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Bronchopulmonary dysplasia in 2013

Advances in perinatal medicine over the last few decades have resulted in the survival of many more preterm babies who are at risk of long-term complications of prematurity. This review will discuss the changing characteristics of bronchopulmonary dysplasia over time and look at progress in current management strategies, considering both prevention and treatment of established lung disease.

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Key points

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1. BPD is an important cause of morbidity and mortality in preterm infants.
2. Strategies to prevent BPD begin with good antenatal care and lung protection strategies from the initiation of breathing at birth.
3. Non-invasive respiratory support should be used preferentially to avoid mechanical ventilation induced lung injury.
4. BPD is a chronic condition requiring a multidisciplinary approach to management.

Advances in perinatal care in the last few decades have reduced mortality for premature babies born at less than 32 weeks' gestation. This has led to an increasing number of survivors with long-term complications of prematurity. Bronchopulmonary dysplasia (BPD) is the major pulmonary complication of preterm birth and is an important cause of morbidity and mortality in this group of infants.

Background and definition

Before the 1960s and the introduction of neonatal mechanical ventilation, preterm babies who developed respiratory distress syndrome (RDS) either died in the first week of life or survived without respiratory sequelae. BPD, or chronic lung disease, was first described by Northway and colleagues in 1967 in preterm babies who developed oxygen dependency beyond the first 28 days of life[1]. They described the clinical, radiological and histological changes in the lungs of babies who had initial RDS and were treated with oxygen and high-pressure mechanical ventilation. These babies were mature by today's standards, with a mean gestation of 34 weeks and birthweight of 2.4kg. The pathological appearance of the lungs and bronchi was characterised by airway inflammation, fibrosis and smooth muscle hypertrophy.

Over the last four decades, advances in the management of preterm babies including antenatal steroids, surfactant therapy, gentle ventilation techniques, postnatal steroids and improved nutritional strategies, have altered the population of babies affected by BPD. As a result, the definition of BPD has needed to evolve over time. BPD is now infrequent among babies born greater than 1200g or

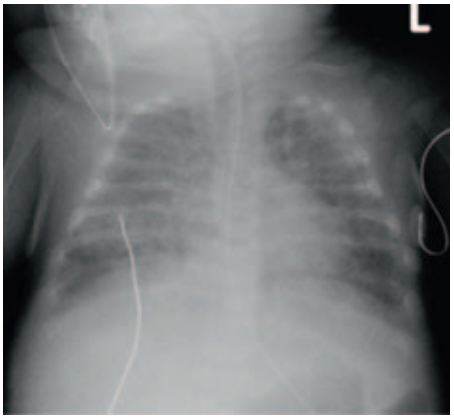

FIGURE 1 A chest radiograph of a baby with BPD born at 26 weeks' gestation (corrected to 36 weeks) showing diffuse bilateral haziness with areas of atelectasis and over inflation.

30 weeks' gestation. In the 'new BPD' there is lung developmental arrest occurring before alveolarisation, which normally begins around 30 weeks' gestation. The lungs become remodelled with larger and fewer alveoli, resulting in a reduced surface area for gas exchange (**FIGURE 1**). Alveolar and lung vascular development are closely related and the developing pulmonary microvasculature is also likely to be affected[2].

The consensus definition of BPD from the US National Institutes of Health (NIH) categorises severity based on the level of respiratory support required at 36 weeks' postmenstrual age[3] (**TABLE 1**). Walsh et al proposed physiological criteria in an attempt to standardise the definition of BPD and reduce the variation in observed rates between centres. In this definition, babies between 35-37 weeks' corrected gestation who are treated with mechanical ventilation, continuous positive airway pressure (CPAP) or supplemental oxygen concentration of 30%, and have oxygen

saturations of 90-96% are diagnosed with BPD without additional testing. Babies requiring supplemental FiO_2 <0.3 require an oxygen reduction test to determine if they have BPD or not[4].

Epidemiology

The incidence of BPD is inversely related to both birthweight and gestational age, with up to 75% of extremely low birthweight (ELBW) babies (<1000g) affected in some studies[5]. BPD is uncommon in babies born after 30 weeks' gestation and the incidence in babies greater than 1500g birthweight has been reported to be as low as 5%[6]. Although the overall incidence is approximately 20% of all ventilated newborns, wide variability exists among centres. This may reflect the numbers of babies with extreme prematurity, variations in patient management and regional differences in the definition of BPD. These differences have led to speculation that some BPD could be preventable with implementation of specific quality improvement initiatives aimed at reducing lung injury[7].

Pathogenesis

BPD has a multifactorial aetiology (**FIGURE 2**). Preterm babies have immature lungs and may also have encountered additional challenges such as chorio-amnionitis. Many of these factors can play a part in the development of BPD by influencing lung architecture or by triggering an inflammatory response during a critical stage of lung growth. Inflammatory lung injury may be followed by abnormal repair and remodelling which results in the histological changes found in BPD[8]. There may also be a genetic predisposition as BPD is more common if there is a family history of reactive airways disease. Racial and gender differences can also affect the severity of the disease[5].

Antenatal and postnatal infection or inflammation are also important factors in the development of BPD. BPD was typically associated with maternal chorioamnionitis in many cohort studies, however more recently some studies have shown no difference or a decreased risk and therefore the relationship may depend on the interplay between inflammation exposure and additional risk factors such as volutrauma[9,10]. Neonatal sepsis is strongly correlated with BPD with coagulase-negative Staphylococcal infection as strongly associated with BPD as infection with other gram positive and gram negative organisms[11].

Gestational age	<32 weeks	>32 weeks
Time of assessment	36 weeks PMA or discharge	>28 days, but <56 days' postnatal age or discharge
No BPD	>21% oxygen for <28 days	>21% oxygen for <28 days
Mild BPD	Room air	Room air by 56 days
Moderate BPD	<30% oxygen	<30% oxygen to 56 days
Severe BPD	>30% oxygen or respiratory support	>30% oxygen or respiratory support

TABLE 1 Definition of BPD by gestational age for babies receiving oxygen treatment for longer than 28 days, according to US National Institutes of Health (NIH).
Key: PMA = postmenstrual age.

Mechanical ventilation may cause damage if the lungs are inadvertently stretched by using high tidal volumes (volutrauma). Even a small number of large volume breaths can cause lung damage, especially in non-compliant surfactant-deficient lungs, although BPD is seen most frequently in babies who need prolonged mechanical ventilation. Mechanisms of ventilator-induced lung injury (VILI) also include high airway pressure (barotrauma), alveolar collapse and re-expansion (atelectotrauma) and increased inflammation (biotrauma). Injury may occur during the initial delivery room stabilisation, when there is a fine balance between inflating the lungs using positive pressure ventilation while attempting not to overdistend them.

The presence of a haemodynamically significant patent ductus arteriosus (PDA) is also associated with an increased risk of BPD. Damage to the lung endothelium from a left-to-right shunt in addition to the increased need for ventilatory support due to pulmonary fluid overload, may be the reason for this. However PDA ligation increases the risk of BPD rather than reducing it[12].

Prevention of BPD

Prevention of BPD begins with optimising antenatal care of women at risk of delivering prematurely followed by careful early respiratory management of the preterm baby, including strategies for lung protection.

Antenatal

BPD prevention begins with good obstetric care. There are circumstances where pregnancy can be prolonged with the correct treatment, such as progesterone for short cervix or antibiotics for preterm prelabour rupture of membranes, although there is no evidence that these directly affect the risk of BPD. Administration of antenatal corticosteroids is now the standard of care for women who are at high risk of delivering prematurely in order to assist fetal lung maturation. The use of antenatal steroids reduces the rate of death and RDS by 50%, however does not improve rates of BPD. In animal studies, antenatal steroid exposure reduces the amount of collagen in the lung extracellular matrix and this may theoretically predispose the lung to an increased risk of stretch-related damage[13].

Postnatal

Ventilation strategies and pharmacological treatments play a role in prevention of BPD, and lung protection should be implemented from initiation of breathing in the delivery suite.

Strategies for lung protection

One approach to attempt to reduce BPD is to avoid intubation and mechanical ventilation altogether by using non-invasive respiratory support as much as possible. Recent trials comparing initiation of early CPAP rather than intubation and surfactant show that the babies who commenced CPAP from birth had no increased risk of BPD or death, and were less likely to be in oxygen at 28 days[14]. Initial CPAP followed by rescue surfactant administration as part of the INSURE approach (INtubate-SURfactant-Extubate) has been associated with lower rates of BPD, compared with initial CPAP followed by surfactant administration and continued ventilation[15]. A large clinical trial from the Vermont-Oxford Network compared three different approaches to initial respiratory management of preterm babies. They were randomised to one of three groups:

1. Intubation, surfactant and ventilation
2. Intubation, surfactant and extubation to CPAP
3. CPAP with selective surfactant treatment.

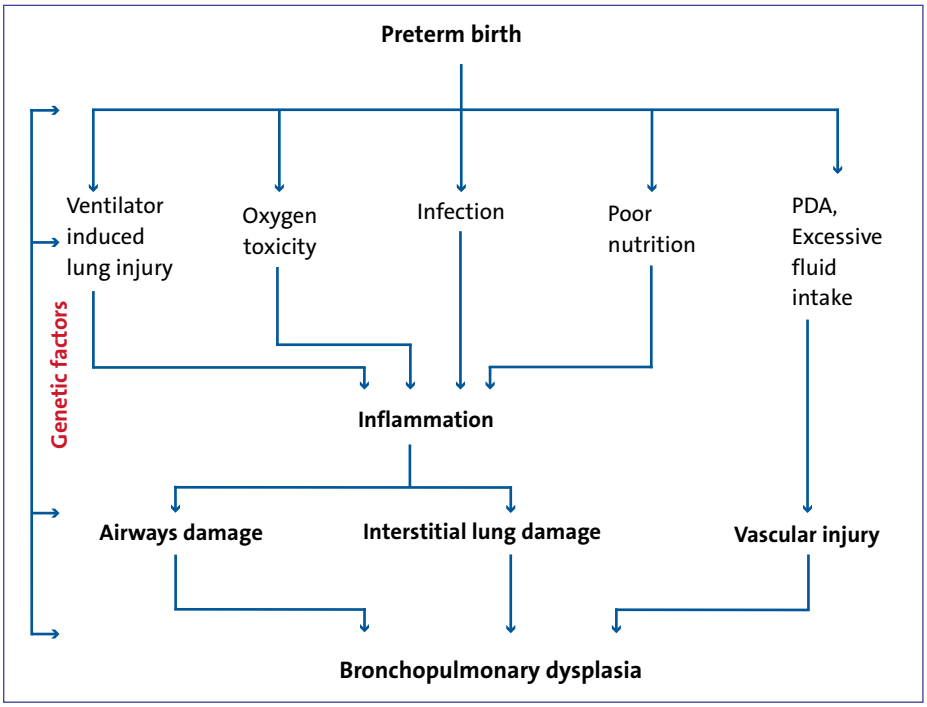

FIGURE 2 The pathogenesis of BPD. Key: PDA = patent ductus arteriosus.

In this trial the outcomes of death or BPD were not different between groups, but qualitatively favoured the CPAP groups[16]. New techniques are being evaluated to deliver surfactant to preterm babies on CPAP using a narrow-bore tracheal catheter (minimally invasive surfactant therapy) and this appears to be a feasible alternative to intubation[17]. Nasal intermittent positive pressure ventilation (NIPPV) was shown in small trials to have benefits over nasal CPAP in terms of reducing extubation failure; however a recent large randomised trial of over 1,000 babies has concluded that NIPPV does not confer additional benefit or risk for survival to 36 weeks without BPD[18].

When mechanical ventilation is necessary, the overall aim is to provide 'gentle' ventilation ie to give the smallest amount of respiratory support needed to adequately oxygenate and ventilate, in order to minimise the risk of lung damage caused by VILI. Many clinical trials have attempted to identify the optimal mode of mechanical ventilation for preventing BPD. High frequency oscillation ventilation and conventional ventilation are equivalent in terms of BPD prevention[12]. However lower rates of BPD are found when using volume-targeted ventilation rather than pressure-limited modes[19]. Volume-targeted strategies aim to deliver a consistent tidal volume in order to reduce lung damage from overdistension and stabilise pCO_2. When mechanical ventilation is needed, a short inspiratory time should be used (0.24-0.4 seconds), in addition to minimising peak inspiratory pressures (14-20cmH_2O), using moderate positive end-expiratory pressure (4-6cmH_2O) and targeting tidal volumes (3-6mL/kg)[20,21]. Tolerating a moderately higher $PaCO_2$ (permissive hypercapnia) has shown a trend towards reduction of BPD without significant adverse effects[22].

Avoidance of hyperoxia

Oxygen is one of the most frequently used drugs in the NICU, however it is clear that high inspired oxygen concentrations contribute to the development of BPD[3]. The goal of oxygen therapy is to deliver adequate oxygenation to the tissues without causing oxygen toxicity. The appropriate level of oxygenation for preterm babies to maximise survival without causing significant morbidity remains unknown and is the subject of ongoing clinical trials. Results from the NeOProM Collaboration, a prospective meta-analysis of five large randomised trials of oxygen saturation targeting will be published in 2014, and should offer some guidance. Currently a wide variation in oxygen saturation target levels exists among centres but is generally 90-95%[23]. Lower targeted saturations can reduce retinopathy of prematurity (ROP) and, to a lesser extent, BPD but are associated with increased mortality, particularly in extremely preterm babies.

Methylxanthines

Caffeine therapy improves successful extubation and reduces BPD (36% vs 47%)[24,25]. The mechanism by which caffeine decreases the incidence of BPD is unknown, although it is likely to be due to the fact that babies on caffeine can be extubated more quickly, resulting in less VILI.

Systemic corticosteroids

Postnatal steroids, of which dexamethasone has been the most studied, remain a controversial therapy to reduce BPD. Steroids were previously widely used to facilitate extubation, however their use has declined due to concerns about adverse effects on head growth and worse long-term neurodevelopmental outcomes. Follow-up studies from some of the original randomised trials have shown an increased incidence of neurological sequelae with early use (<8 days)[26]. However dexamethasone is very effective for weaning from mechanical ventilation and reducing BPD if used 'moderately early' (7-14 days) or 'delayed' (>3 weeks)[27,28]. Given the evidence of both benefits and potential adverse effects of postnatal steroids they should be used on a case-to-case basis rather than prescribed routinely and the dose and duration of any course of steroid treatment should be minimised. The higher the risk of BPD, the more likely the benefit of steroids will outweigh the risks[29]. Recent case series have suggested that even tiny doses of dexamethasone may be effective at facilitating extubation[30].

Antioxidants

Vitamin A (retinol) is required for promotion of growth and differentiation in many organs, including the lung. Preterm babies have low vitamin A levels at birth, and this has been associated with an increased risk of BPD[12]. Intramuscular vitamin A therapy reduces BPD in ELBW babies, with one additional infant surviving without BPD for every 14-15 treated[31]. The need for intramuscular injections, perceived small clinical benefit and lack of improved neurodevelopmental outcomes have limited use of this treatment. There is no apparent benefit of vitamin E or the enzyme superoxide dismutase in BPD prevention.

Nutrition

Nutrition has a direct effect on the developing lung and postnatal

malnutrition compromises lung growth. Preterm babies are often fluid restricted, as excessive fluid intake in the first ten days after birth increases the risk of BPD. However babies with established BPD have increased nutritional demands and may need between 20-40% more calories[32]. Nutritional management of very low birthweight (VLBW, <1500g) babies should therefore be addressed from the first day of life.

Nitric oxide

Inhaled nitric oxide therapy does not improve pulmonary outcome in preterm babies with hypoxic respiratory failure, nor is it beneficial in well preterm babies in terms of promotion of lung angiogenesis to prevent BPD, and therefore its use in this population is not recommended[33].

Surfactant therapy

Surfactant therapy has dramatically improved respiratory outcomes in ELBW babies, although has not in itself led to a decrease in BPD.

Mast cell stabilisers

Cromolyn sodium is a mast cell stabiliser that is used in the management of asthma. Clinical trials have not shown any benefit in the prevention of BPD.

Azithromycin

Azithromycin and other macrolide antibiotics have both anti-inflammatory actions in addition to their antibiotic properties. They are used to treat ureaplasma infections, which can be found in chorioamnionitis and have been studied as potential therapies for BPD prevention. In a randomised trial of VLBW babies, treatment with azithromycin compared with placebo showed no benefit, except in a subgroup of babies who were infected with ureaplasma and had reduced incidence of BPD[34]. A further larger trial is planned to determine the role of azithromycin in BPD prevention (TINN2 trial).

Treatment of established BPD

Despite best efforts, a number of babies become stuck on prolonged respiratory support and supplemental oxygen related to lung injury incurred during the course of their hospital stay. Beyond a certain point, the focus will change from prevention of BPD to consideration of management of established BPD, and in many centres this is done in collaboration between neonatology teams, pulmonologists and sometimes cardiologists. Treatments are directed at trying to optimise lung mechanics, improve pulmonary blood flow and prevent further lung injury.

Nutrition

Malnutrition can worsen BPD by compromising lung growth. In addition, some medications used in BPD management (eg steroids and diuretics) can have adverse effects on growth. Feeding difficulties in these babies, such as swallowing difficulties and gastro-oesophageal reflux (GOR) can further affect nutritional status. Provision of adequate calories is critical. Infants who have established BPD continue to have increased calorie expenditure around 25% above their usual needs, and 30-65% have growth failure soon after initial hospital discharge[32].

Diuretics

Diuretics are often used in babies with established BPD to decrease pulmonary oedema and improve lung function. A systematic review of furosemide showed no or inconsistent effects and therefore use of systemic loop diuretics is not recommended[35]. There has been more success shown, in terms of improved pulmonary function, using the combination of thiazides and spironolactone in babies with moderate BPD, however there is no evidence to show that it improves long-term outcomes[36].

Management of pulmonary hypertension

There is a lack of consensus for when to screen babies who have BPD for pulmonary hypertension, however the incidence is reported to be up to 43% and the condition carries significant mortality[37]. The severity of pulmonary hypertension correlates with the severity of BPD. Treatment options that are occasionally considered include sildenafil and bosentan, usually given under the direction of a paediatric cardiologist or pulmonologist.

Home oxygen therapy

Low flow supplemental oxygen can be administered at home and facilitates earlier hospital discharge for babies requiring oxygen, most of whom are not ready to go home until their oxygen requirement is ≤0.5L/min. The benefits of oxygen therapy are to prevent pulmonary hypertension, reduce intermittent desaturations, reduce airway resistance and optimise growth[38]. Careful consideration of the suitability of families for home oxygen is needed, including a smoker-free household, ability to operate oxygen cylinders and training for when to seek assistance. The duration of oxygen therapy varies but most babies can discontinue treatment by their first birthday.

β agonists

Salbutamol inhalation may result in short-term improvement for babies with BPD during an exacerbation by increasing compliance and reducing pulmonary resistance. However, when used for chronic management of BPD there is no significant effect on duration of the disease.

Passive immunisation

Respiratory syncytial virus (RSV) can cause severe and sometimes fatal respiratory infections in babies with BPD. Palivizumab is a recombinant monoclonal antibody against RSV that can be administered intramuscularly to confer passive immunisation and decrease the incidence of hospital readmission and morbidity in babies with BPD. The current UK Department of Health guidelines advise prophylaxis with palivizumab for children less than two years' old who have received treatment for BPD within the previous six months.

Long-term outcomes

The majority of babies with BPD now ultimately survive. It is a chronic illness that persists long after hospital discharge, with effects that can be seen into adulthood. Apart from pulmonary disease, BPD has other multisystem complications that affect growth, cardiovascular status and neurodevelopment. Following discharge infants often require frequent hospital readmission for respiratory illnesses, which are most common in the first two years of life. Babies with severe BPD are at high risk of long-term pulmonary and neurological sequelae. Even when controlling for gestation, BPD is an independent risk factor for neuro-developmental impairment. VLBW infants with BPD have greater language delay in addition to more marked fine and gross motor impairment[39]. Recently published follow-up of children with BPD until eight to nine years of age has shown significantly abnormal lung function compared with term controls[40].

Conclusion

BPD remains a major complication of preterm birth and presents an ongoing challenge for the future. Progress in prevention and management strategies has been made and in the future neonatologists will aim to avoid mechanical ventilation in many more babies and improve non-invasive ventilation techniques. New ideas to prevent BPD show promise, such as the administration of surfactant with added budesonide as an anti-inflammatory agent. Continued research to develop management strategies will hopefully lead to a sustained improvement in the outcomes of preterm babies in the future.

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