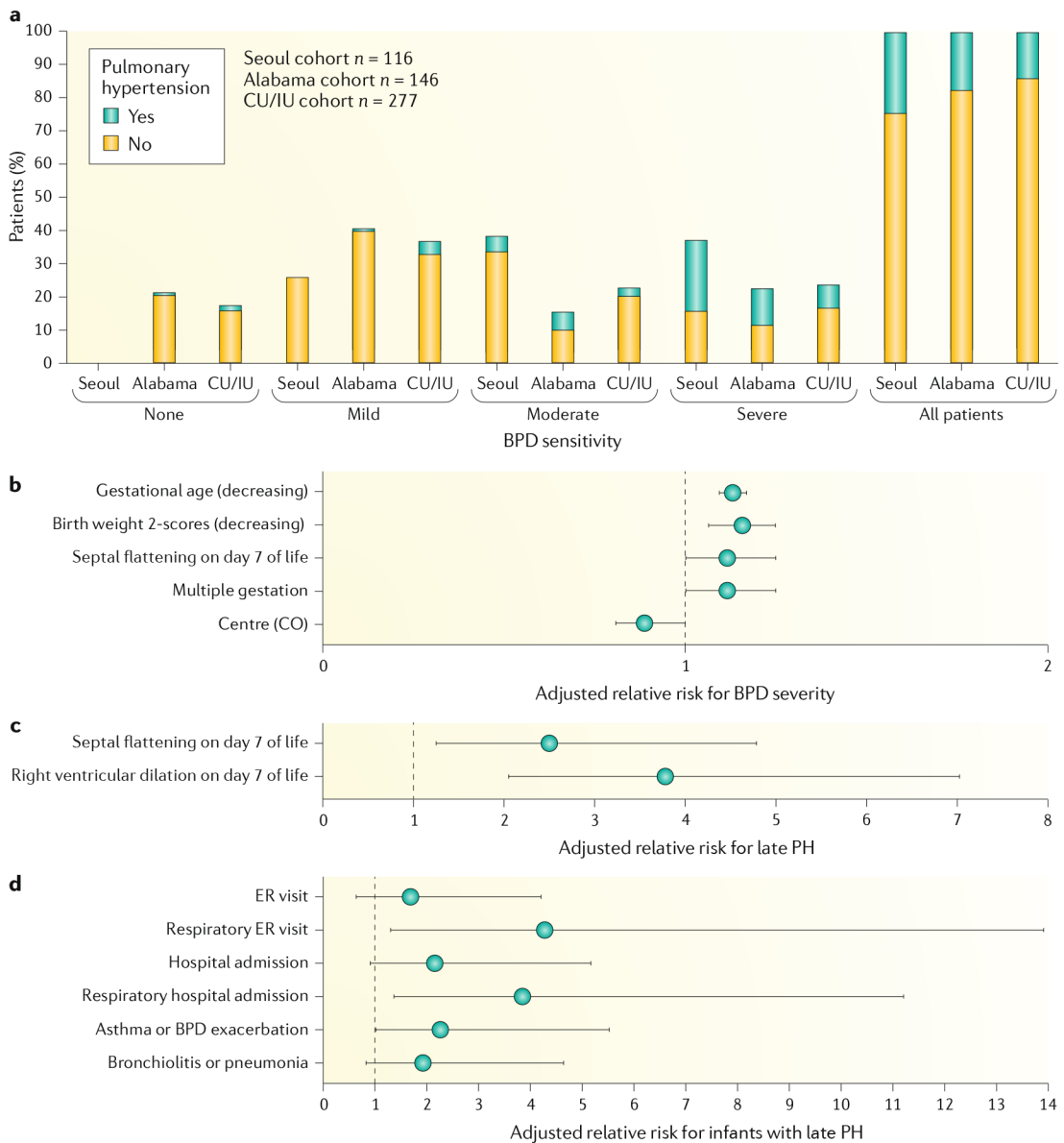


Fig. 6 | Pulmonary vascular disease in BPD.

a | Prevalence of pulmonary hypertension in preterm infants, as assessed by echocardiography at 36 weeks post-menstrual age. Pulmonary hypertension was diagnosed in 14–25% of preterm infants in different cohorts (Seoul, Korea⁸¹; Alabama, USA⁸²; and Colorado (CO) and Indiana (CU/IU), USA⁸³), with the highest incidence of pulmonary hypertension associated with severe bronchopulmonary dysplasia (BPD). **b–d** | Early pulmonary vascular disease, as assessed by echocardiography on postnatal day 7, is strongly associated with adverse outcomes, including severe BPD (part **b**), risk of pulmonary hypertension (PH) at 36 weeks (part **c**) and risk of respiratory disease during the first 2 years of life^{80,83,100} (part **d**). ER, emergency room. Part **a** adapted with permission from REF.⁸⁰, Elsevier. Parts **b** and **c** adapted with permission from REF.⁸³, of the American Thoracic Society. Copyright 2019 American Thoracic Society. Part **d** adapted with permission from REF.¹⁰⁰, of the American Thoracic Society. Copyright 2019 American Thoracic Society.

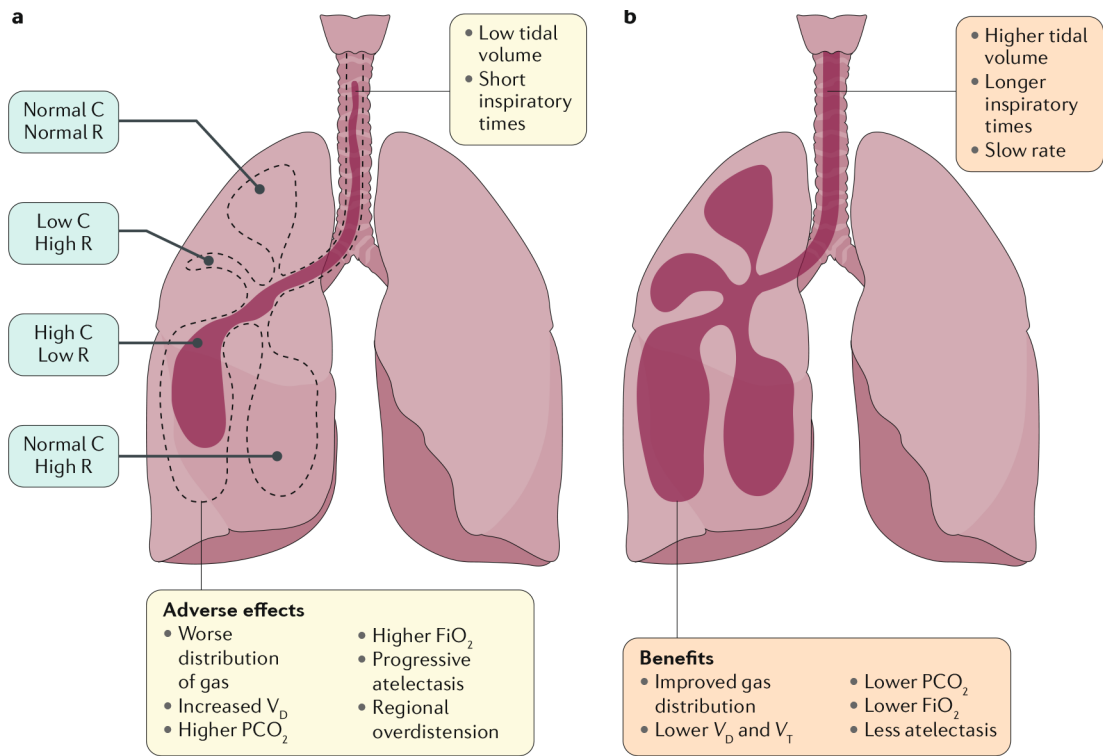


Fig. 7 |. Alternative ventilation strategies in the treatment of heterogeneous lung disease in severe BPD.

Schematic of the physiological effects of small-volume, rapid-rate ventilator support (panel **a**) and larger tidal volume, prolonged inspiratory time strategies (panel **b**) in a lung that contains regional heterogeneity in the severity of lung disease, as is observed in infants with severe bronchopulmonary dysplasia (BPD). **a** | Small tidal volume breaths probably increase dead space ventilation, leading to atelectasis, hypercapnia and high oxygen requirements. **b** | Increased tidal volumes and inspiratory times may enhance the distribution of gas, leading to lower oxygen requirements, improved ventilation and less atelectasis. Compliance (C) is a measure of the lung's ability to stretch and expand (distensibility of elastic tissue). Resistance (R) is the resistance of the respiratory tract to airflow during inhalation and expiration. FiO_2 , fraction of inspired oxygen; PCO_2 , partial pressure of carbon dioxide; V_D , dead-space ventilation; V_T , tidal ventilation. Adapted with permission from REF.²⁰⁰, Elsevier.

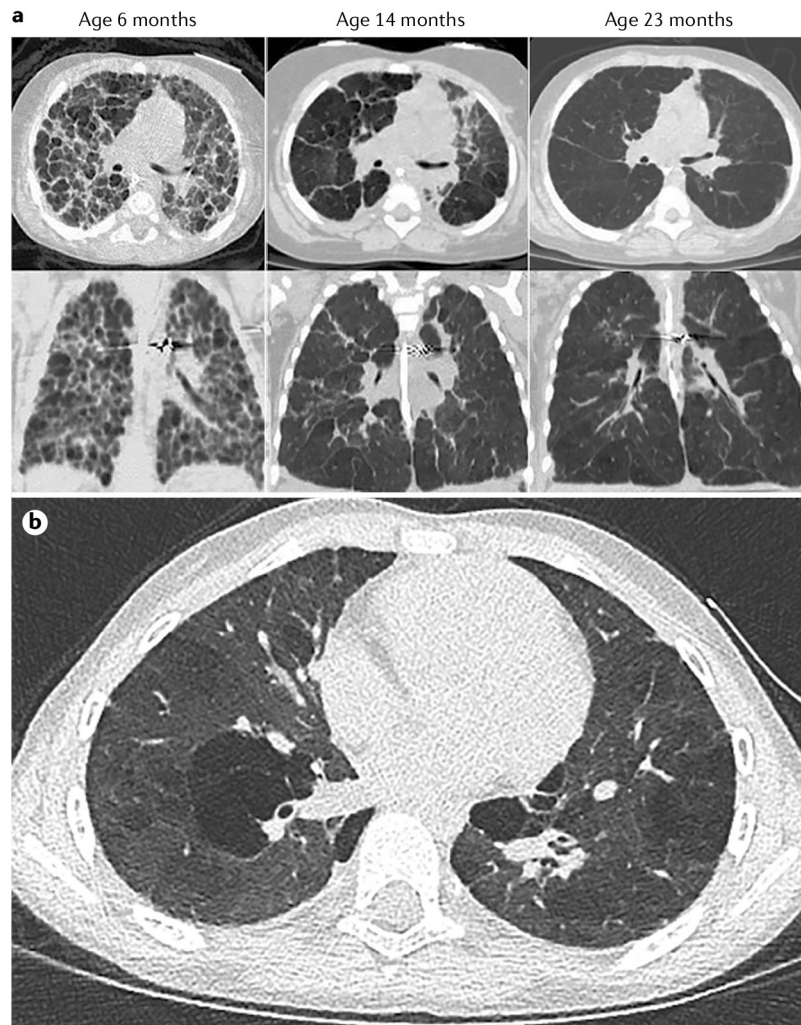


Fig. 8 |. Structural changes in the lungs in severe BPD.

a | Serial high-resolution CT scans illustrate time-related changes in lung architecture with regional heterogeneity in an infant with severe bronchopulmonary dysplasia (BPD). Extensive remodelling occurs over time, but persistent lung hyperinflation with abnormal lung parenchyma persists at 23 months. **b** | Chest CT scan of an 8-year-old girl who was born at 26 weeks gestation and had a history of severe bronchopulmonary dysplasia and pulmonary hypertension. Part **a** reproduced with permission from REF.²⁰⁰, Elsevier.

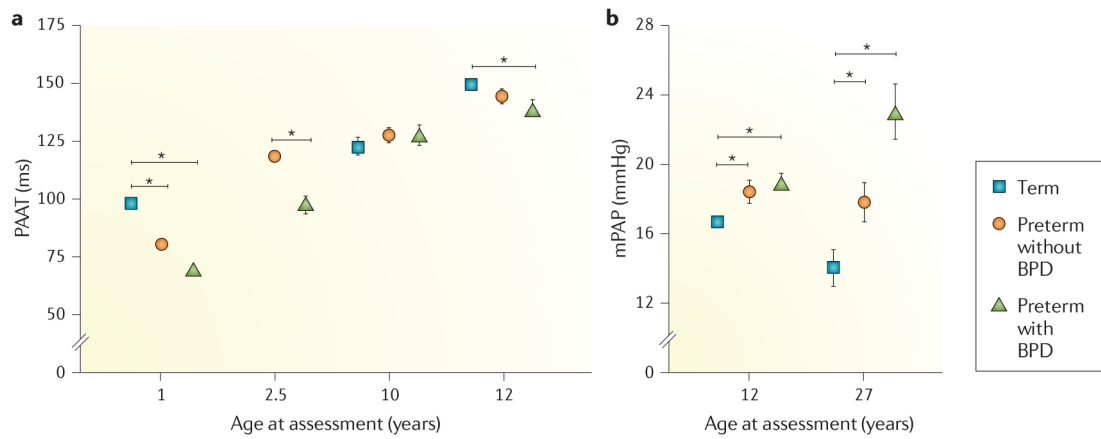


Fig. 9 |. Persistent subclinical pulmonary vascular disease in BPD.

a | After extreme preterm birth (average gestational age of 27 weeks), several echocardiography-based studies demonstrate lower pulmonary artery acceleration time (PAAT) beyond infancy into early adolescence, suggesting higher pulmonary vascular pressure and resistance^{210,247–249}. **b** | Mean pulmonary artery pressure (mPAP) is consistently highest during adolescence and early adulthood among those who were preterm infants with bronchopulmonary dysplasia (BPD)^{205,210}. * $P < 0.05$ by two-way ANOVA with Sidak's multiple comparisons test.

Table 1 |

Definitions of BPD

Study	Year	Comment	Ref.
Northway et al.	1967	Initial report of chronic pulmonary disease in survivors of severe RDS; stages 1–4 describe progressive emphysema and fibrosis attributed to oxygen toxicity and high ventilator pressures	1
Shennan et al.	1988	Defined BPD as requirement for supplemental oxygen at 36 weeks PMA, based on a positive predictive value of 63% for abnormal pulmonary outcomes at 2 years of age	106
NHLBI workshop	2001	Developed a more comprehensive definition for BPD, made after 28 cumulative days of supplemental oxygen; severity classified based on oxygen use at 36 weeks PMA, with a scale of mild (room air), moderate (<30% supplemental oxygen) and severe (>30% supplemental oxygen or positive pressure)	108
Walsh et al.	2004	Adds a 'physiological' test to the NHLBI workshop definition to assess need for supplemental oxygen at 36 weeks PMA; infants classified as having BPD if oxygen saturation falls to <90% within 60 min of a room air challenge test	27
NICHD workshop	2018	Revision of BPD definition that removed the requirement for 28 days of oxygen therapy prior to 36 weeks PMA, added a requirement for radiographic confirmation of parenchymal lung disease and used a severity grading of I-III that incorporated newer modes of non-invasive ventilation	3
Isayama et al.	2017	Proposed the use of oxygen and/or respiratory support as a better indicator of chronic respiratory insufficiency than oxygen alone, and that assessment at term equivalent (40 weeks PMA) increases the predictive value	14
Svedenkraans et al.	2019	Proposed modification of the 'physiological test' that uses simultaneous measurement of FiO ₂ and peripheral saturation to calculate rightward 'shift' of the oxyhaemoglobin dissociation curve at any given point in time	112
Jensen et al.	2019	Proposed modification of NICHD workshop definition, which uses positive pressure instead of supplemental oxygen to classify BPD severity at 36 weeks PMA; scale is: no BPD (no support), grade 1 (nasal cannula 2 l/min), grade 2 (nasal cannula >2 l/min or non-invasive positive airway pressure) and grade 3 (invasive mechanical ventilation)	113

BPD, bronchopulmonary dysplasia; FiO₂, fraction of inspired oxygen; NHLBI, National Heart, Lung, and Blood Institute; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; PMA, post-menstrual age; RDS, respiratory distress syndrome.

Table 2 |

Selected biomarkers associated with BPD pathogenesis

Category or causal pathway	Biomarker ^a	Refs
Endothelial injury and dysfunction	Circulating endothelial progenitor cells	124
Growth and angiogenesis factors	VEGF and VEGFR, endoglin (CD105), angiotensin II, endostatin, PIGF and EMAP II	125-128,130,131
Epithelial injury and fibrosis	KL6, MMP9, TIMP1, TGFβ1 and NGAL	82,132-135
Nitric oxide deficiency and insufficiency	NO _x and citrulline	120,136-140
Oxidative stress, redox status	Elastase, myeloperoxidase, xanthine oxidase, catalase, total sulfhydryls, carbonyls, 3-chlorotyrosine, malondialdehyde and 3-nitrotyrosine	144,284-286
Inflammation and host immune responses	Inflammatory biomarker panels and hyaluronan	129,145,146
Omics	Genomics, epigenomics, metabolomics, microbiomics, methylomics and transcriptomics	34,119,147-149,243
Vascular injury and pulmonary hypertension	BNP and NT-proBNP and echocardiographic measurement	83,123,140,151
Lung function	Dynamic compliance, airway resistance, functional residual capacity, etCO and exhaled NO	82,119,150
Lung structure	Imaging by hyperpolarized gas MRI and helium-3 MRI	119

BNP, B-type natriuretic peptide; BPD, bronchopulmonary dysplasia; EMAP II, endothelial monocyte-activating polypeptide II; etCO, end tidal carbon monoxide; KL6, Kerbs von Lungren 6 antigen; MMP9, matrix metalloproteinase 9; NGAL, neutrophil gelatinase-associated lipocalin; NO, nitric oxide; NO_x, nitric oxide metabolites; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PIGF, placental growth factor; TGFβ1, transforming growth factor β1; TIMP1, tissue inhibitor of metalloproteinase 1; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

^aSelected biomarkers that have been studied in human infants with and without BPD.

Table 3 |

Interventions to minimize lung injury in premature infants

Intervention	Rationale	Level of evidence	Clinical implications	Refs
Caffeine	Reduced time on ventilator leading to less lung damage	High quality: large RCT with long-term follow-up	Recommended for use in extremely preterm infants at the doses used in the CAP trial	174,175
Ventilation (conventional, high-frequency oscillation or jet ventilation)	Volutrauma is an important pathophysiological mechanism	Moderate quality: despite many RCTs, evidence of a substantial benefit of one mode is lacking	BPD rates remain high in all trials, suggesting that establishing and maintaining skills with a chosen mode may be the most important factor	256,257
Less-invasive surfactant therapy	Avoids the risks of endotracheal intubation	Low quality: small RCTs, imprecise estimates of safety and efficacy	Very promising, but more research required	166-168
Vitamin A	Low levels seen in preterm infants; vitamin A required for normal lung growth	Moderate quality: meta-analysis suggests a small reduction in rates of death or BPD	Depends on local incidence of BPD; trade-off between the modest reduction in BPD and acceptability of intramuscular treatment	261
Targeting lower oxygen saturation levels throughout NICU stay	Avoidance of high oxygen levels may reduce BPD	High quality: individual patient data meta-analysis of five high-quality RCTs	Targeting higher oxygen saturations (91–95%) improves survival rates without increasing risk of BPD	198
Glucocorticoids				
Dexamethasone	Reduced inflammation allowing earlier extubation	Moderate quality: meta-analyses and meta-regression of numerous small trials	Low-dose, short courses that are useful for ventilated infants at highest risk of BPD	259,260
Hydrocortisone	Avoids adverse neurodevelopmental effects of dexamethasone	Moderate quality: small RCTs, imprecise estimates of safety and efficacy	Promising, but more research into neurodevelopmental outcomes is required	
With surfactant	Better distribution of steroids and reduced systemic effects	Low quality: small RCTs, imprecise estimates of safety and efficacy	Very promising, but more research required	191

BPD, bronchopulmonary dysplasia; CAP, Caffeine for Apnea of Prematurity; RCT, randomized controlled trial.