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Advances in treating bronchopulmonary dysplasia

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SUMMARY

Introduction: Bronchopulmonary dysplasia (BPD) is a common long-term adverse complication of very premature delivery. Affected infants can suffer chronic respiratory morbidity including lung function abnormalities and reduced exercise capacity even as young adults. Many studies have investigated possible preventative strategies, but it is equally important to identify optimum management strategies for infants with evolving or established BPD and the focus of this review.

Areas covered: Respiratory support modalities and established and novel pharmacological treatments.

Expert commentary: Respiratory support modalities including proportional assist ventilation and neurally adjusted ventilatory assist are associated with short term improvements in oxygenation indices. Such modalities now need to be investigated in appropriate RCTs. Many pharmacological treatments are routinely used with a limited evidence base, for example diuretics. Stem cell therapies in small case series are associated with promising results, but more research is required before it is possible to determine if such therapies should be investigated in large RCTs with long-term outcomes.

Keywords

Bronchopulmonary dysplasia

Prematurity

Pulmonary

Mesenchymal stem cells

Diuretics

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common long-term adverse outcome of very premature delivery. BPD is currently defined as a requirement for treatment with supplemental oxygen for more than twenty-eight days and then categorised at 36 weeks post-menstrual age for severity according to the level of respiratory support required [1]. The so-called 'new BPD' is characterised by impairment of alveolarisation and vascularisation of pulmonary vessels [1]. Unfortunately, it is associated with chronic respiratory morbidity [2, 3]. This includes chronic oxygen dependency which, in the most severely affected cases results in a supplementary oxygen requirement at home [3]. In addition, children who have had BPD can have troublesome respiratory symptoms requiring treatment and lung function abnormalities at follow up. These problems may persist at least into young adulthood [4]. It is, therefore, essential infants with BPD are appropriately treated to reduce long term adverse outcomes. It has, however, been demonstrated amongst infants with severe BPD cared for in eight neonatal intensive care units in the USA, there was variation between centres in the use of mechanical ventilation at 28 days and 36 weeks post-menstrual age (PMA) and the use of diuretics, inhaled corticosteroids and inhaled β-antagonists. The authors concluded that the variation likely reflected the lack of evidence in guiding optimal management of such infants [5]. Our aim, therefore, was to review the literature to identify evidence-based management strategies and promising treatments for infants with BPD.

1. Respiratory support modalities

Many infants with evolving or established BPD require mechanical ventilation. Indeed, we have shown that infants who were ventilator dependent at seven days were extremely likely to develop BPD (99% sensitivity) [6]. There is, however, limited evidence to determine which ventilator mode should be used in infants with evolving or established BPD.

1.1 Volume targeted ventilation (VTV)

VTV has been demonstrated in a systematic review of eighteen trials to be associated with a lower incidence of BPD at 36 weeks post menstrual age when compared with pressure limited ventilation strategies [7]. In a study of eighteen infants with evolving or established BPD the work of breathing (WOB), determined by measurement of the pressure time product of the diaphragm, was assessed at different levels of targeted volume ventilation. Only at a target tidal volume of 7 mls/kg was the WOB reduced significantly below baseline [8], that result likely reflects the increased physiological dead space in infants with BPD [9]. Whether use of such a target tidal volume in infants with BPD improves their long-term outcome needs investigating.

1.2 Proportional assist ventilation (PAV)

During PAV, the applied pressure is servo controlled throughout each spontaneous breath. The applied pressures increase in proportion to the tidal volume (elastic unloading) or flow (resistive unloading) generated by the patient. The frequency, timing and magnitude of lung inflation are controlled by the patient [10]. In a randomised, crossover study of four-hour epochs, PAV compared to patient triggered

ventilation (PTV) was associated with significantly lower mean airway pressure (MAP) and peak inflation pressure (PIP), but similar blood gases. The duration of desaturations, however, was significantly longer during PAV [11]. Since then, the back-up facility has been enhanced. Two recent studies in infants with evolving or established BPD have shown PAV was associated with a reduction in the oxygenation index compared to assist control ventilation (ACV) when each were studied in one hour epochs [12] and similarly when each were studied for four hour epochs [13]. In addition, the WOB was lower after one hour of PAV compared to one hour of ACV [12].

1.3 Neurally adjusted ventilatory assist (NAVA)

During NAVA, the diaphragmatic electrical (Edi) activity triggers ventilator inflations [14] and also unloads the infant's respiratory abnormalities by delivering pressure proportional to the Edi signal. The clinician can set the NAVA level (or gain factor) to increase or decrease the level of respiratory support delivered by the ventilator. In one study of 29 preterm infants, 21 of whom had severe BPD and were mechanically ventilated at greater than four weeks post menstrual age, there was a significant improvement in oxygen saturation levels and reduced $PaCO_2$ levels when the infants were transitioned to NAVA [15]. The WOB was measured in only nine of the infants, but in all it was significantly lower on NAVA [15]. In a randomised crossover study of preterm infants with evolving or established BPD, nine infants were randomised to receive assist control ventilation (ACV) or NAVA for one hour and then switched to the other mode of ventilation for a subsequent hour. On NAVA, the oxygenation index was significantly lower [16]. A retrospective study of 14 preterm infants who underwent tracheostomy and mechanical ventilation for more than six months

demonstrated that the nine who had been supported by NAVA for at least two months had less cyanotic episodes and received less sedation and dexamethasone [17]. Both PAV and NAVA give the ability to unload the infant's lung function abnormalities, hence the explanation for the improvements in oxygenation indices in short-term studies compared to traditional triggered modes. The two modes now need to be compared to determine which mode should be investigated further in a large RCT investigating long-term efficacy in infants with BPD.

1.4 Home ventilation

Infants with severe BPD when ventilated at home require to be able to trigger a portable ventilator [18]. Portable ventilators such as the LTV 1200 (CareFusion, Yorba Linda, CA) and Trilogy 202 (Philips Healthcare, Andover, MA) have less rapid response times with an increase in dead space compared to intensive care ventilators [18]. Infants with poor trigger response on portable ventilators can experience ventilator asynchrony requiring sedation and an increase in ventilatory settings [18]. It is, therefore, crucial in order to be able to transition these infants early to portable home ventilators that the most appropriate ventilator is used. A pilot study of six infants with severe BPD who were mechanically ventilated via tracheostomy demonstrated with each infant acting as their own control, there was a statistically significant higher number of spontaneously triggered breaths with the Trilogy 202 ventilator compared to the LTV 1200 and infants had a lower work of breathing and better synchrony [18]. Clearly, larger studies are required to identify the optimum ventilator type and more studies developing devices to optimise home ventilators are required.

1.5 Non-invasive ventilation

Volutrauma is an important risk factor for lung injury, thus in infants with BPD it is important to extubate them as soon as possible. Unfortunately, there are few studies to determine which is the most appropriate non-invasive mode to support such infants. In a crossover study of twenty infants with evolving or established BPD, and a median postnatal age of 30.9 weeks, the WOB did not differ significantly when the infants were supported by positive airway pressure (CPAP) or heated humidified, high-flow nasal cannulae (HHFNC). There were also no significant differences in the oxygen saturation levels of infants between the two modes [19]. The infants included in the study had relatively mild chronic respiratory distress and it would be important to assess if such results are generalisable to all BPD infants and confirmed in randomised trials.

1.6 Heliox

Heliox is a helium-oxygen mixture (80:20 ratio) and due to its reduced density may improve gas flow in the airways by reducing turbulence and increasing oxygen and carbon dioxide diffusion in the alveoli. In a pilot study of 15 infants with severe BPD who were ventilation dependent, heliox during mechanical ventilation was associated with a reduction in the oxygenation index and improvement in compliance and peak expiratory flow rate. The study, however, was very short-term, comparison of two epochs of sixty minutes. Longer term studies are required to appropriately assess the efficacy of this treatment [20].

2. Pharmacological

2.1 Corticosteroids

2.1.1 Systemic corticosteroids

A systematic review of nineteen randomised controlled trials which in total included 1345 preterm infants who were either oxygen or ventilator dependent at greater than three weeks of postnatal age demonstrated corticosteroid treatment aided extubation success and reduced chronic lung disease at 36 weeks PMA aiding discharge to home oxygen therapy [21]. Systemic administration of corticosteroids, however, has been demonstrated to have long-term adverse effects. A retrospective study which included preterm infants who were either ventilator dependent or requiring continuous positive airway pressure support with an oxygen requirement of greater than 30% at beyond twenty-one days after birth [22] demonstrated infants who received dexamethasone had worse neurodevelopmental impairment at 18-22 months of corrected age [22]. Within the corticosteroid group, a cumulative dose greater than 5mg/kg was shown to be significantly associated with adverse neurodevelopmental outcomes [22]. Respiratory function at 11 to 14 years has been shown to be significantly impaired in those who received postnatal dexamethasone either as prevention or treatment for BPD [23]. It has also been reported that 18 year olds who were born extremely prematurely and received a cumulative mean dose of 7.7 mg/kg had smaller total brain volumes and smaller white matter, thalami and basal ganglia volumes on T1-weighted magnetic resonance imaging. There was a trend of small total brain and white matter volumes with increasing doses of postnatal dexamethasone [24].

A moderate ($\leq$ 4 mg/kg cumulative dose) versus a high (> 4mg/kg cumulative dose) was associated with an increased risk of BPD (RR 1.5 (1.01-2.22)) and increased

abnormal neurodevelopment (RR 8.33 (1.63-42.48)), but early versus moderately early or delayed administration was not associated with an increased risk in the primary outcome. A pulse (three days of 0.5 mg/kg/day) versus a continuous course was associated with an increased risk of death or BPD [25].

2.1.2 Inhaled corticosteroids

In a review of 1429 infants with evolving BPD at 28 days, born less than 29 weeks of gestation in 335 USA units, 25% (0-60%) received inhaled steroids (betamethasone, budesonide or fluticasone) from three weeks of age, use peaking on day 67. Use was most common in those born below 24 weeks of gestational age and who required prolonged ventilation [26]. The evidence to support such usage is, however, limited. Late inhalation of inhaled steroids (> 7 days) had been assessed in eight trials, but only including in total randomisation of 232 infants. There were no significant differences in BPD or death or in the durations of mechanical ventilation of oxygen dependency. There was, however, a reduced risk of failure to extubate (RR 0.80, 95% CI 0.66-0.98) [27]. Long-term outcomes have rarely been reported, but short-term efficacy appears dose related [28]. Hydrofluoroalkane-beclomethasone diproprionate is a new inhaled corticosteroid with a unique small size (1.1μm) compared to 3.4 to 4 μm of chlorofluorocarbon-beclomethaonse diproprionate, 2 to 3.2 μm of fluticasone and 3.5 μm of budesonide. This means there is greater lung deposition thus a small dose can be used. In a double-blind, randomised placebo- controlled pilot study assessing the efficacy of hydrofluoroalkane beclomethasone dipropronate in infants with moderate to severe BPD, no significant differences were seen between the two groups with regard to length of stay, rehospitalisations or requirement for additional

steroids. The authors, however, admit the study was underpowered as only 38 infants were included [29].

2.1.3 Inhaled versus systemic corticosteroids

Randomised or quasi-randomised trials have compared inhaled versus systemic steroids in infants ventilator dependent after the first weeks after birth, such infants are extremely likely to develop BPD [6]. Systematic review of three trials which included in total 431 infants randomised at 12 days or later demonstrated that there was no significant difference in the incidence of death or BPD at 36 weeks PMA, the relative risk was 1.04 (95% CI (0.86-1.26)). Equally, there was no evidence of difference in adverse events profile [30].

2.1.4 Inhaled bronchodilators

A retrospective review of 1429 infants born at less than 29 weeks of gestational age demonstrated 33% had received bronchodilators. The length of mechanical ventilation (>54 days OR 19.6) best predicted bronchodilator use. The frequency and duration, however, were very variable between centres [31]. That variability likely reflects the lack of evidence to support bronchodilator use. Studies in ventilated infants have shown only short-term benefits in ventilated infants. At follow up, however, RCTs in wheezy prematurely born infants have highlighted reduced symptoms [32, 33].

2.2 Leukotriene receptor blockade

Montelukast is a selective leukotriene receptor antagonist of cysteinyl leukotriene [34]. Cysteinyl leukotriene causes bronchoconstriction, mucus secretion, airway

hyperactivity and increased vascular permeability [35]. The effect of daily montelukast therapy (1 mg/kg increasing to 1.5 mg/kg and finally 2 mg/kg) for at least three weeks administered to 11 preterm infants who required mechanical ventilatory support at twenty-eight days after birth was compared to eleven controls [36]. Seven controls died due to respiratory failure, whereas the one non-survivor in the montelukast group died post operatively from sepsis following necrotizing enterocolitis. There was also a significant decrease in the pulmonary severity score or the duration of ventilation between the groups [36]. No adverse effects related to montelukast therapy were reported. The study, however, was not randomised nor blinded, but the controls were matched for gestational age, birth weight and pulmonary severity score [36]. A subsequent study which was a prospective, multicentre, randomised controlled trial of 66 infants born at less than 32 weeks of gestational age with a postnatal age greater than 14 days, all ventilator or supplementary oxygen dependent demonstrated no significant difference in the incidence of moderate to severe BPD (43.4% versus 52.8%, p=0.912) [37]. The long-term efficacy of montelukast needs to be determined in an appropriately randomised trial.

3. Pulmonary vasodilators

Infants with severe BPD can experience both systemic and pulmonary hypertension which contributes to their respiratory and cardiovascular morbidity [38]. Infants with severe BPD and pulmonary hypertension are at greater risk of mortality [39]. Systemic hypertension, arterial thickness and stiffness and increased systemic afterload may all contribute to BPD pathophysiology by altering left ventricular (LV) function and increasing pulmonary venous congestion by lowering end-diastolic

compliance [40]. A systematic review demonstrated that risk factors for the development of pulmonary hypertension in BPD infants were the duration of mechanical ventilation, length of stay, oligohydramnios, use of high frequency oscillation, small for gestational age, sepsis and severity of BPD. Birth weight and gestational age were inversely related to pulmonary hypertension development [41].

3.1 Inhaled nitric oxide

Inhaled nitric oxide was shown in a non-randomised study to improve oxygenation in infants with BPD, but only 11 of 16 infants (gestational age 23-29 weeks) responded to 20 ppm of iNO, that is a 15% reduction in the inspired oxygen concentration (FiO_2) [42]. Pulmonary hypertension in children with BPD has been shown to be responsive to changes in oxygen tension [43] and the combined treatment of supplemental oxygen and inhaled nitric oxide reduces pulmonary arterial pressures to almost within the normal range [43]. The most recent Cochrane review of three trials of late treatment of iNO did not show a significant reduction in mortality or BPD (RR 0.92, 0.85-1.01) [44]. Consensus recommendations for the care of infants and children with pulmonary hypertension and BPD have been developed by the Pediatric Pulmonary Hypertension Network [45]. The report recommends that inhaled nitric oxide should be used for acute pulmonary hypertensive crises and weaned after a period of stabilisation.

3.2 Sildenafil

Sildenafil is a pulmonary vasodilator and, in infants with BPD associated pulmonary hypertension (BPD-PH), sildenafil can reduce pulmonary vascular resistance [46]. Sildenafil can also reduce pulmonary artery vaso-reactivity and prevent pulmonary

vessel remodelling [47]. In a case series of three extremely low birth weight (ELBW) infants with severe BPD, after four weeks of sildenafil treatment N-terminal pro b-type natriuretic peptide (NTproBNP) levels decreased significantly, but only in one infant was there improvement in echocardiographic findings and respiratory scores [46]. A larger case series included twenty-three infants with BPD and pulmonary arterial hypertension [48]. Significant improvement in pulmonary arterial hypertension as assessed by ECHO was seen in 71% of infants, but only 35% of infants showed a significant clinical response to sildenafil treatment [48]. Retrospective data collection of twenty-two prematurely born infants with BPD-associated pulmonary arterial hypertension who were treated with sildenafil was performed [49]. Infants were commenced on treatment with sildenafil at a median postnatal age of 49 weeks. Sildenafil use improved the ECHO markers of pulmonary arterial hypertension [49]. Four weeks after commencement of sildenafil, the infants had experienced a significant decrease in the FiO_2 (0.57 to 0.42) with no change in the mean pCO_2 levels. Sildenafil was well tolerated and both clinical and imaging improvements were seen [49]. Larger prospective studies are needed to assess whether sildenafil improves the long-term outcome in infants with severe BPD and pulmonary arterial hypertension. Other pulmonary vasodilators are available, but have not been evaluated in infants with BPD beyond often single case reports.

4. Anti-hypertensives

The incidence of systemic hypertension has been variously reported to be between 7 and 43% [38]. Infants have increased aorta wall thickness and stiffness [50], hypertrophy of the heart and reduced cardiac function [51]**.**

4.1 Captopril

Captopril, an angiotensin-converting enzyme (ACE) inhibitor, has been used in neonates with hypertension and is thought to improve endothelial function and nitric oxide release [38]. It, has, however, only been reported to be evaluated in a case series of six infants with severe BPD unresponsive to sildenafil and diuretics, five weeks after commencing treatment with captopril there was a significant reduction in the mean fraction of inspired oxygen (FiO_2) (0.55 versus 0.29, p=0.03) and ventilatory requirements with a reduction in aorta intima media thickness [38]. Further studies are warranted to optimise management of this important complication.

5. Surfactant

The trial of late surfactant (TOLSURF) was a randomized trial which enrolled those infants less than 28+7 days of gestational age who continued to require mechanical ventilation between seven to fourteen days after birth. All infants received inhaled nitric oxide with either surfactant or a placebo every one to three days up to a maximum of five doses. No significant effect of late surfactant use was demonstrated with regard to survival without BPD development [52]. At one year of age the infants who received late surfactant, however, required fewer hospital admissions for respiratory problems post discharge (p=0.03) [53]. Whether late surfactant improves longer term outcomes needs further study, not least given the surfactant abnormalities that have been reported in infants with evolving BPD.

6. Diuretics and fluid restriction

Lung injury and arrested pulmonary and alveolar lung growth in infants with BPD can result in fluid overload, lung oedema and ineffective diuresis [54]. This occurs

because of increased permeability of pulmonary capillaries, which in turn increases airway resistance and reduces lung compliance [55]. Infants with BPD often tolerate fluid loads poorly and fluid restriction is a common practice. Yet, there is no evidence from RCTs to support such management. Indeed, the only RCT to compare two fluid regimens in infants with BPD (145 ml/kg/day concentrated formula versus 180 ml/kg/day) did not show any significant difference in the duration of supplementary oxygen or mechanical ventilation, weight loss or length of stay [56]. Nevertheless, diuretics were shown to be the seventh most frequently prescribed medication on the NICU in a comprehensive literature review [57]. In one study, more than 37% of infant born at less than 32 weeks of gestational age and weighing less than 1500 gms were exposed to diuretics [57]. A systematic review of studies of administration of frusemide, a loop diuretic, however, found limited data and inconclusive results regarding efficacy in infants with a developing chronic lung disease. It was concluded that a single dose of 1mg/kg of intravenous furosemide to such infants had a transient increase in oxygenation and lung compliance, but had no detectable or consistent positive effects when given earlier than three weeks of age [58]. A systematic review of six small trials assessed treatment of frusemide in preterm infants less than three weeks of age developing BPD had either inconsistent or no detectable effects [59]. Treatment with frusemide has, however, been shown to be an independent risk factor for the development of nephrocalcinosis [60] and is associated with electrolyte disturbances, osteopaenia of prematurity and ototoxicity [57].

Other diuretics used in infants with BPD are thiazides such as chlorothiazide which acts on the distal convoluted tubules. They can cause hypokalaemia, hence they are often used in combination with potassium sparing diuretics such a spironolactone

[57]. A single study showed thiazide and spironolactone decreased the risk of death and tended to decrease the risk for remaining intubated after eight weeks of age in infants [59]. A systematic review of six studies of a four-week treatment with thiazide and spironolactone in preterm infants aged greater than three weeks with BPD showed only an improvement in lung compliance and reduced need for frusemide. In addition, the authors concluded the positive effects should be interpreted with caution as the numbers of patients included in the studies were small. Nevertheless, dual therapy of chlorothiazide and spironolactone is often given to infants with BPD [61]. Yet, spironolactone used with thiazide diuretics can cause hypercalciuria.

Aerosolized diuretics can be used to specifically target pulmonary oedema, whilst avoiding adverse systemic side effects. A systematic review included eight studies of preterm infants less than three weeks of age with evolving or established BPD randomly allocated to receive an aerosolized loop diuretic. A single dose was found to transiently improve respiratory mechanics, however, there was no information available on the chronic administration effects and long-term outcomes [62]. It is important to develop a further evidence base for use of diuretics in infants with evolving or established BPD.

7. Immunisation

Prematurely born infants with BPD are at a greater risk of respiratory viral infections in early childhood than term infants [63] and re-admission to hospital due to respiratory syncytial virus (RSV) [64]. Indeed, they are also at increased risk of reduced lung function [65] as are prematurely born infants who suffer rhinovirus infection [66]. The Palivizumab Consensus Group [67] recommended prophylactic

palivizumab to infants with BPD who were less than twelve months of age at the beginning of the RSV season. In addition, amongst infants between 12 and 24 months of age requiring medical management for BPD, such as supplemental oxygen, diuretics, corticosteroids or bronchodilators, in the six months before the RSV season then such infants should also be offered prophylactic therapy [67]. A prospective, cross-sectional study assessed 63 ex-preterm infants which included a control group who did not receive palivizumab and a matched group of infants who received palivizumab [68]. Fifty three percent of infants in the treatment group had a diagnosis of BPD. Within the first two years after birth, 27% of infants in the treatment group experienced wheeze compared to 70% of infants in the control group ($p=0.001$), but when assessed at school age, there was no significant difference between the two groups regarding lung function abnormalities or bronchodilator use [68]. Further evidence is required to determine whether immunisation in the second year will benefit BPD infants with regard to long-term outcomes.

8. Novel therapies

8.1 Stem cell therapies

In the prematurely born infant, neonatal lung arrested alveolar growth is associated with a decrease in the number of host mesenchymal stem cells (MSCs) [69]. MSCs, or multipotent stromal cells have immuno-modulatory properties and an ability to secrete trophic factors [70]. MSCs can be derived from adult bone marrow. Recent studies have shown promising results with MSCs obtained from the umbilical cord [71]. They are considered to be more primitive and superior in nature compared to adult derived MSCs [71], as they have low immunogenicity and anti-inflammatory and restorative properties [72]. Exogenous MSCs have been shown to act via both

direct and paracrine mechanisms to alter the biological properties of host MSCs via signalling of cells within the lung epithelium [72].

Intratracheal umbilical cord blood derived MSCs administered to newborn rat pups in an experimental BPD model found treatment with MSCs restored lung structure and function where alveolar growth had previously been arrested [73]. Long term outcomes at six months of age showed that there were no adverse events in the stem cell group and there was a continued improvement in both lung structure and exercise capacity [73]. Those findings are consistent with neonatal mice exposed to hyperoxia treated with intravenous bone marrow derived MSCs who had normal numbers of alveoli on day fourteen of hyperoxia and reduced lung inflammatory markers [74]. A systematic review of 25 preclinical studies of assessment with MSCs demonstrated regardless of timing, dosage or route of administration, MSC administration was associated with significantly improved alveolarisation [75].

There have been a few studies which have investigated the efficacy of MSCs in preterm infants with BPD. Six ex-prematurely born infants with established severe BPD were recruited into one study [76]. They had a median postnatal age of eight-nine days. The infants were administered human amnion epithelial cells at a dosage of one million cells/kg intravenously. The first infant receiving treatment had a transient episode of cardiopulmonary instability during cell delivery with subsequent recovery. Subsequent ethical approval was gained to slow the infusion rate and include a cell filtration step prior to treating the remaining five infants. The results did not show any significant change to the infants' respiratory support requirement following treatment [76]. The authors' stated that the lack of significant effect in the infants, compared to

preclinical animal models might have been due to there being no dose escalation arm to the trial. A phase I clinical trial assessing the safety and feasibility of intratracheal human umbilical cord MSC in preterm infants used either $1x10^7$ cells/kg in the first patient and the next six patients were given a higher dose ($2x10^7$ cell/kg) and delivered the cells between the 5th and 14th day after birth [77]. Nine preterm infants were recruited with a median birth weight of 793grams who had required continued ventilatory support after day five after birth. The median postnatal age of the infants when MSCs were administered was 10.4 days. The severity of BPD was lower in the MSC recipient group when compared to a matched untreated comparison cohort [77]. At two year follow-up, none of the infants in the two treatment groups were discharged home on oxygen therapy, compared to 22% of the control infants [78]. In addition, in the treatment group, there were no long-term respiratory complications such as wheeze and asthma were observed and none of the infants were receiving continuous steroid or bronchodilator therapy [78]. It is important, however, to emphasize these results are not from a randomised trial.

Due to the different harvesting and culture techniques of MSCs between laboratories it can be difficult to fully compare data from different clinical trials [79]. Robust quality controls and standardisation of techniques needs to be fully considered before approval of MSC derived therapies becomes routinely tested in neonates [79], not least despite early clinical trials showing some promising and positive results, there can be adverse outcomes due to the pro-inflammatory and myofibroblastic characteristics that MSCs possess [80]. MSCs exist in more than one different phenotype and can have the capability of promoting fibrosis and inflammation [81]. A meta-analysis of intravenous MSC treatment in adults and older children, however,

has not found any evidence of adverse events or malignancy up to sixty months following therapy [82]. In any subsequent study, robust follow up to assess long term outcomes needs to be included. It has been suggested that a national registry of infants treated with this novel therapy should be established to ensure a standardised approach and allow adverse events and outcomes to be closely monitored.

8.2 Erythropoietin

Erythropoietin (EPO) has both anti-inflammatory and anti-oxidative properties [83] and EPO treatment during exposure to hyperoxia has been shown to improve alveolar structure and reduce fibrosis [84]. Administration of MSCs combined with EPO in a newborn mouse model in BPD resulted in a significant reduction in alveolar injury and degree of fibrosis compared with MSC therapy alone [83]. The mice treated with the combination therapy were shown to have smaller and more numerous alveoli [85]. These promising results need to be further explored.

8.3 Deferoxamine

The hypoxia-inducible factor (HIF)-1α is particularly important for the development of normal organs. HIF1α promotes angiogenesis by upregulating vascular endothelial growth factor (VEGF). The expression of HIF1α is immediately decreased in oxygen-exposed preterm infants, leading to impaired alveolarization and angiogenesis. Deferoxamine is a bacterial siderophore and is most commonly used to chelate iron. In a mouse model aerosolised deferoxamine resulted in increased expression of HIF1α and activated downstream VEGF angiogenesis. These promising results merit further study [86].

Expert commentary

Bronchopulmonary dysplasia (BPD) is the most common long-term adverse outcome of very premature delivery and is associated with chronic respiratory morbidity. This includes chronic oxygen dependency which, in the most severely affected cases results in a supplementary oxygen requirement at home and affected children have troublesome respiratory symptoms requiring treatment and lung function abnormalities at follow up. These problems may persist at least into young adulthood. Many studies have investigated possible preventative strategies, but it is equally important to identify optimum management strategies for infants with evolving or established BPD and the focus of this review. Very few respiratory modalities have been robustly assessed in infants with evolving or established BPD and only short-term outcomes have been considered. The worrying long-term effects of systemic corticosteroids, including neurological and respiratory problems needs further investigation and exploration of which infants are at greatest risk. Whether the newer inhaled steroids will be efficacious in preventing long-term complications without adverse effects needs investigation. Whether leukotriene receptor blockade may have any overall long-term advantages or be useful for individual infants merits study. The incidence of pulmonary hypertension associated with BPD needs robustly assessing, as does the impact of inhaled nitric oxide in affected patients. The role of sildenafil versus nitric oxide in hospitalised patients needs assessing as does its efficacy in infants discharged home on supplementary oxygen. The evidence suggests diuretics are over-prescribed and have complications, evidence-based guidelines need to be produced. Further evidence is required to determine whether immunoprophylaxis against RSV in the second year will benefit BPD infants with regard to long-term outcomes. The preliminary data on MSCs are interesting, but there needs to be much

more research to determine if such therapy should be investigated in RCTs with long-term outcomes. Equally, whether erythropoietin enhances the effects of MSCs needs further investigation.

Five-year view

Bronchopulmonary dysplasia is a common adverse, long term respiratory outcome of extremely premature birth. Regardless of whether BPD development occurs in the mild, moderate or severe form, many infants will face ongoing respiratory problems even into adulthood. Stem cell treatment will in five years be likely established (or discredited) as the treatment of choice to prevent/treat BPD. During that time the safety of MSCs will have been established, but there will remain doubt as to the longer safety issues. There is a growing interest in delivering quality improvement projects which will mean that evidence based practice will be increasingly adopted. This may result in reduction in, for example, the use of diuretics and corticosteroids. Given the increasing number of infants with BPD, hopefully appropriate RCTs of novel modes of ventilation will have established the optimum mode of respiratory support for that population. In addition, effective, preventative strategies will have been identified, but given the multifactorial nature of BPD, there is unlikely to be a single magic bullet.

Key issues

- It should be noted that extremely prematurely born infants who did not develop BPD may also suffer such long-term adverse respiratory outcome. As a consequence, it is important to assess the long-term efficacy of all treatments in extremely preterm infants regardless of the development of BPD.

- Effective, preventative strategies may reduce the proportion of infants developing BPD, hence it is important that multicentre, often international, studies are undertaken to ensure the sample size ensures robust results.
- All RCTs must include long-term outcomes as many studies which have shown reductions in BPD or otherwise, have yielded different results at follow-up.
- It is important to horizon scan to identify novel treatments.

Recommendations

In infants with evolving or established BPD who remain ventilator dependent:

- Systematic corticosteroids should be considered in those who have made no progress over the first two weeks despite the absence of a PDA or infection and are requiring a high level of mechanical ventilatory support.
- Diuretics should be considered in those who are not tolerating fluids and have poor growth. BPD infants who have received prolonged diuretics should be screened for nephrocalcinosis.
- Bronchodilators should only be given to those infants who are wheezy and continued if they show a response ie a reduction in respiratory support.
- BPD infants should be exubated as soon as possible.
- BPD infants should be screened for systemic hypertension regardless of the use of corticosteroids.

BPD infants should be screened for pulmonary hypertension

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   ** A review discussing appropriate end points for lung development other than BPD*

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