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A Review of Present and Emerging Treatment and Prevention Strategies for Bronchopulmonary Dysplasia in Preterm Neonates

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Abstract

Context: One of the most important chronic clinical conditions seen in preterm babies is Bronchopulmonary Dysplasia (BPD) With improvement in technology and available therapeutic options, the survival rates have dramatically improved over time, how ever, the incidence of BPD still continues to remain the same even today. The injury resulting in BPD likely begins as altered lung development before delivery in many infants and can be initiated by resuscitation at birth and then amplified by postnatal exposures. The multifactorial pathogenesis implicated in the development of BPD necessitates a multidimensional therapeutic approach, to manage all the complex manifestations of the disorder.

Aims: The presently used approaches for prevention as well as management are being used for more than a decade, and lack definite evidence. The aim of this literature review is to gather evidence on the presently available prevention and management approaches for bronchopulmoanry dysplasia, as well as newer, promising therapeutic agents being experimented, in order to provide data to help optimize strategies in the NICU as well as OPD settings and help reduce the incidence of BPD and promote more definitive studies.

Methods and Materials: We carried out an extensive series of searches on PubMed database and tried to capture as many citations as possible for Bronchopulmonary dysplasia in preterm neonates, with peer-reviewed publications from 2000-2022. Approximately 96 studies, including animal studies, RCTs and systematic review and meta-analyses were considered. On going experiments were queried from Clinical Trials.gov. The searches were carried out using the terms: "Bronchopulmonary dysplasia", "BPD", "Preterm neonates", "low birth weight", "pathogenesis", "diagnosis","prevention","treatment". Further manual assessment was also done to include other relevant publications.

Results: Prevention of prematurity, systematic use of non-aggressive ventilator measures, avoiding supraphysiologic oxygen exposure and administration of surfactant, caffeine and vitamin A, antenatal glucorticosteroids, and pharmacotherapeutics agents like diuretics, vasodilators, nitric oxide etc. can significantly reduce the risk of BPD development. MSC therapy, IGF-1 and clara cell protein administration are the most fascinating new measure to address the lung damage due to BPD.

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Conclusion: Despite advancement in technology and availability of a myriad of treatment options, the multifactorial nature of BPD makes it a persistently challenging disorder to treat and even more so to prevent. While multiple therapies are used routinely either alone or in combination (potentially increasing drug–drug interactions and associated side effects), there is insufficient evidence supporting short and longer-term use of many of these agents. There is continued need for future meta-analyses and prospective randomized controlled studies designed to measure clinically meaningful outcomes, and an even greater need to design trials evaluating the safety, efficacy, and dosing of pharmacologic agents in this population. Stem cell treatment and other such innovative strategies may be the beginning of a new era in the treatment of BPD. New ways of preventing or modulating BPD are on the horizon, and will hopefully lead to continued improvement of long-term outcome of prematurely born infants.

Keywords: Neonates; Newer Therapies; Bronchopulmonary Dysplasia; Preterm; Prevention; Treatment.

INTRODUCTION

Bronchopulmonary Dysplasia (BPD)

Pre-maturity is known to be associated with a wide spectrum of respiratory disorders and both early and late complications are seen as a result. One of the most important chronic clinical conditions seen in these preterm babies is Bronchopulmonary Dysplasia (BPD).[1] Its implicated pathophysiology includes a confluence of pre and post natal factors, both of which contribute towards the interference in lung development, making BPD a long-term disorder with substantial morbidity.[2] With improvement in technology and available therapeutic options, the survival rates have dramatically improved over time, however, the incidence of BPD still continues to remain the same even today.[3] While the exact incidence has been difficult to calculate due to the varying definitions for the disorder, studies show that based on how one defines BPD, the incidence can vary from 4% to 40%[4] The first definition of Bronchopulmonary dysplasia was given by Sheenan et al.[5] in 1988, and it was: "the use of supplemental oxygen at 36 weeks PMA", later in 2001 an NIH consensus said that it is "the oxygen use for 28days (not consecutive), with severity based on the amount of supplemental oxygen and mode of respiratory support at 36 weeks PMA" they further classified it into; mild (room air), moderate (<30% supplemental oxygen), severe (>=30% supplemental oxygen and/or positive pressure)." Walsh et al[6] in 2004 defined it as the "receipt of positive pressure or supplemental oxygen at 36 weeks PMA. In infants receiving <=30% oxygen via hood or cannula, a stepwise room air challenge test is performed. Failure of the room air challenge or need for mechanical ventilation and/ or positive pressure are classified as BPD."[7]After a long gap, in 2017 a study published by Isayama et al defined it as "use of oxygen and/or respiratory support (including invasive and non-invasive support) at 40 weeks PMA."[8] In 2018 an NICHD workshop concluded that BPD is "supplemental oxygen or positive pressure at 36 weeks PMA along with radiographic evidence of parenchymal lung disease, irrespective of prior duration of oxygen supplementation. It incorporates 3 grades of severity, depending on levels of supplemental oxygen and mode of support."[9] The latest definition is however, the one published in a study by Jensen et al in 2019. It defines BPD as, "any respiratory support at 36 weeks PMA, irrespective of prior duration of or current level of oxygen therapy. It is further categorized according to disease severity: grade 1, nasal cannula at flow rates <=2L/min; grade 2, nasal cannulae at flow rates >2L/min or non-invasive positive pressure airway and grade 3, invasive mechanical ventilation.[10]

2 Types of BPD Old and New

BPD was not originally considered a lung development problem, but it was rather attributed to the damage done due to aggressive mechanical ventilation and oxygen toxicity on a mature lung lacking surfactant. This "old BPD", was diagnosed and described in premature babies as a chronic lung disease developing in those ventilated with high pressures and concentration of oxygen. [11]The pathological picture was classically characterized by areas of alveolar emphysema, atelectasis, inflammation, fibrosis, prominent airway injury and smooth muscle hyperplasia and hypertrophy resulting in a diffuse airway damage. This damage done can be ascribed to high concentrations of TNF-alpha and Macrophage inflammatory protein, Interleukin 1 beta, interleukin 6, which as seen following ventilation with high positive pressure and excessive volume, leading to inflammation and alveolar damage.[12] Antioxidant enzymes like catalase and copper zinc superoxide dismutase develop and mature in babies after inhalation of air after birth. Until then, reactive oxygen species are present in the lung, so even a small increase in these

oxygen species in preterm babies can cause lung damage.[13]This was also shown in a study, where experimental animals exposed to high oxygen concentrations during early neonatal period showed findings of smooth muscle hypertrophy, oxidative stress and compromised alveolarization; all of which were also demonstrated in lung sections of premature babies who developed RDS and were subjected to aggressive ventilation.[14]

With improvement in the quality of care in NICUs, this "old BPD", is no longer seen, but is rather replaced by another form; the "new BPD". This is typically seen in extremely premature neonates who are born at the brink of viability and survive due to modern technology. The frequency of BPD increases with decrease in the gestational age of these babies.[15] The pathophysiology of this form is attributed to multifactorial causation, involving both pre and postnatal factors that result in dysfunction of alveolar as well as vascular development. During the first few weeks of life, the lungs of very low birth weight babies are in the canalicular (17th to 26th week of gestation) or alveolar (27th to 36th week of gestation) phase of development. The respiratory bronchioles, pre capillaries and mucous glands in the bronchi are not completely developed, the interstitium has not thinned adequately to form the blood air barrier, and surfactant production by the lung epithelial cells has not started. Exposure to harmful stimuli can considerably disturb this vital morphogenesis. On histopathology, it is seen as a reduction in alveolarization with hypertrophied air spaces, immature or simple vascularization and inflammation and fibrosis. [16]Further, the capillaries are decreased in number, and abnormal in shape and distribution. A study published by Jobe explained that "the injury resulting in BPD likely begins as altered lung development before delivery in many infants and can be initiated by resuscitation at birth and then amplified by postnatal exposures".[17]

Essentially, this new BPD is a due to a combination of prenatal factors such as placental abnormalities, IUGR, multiple births, chorioamnionitis and maternal smoking, as well as post natal factors that hinder lung development such as: mechanical ventilation and oxygen supplementation, post -natal steroids administration, infections (sepsis, necrotizing enterocolitis, lung infections etc), ventricular dysfunction, intracardiac shunts, or pulmonary vein stenosis.[18] The role of genetic predisposition as well as mechanical trauma and oxygen toxicity should not entirely be dismissed either. The timing, type and duration of exposures, together with the genetic characteristics of the child, influence the pattern of lung damage that can occur. The "new BPD thus, is far more severe than the old one in terms of alveolar and vascular damage and thus needs to be studied in greater detail.[19]

Factors Involved in the Development of BPD:

As previously discussed, the pathogenesis of BPD is multifactorial. However, some important pre and post natal factors that disturb the lung development either alone or in combination with other factors need to be defined and discussed. These factors include: prematurity, genetic predisposition, gender, mechanical ventilation and hyperoxia, infection and blood transfusion.

1. *Prematurity:* the most important risk factor for BPD is premature birth (gestational age of < 37 weeks). As discussed before, the lungs are in the canalicular and alveolar or saccular stage of development during this age and the immature lung is at most risk of damage if birth occurs during this time, due to surfactant deficiency and under developed antioxidant enzymes.[20]
2. *Genetic predisposition:* A study by Bhandari et al used models and logistic regression to demonstrate statistically significant genetic predisposition for Bronchopulmonary dysplasia in twin births of less than 32 week gestation.[21] Another study has shown that occurrence of BPD in first born twin, increases the risk of BPD in the subsequent twin.[22]
3. *Gender:* Surfactant production occurs earlier in female fetuses and the delay in males is attributed to the effect of androgen. Some animal studies on mice, where long term androgen treatment was found to inhibit the surfactant protein gene expression in type 2 pneumocytes is proof of the same. Similarly, studies involving administration of estrogen to rabbits, showed increased surfactant production. Therefore, the early synthesis of surfactant means that the airflow rates and patency of airways is greater in females, which greatly reduces their risk to develop RDS. As physiological differences of gender are most likely not expressed in extreme prematurity, female gender does not remain protective in neonates born at 22-25 weeks.[23]
4. *Mechanical ventilation:* High tidal volume during mechanical ventilation can cause over distension of small airways and alveoli and using insufficient positive end expiratory

pressures (PEEP) can cause repetitive opening and collapse of unstable lung unit which is injurious for alveolar capillary integrity. Also, high concentration of inspired oxygen (FiO2) can cause oxidative stress and subsequent lung injury. A study by Albertine et al. compared two ventilation strategies to test the hypothesis that differences in tidal volume (VT) influence histopathologic outcome and found that slow, deep ventilation was associated with less atelectasis, less alveolar formation, and more elastin when compared with rapid, shallow ventilation. The avoidance of intubation and mechanical ventilation with the use of continuous positive airway pressure (CPAP) in the delivery room was associated with a lower incidence of BPD. Further a meta-analysis of six RCTs demonstrated that intubation and early surfactant followed by extubation to CPAP compared with later selective surfactant was associated with a lower incidence of mechanical ventilation, air-leak syndromes and BPD. Studies in animals have demonstrated that prolonged mechanical ventilation disrupted lung development and produced pulmonary histopathologic changes that were very similar to those seen in the lungs of preterm infants who die with BPD.[24]

5. *Hyperoxia:* High concentrations of inspired oxygen can damage the lungs, although the exact level or duration of exposure that is unsafe is not know. Immature preterm lungs often are not capable of producing antioxidant enzymes like catalase and zinc super oxide dismutase, so reactive oxygen species like hydroxyl free radical, hydrogen peroxide etc cause greater cellular damage. This finding has been proven by animal studies, which showed similar patterns of lung injury in preterm neonates and mice exposre to hyperoxia. Since oxygen toxicity is indicated as a risk factor, many antioxidants are considered as a viable treatment option for BPD. [25]
6. *Antenatal infection:* The risk of developing chorioamnionitis increased in extremely preterm babies. And the increased concentration of inflammatory mediators such as IL-6, IL-1 beta, TNF-alpha etc are responsible for the impaired lung development. Infection with Ureaplasma urealyticum has been shown to have a significant inflammatory response in the body that greatly affects lung development in babies, leading to BPD. [26]
7. *Postnatal infection:* Studies have shown increased risk of BPD in preterm neonates who were reported to have neonatal sepsis. [27]
8. *Blood transfusion:* Increased level of free iron (which forms hydroxy l free radicals) as well as increased pulmonary blood flow and volume can trigger oxidative as well as mechanical damage in immature lungs and lead to progression of BPD.[28]

Long Term Outcomes of BPD

The respiratory abnormalities that are seen in patients of BPD continue to manifest not only in childhood, but also in adolescence and adulthood. During school going years, children with BPD have greater cognitive, educational and behavioral issues than others, along with reduced lung function and fine and gross motor skills.[29] In adulthood, it manifests as early onset COPD, most likely due to impaired lung function which prevents most adults with BPD from exercising as much as the rest of the population. Parents of children diagnosed with BPD should ensure that they get enough exercise and do not indulge in smoking, especially during adolescence.[30] While it is difficult to exactly point out the long term outcomes of BPD, as most of the adults with BPD have received older forms of treatment, but it is still clear that BPD, due to its association with lung function impairment, greatly reduces the quality of life of patients.

Structural and functional alterations of the respiratory tract, increased risk of hospital readmission, respiratory infections and asthma as well as lung arterial hypertension are frequently noted as the most common long term outcomes of preterm neonates with BPD.

1. *Structural alteration of the respiratory tract:* Patients of both old as well as new BPD share this feature of physical damage to the lungs due to aggressive ventilation. The incidence is however, comparatively more in old BPD. Studies have shown that patients with BPD show considerable abnormalities on chest CT scans. Linear and triangular subpleural opacities and hyperlucent areas are seen on most of the scans and it is associated with the duration of oxygenation, despite improvements in the quality of care over time.[31]
2. *Functional alterations of the respiratory tract:*

All patients of BPD show note able functional alterations of the lower respiratory tract which worsens in adulthood. A study conducted on the same showed that that 68% of the subjects with BPD had airway problems [lower forced vital capacity (FVC), lower forced expiratory volume in 1s (FEV1) and lower forced expiratory flow between 25 and 75% of vital capacity (FEF25%–75%) than individuals included in the preterm group without BPD and term controls. Further more, 24% of the subjects with old BPD had fixed airway obstruction, and 52% had reactive airway disease, as indicated by their responses to the administration of methacholine or a bronchodilator. It was also reported that Although lung volumes increased with time, persistent flow limitation was evidenced. At 6, 12 and 24 months, low partial expiratory airflow, measured by maximum flow at functional residual capacity (V max FRC), was shown, without any significant increase over time.[32]

3. *Hospital readmission:* It has already been proven that preterm neonates are more likely to be re-hospitalized than term neonates. That risk is even greater if they develop BPD. Despite pre and post natal preventive measures, infants who receive oxygenation and develop BPD have a higher rate of readmission to hospitals. It is also proved by a study which estimated the rate of re-hospitalization in extremely preterm babies during their first 9 months post discharge and found that 47.3% patients were re-admitted atleast once and over half of these were respiratory disorders.[33]
4. *Respiratory tract infections:* Preterm neonates suffer from respiratory infections more than term neonates and that risk is higher if they also suffer from BPD. The already damaged lung in these patients stands at a higher risk of further damage and hence longer duration of hospitalization as evidenced by most studies.[34]
5. *Asthma:* It has been seen that children born preterm and diagnosed with BPD, at 11 years of age suffered from clinically evident asthma in 25% of cases. Children with BPD have neutrophilic airway inflammation and lower values of exhaled nitric oxide and exhaled breath temperature. The airway obstruction is only partially reversed by beta 2-agonists, the response to inhaled corticosteroids is poorer, and the acute exacerbations are fewer because patients with BPD suffer from fixed airway narrowing.[35] Children with BPD might be intolerant to exercise due to abnormal bronchial function. Karila et al. reported that children with BPD examined at 7–14 years old had ventilatory limitations on exercise, with greater use of the ventilatory reserves ($p < 0.01$) and lower maximal ventilation ($p < 0.01$) and tidal volume ($p = 0.01$). Moreover, changes in ventilation ($p < 0.0001$) and tidal volume ($p = 0.003$) during exercise were significantly smaller in the BPD group than in controls.[36]
6. *Lung arterial hypertension:* Lung arterial hypertension is a result of vascular development anomalies that develop alongside lung development anomalies. Studies have shown that this complication can be seen in around 17% diseases, irrespective of the grade of severity, but is more commonly found in moderate severe disease. Pulmonary arterial hypertension needs to be diagnosed early on, and while cardiac catheterization is a gold standard investigation, transthoracic echocardiography is mostly used in infants as it is non-invasive, and has a diagnostic accuracy of 79% for incidence and 47% for severity.[37] Management of these patients if focused on vasodilation to reduce the pressure and includes drugs such as oral sildenafil (drug of choice), prostacyclin analogues, intravenous phosphodiesterase III inhibitors and nitric oxide. Nitric oxide is particularly advised in preterm infants with associated complications such as PROM, oligohydramnios, and pulmonary hypoplasia.[38]

Why We are Writing this Review

The multifactorial pathogenesis implicated in the development of BPD necessitates a multidimensional therapeutic approach, to manage all the complex manifestations of the disorder. A team of clinicians is needed to not only manage the condition on NICUs, but also to focus on prevention where possible. The presently used approaches for prevention as well as management are being used for more than a decade, and lack definite evidence. More studies need to be performed that show a positive outcome and a significant decrease in the incidence of BPD. In this review, we will discuss all therapies in use currently with appropriate evidence as well as introduce certain newer

therapies under research.

MATERIALS AND METHODS

The aim of this literature review is to gather evidence on the presently available prevention and management approaches for bronchopulmoanry dysplasia, as well as newer, promising therapeutic agents being experimented, in order to provide data to help optimize strategies in the NICU as well as OPD settings and help reduce the incidence of BPD and promote more definitive studies.

We carried out an extensive series of searches on Pub Med database and tried to capture as many citations as possible for Bronchopulmonary dysplasia in preterm neonates, with peer-reviewed publications from 1996-2022. Approximately 96 studies, including animal studies, RCTs and systematic review and meta-analyses were considered. On going experiments were queried from Clinical Trials. gov. The searches were carried out using the terms: "Bronchopulmonary dysplasia", "BPD", "Preterm neonates", "low birth weight", "pathogenesis", "diagnosis","prevention","treatment". Further manual assessment was also done to include other relevant publications.

Current Treatment and Prevention Strategies

Ventilation:

While BPD is a multifactorial disease, one of the most important risk factors still remains mechanical ventilation. The last decade has witnessed the concept of delivery room stabilization where nasal continuous positive airway pressure (CPAP) has been increasingly used to manage preterm infants <1,500 g birth weight in the delivery room and the first few days in the neonatal intensive care unit. This has however not affected the number of neonates needing mechanical ventilation.[39] Hence, ventilation remains an important treatment modality but comes with its set of challenges. In ventilated preterm infants, permissive hypercapnia with a partial pressure of CO2 in the arterial blood (PaCO2) between 45 and 55 mmHg and a pH > 7.20 has been suggested to avoid high tidal volumes and lung over inflation. However, no strong advantage of the same has been established.[40]As previously described, mechanical ventilation via an endotracheal tube exposes the developing lung to volutrauma and barotraumas which lead to lung fibrosis and inflammation and thus BPD. Also, weaning infants with BPD from mechanical ventilation is difficult and has to be accomplished gradually. When the patient is able to maintain an acceptable arterial oxygen partial pressure (PaO2) and arterial carbon dioxide partial pressure (PaCO2), with peak inspiratory pressures between 15 and 18 cm H2O and a fraction of inspired oxygen (FiO2) lower than 0.4, extubation should be attempted. As long as the pH is within acceptable limits, a certain degree of hypercapnia must be tolerated after these patients are taken off the ventilator.[41]

Non-invasive management strategies, in which infants receive respiratory support without the need for an endotracheal tube, have been studied as a strategy to avoid direct trauma to the developing lung, and potentially reduce the risk of developing BPD. The various non-invasive respiratory ventilation strategies that have been adopted, include the use of non-invasive positive pressure ventilation (NIPPV), nasal continuous positive airway pressure (NCPAP) and high flow nasal cannulas (HFNCs). Studies which compared differences between ventilation with and without an endotracheal tube have shown that avoiding the tube had a small but significant beneficial impact in preventing BPD (OR 0.83; 95% CI 0.71–096. Indicating that these methods can be used in neonates to prevent development of BPD. However, the best non-invasive method to decrease the development of BPD has not defined. Several studies as well as two meta-analysis have reached the the conclusion that no difference in respiratory failure or need for intubtation was seen between NIPPV and NCPAP. [42]

The use of high-frequency ventilation has also been recommended as a way to prevent ventilator associated lung injury, but the data is insufficient and studies which focused on trying to find association between first intention high frequency ventilation and reduction of barotrauma and volutrauma found no significant difference in the outcome of death or BPD. Even when compared with conventional ventilation, the difference was small and inconsistent.[43]Lung protective ventilation therefore remains an important intervention available to clinicians. Another new strategy in ventilation of preterm infants is volume targeted ventilation. A study by Wheeler et al. showed that infants ventilated using volume targeted ventilation had reduced death or BPD compared with infants ventilated using traditional pressure limited ventilation. Similar findings were seen in other studies where volume targeted ventilation is physiologically more logical than pressure limited ventilation, and is associated with a reduced risk of pneumothorax, hypocarbia, duration of ventilation,

death or BPD, and severe intra ventricular hemorrhage. Therefore, it should now be adopted as the main mode for mechanical ventilation of preterm neonates.[44]

Oxygenation:

As hyperoxia has been implicated in the development of BPD, a large number of studies have been conducted to find conclusive evidence and lay out guidelines for the optimal range of oxygen saturation to be used in preterm infants, with little merit. A multicenter, double blind, randomized, controlled trial with 358 infants born at <30 weeks, shown no significant differences according to weight, length, or head circumference at a corrected age of 12 months between the groups with standard saturation (oxygen saturation range 91–94%) and high saturation (oxygen saturation range 95–98%).[45] The frequency of major developmental abnormalities also did not differ significantly between the standard saturation group and the high saturation group. Another STOP-ROP study has in a 5-year period shown a higher incidence of BPD and longer hospitalization of infants with oxygen saturation of 96–99% compared with oxygen saturation of 89–94 %.[46]

Studies have shown that a lower target range of oxygenation (85–89%), as compared with a higher range (91–95%), did not significantly decrease the composite outcome of severe retinopathy or death, but it resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors. However, the incidence of BPD is reduced in the lower oxygen saturation group as compared with the higher oxygen saturation group.[47] A recent evaluation of five randomized, controlled trials including more than 4800 infants, in whom lower (85–89%) versus higher (91–95%) SpO_2 targets were compared, concluded that the lower target range did not reduce BPD, severe visual problems or rate of disability at 12–24 months. By contrast, it was associated with increased risks of death and necrotizing enterocolitis. Some authors have indicated that, in the first few minutes of life, SpO_2 of 70–80% might be acceptable. However, after 5 min, SpO_2 must be maintained at between 88 and 92% with a higher alarm limit of 96%. Slightly higher SpO_2 can be tolerated for MPT patients for whom the alarm limit of 97–98% can be accepted. However, more studies need to be conducted to form perfect guidelines.[48]

Surfactant:

Surfactant deficiency in premature neonates leads to increased surface tension and reduced pulmonary compliance. Thus, exogenous surfactant administration is one of the most important ways of reducing preterm infant mortality and modifying characteristics of BPD. Older studies have shown that antenatal corticosteroids coupled with postnatal exogenous surfactant administration significantly reduces incidence of BPD. However, newer analysis have refuted these claims. However it is indicated that the time and manner of administration of the surfactant may play a significant role. Early surfactant administration permits immediate extubation to less aggressive ventilator measures, thus reducing the risk of BPD development.[49]

Surfactant administration is done after intubation and is followed by mechanical ventilation which circles back to ventilator associated lung injury and higher risk of BPD. To circumvent this problem, the INSURE (Intubation Surfactant Extubation) technique of surfactant administration by transient intubation, surfactant administration, and immediate extubation can be tried. It allows medication delivery without excessive lung injury. However, trials comparing INSURE to CPAP found no difference in reduction in incidence or mortality between the two.[50] The IN-REC-SURE (INtubate, RECruit-SURfactant-Extubate) trial was recently published which compared surfactant administration after alveoli recruitment using high frequency oscillatory ventilation, followed by extubation with the traditional INSURE method in preterm infants who failed nasal CPAP. Although there was a reduced requirement for mechanical ventilation during the first 72 hours of age in the IN-REC-SUR-E (40%) group, no difference was found between the two groups in the incidence of moderate to severe BPD.[51] In order to entirely eliminate the mechanical ventilation factor, administration of surfactant has been tried using catheters. When compared to standard administration of surfactant through an endotracheal tube it was found to be associated with decreased risk of BPD (RR 0.71, 95% CI 0.52–0.99), BPD or death (RR 0.74, 95% CI 0.58–0.94), and need for invasive ventilation (RR 0.67, 95% CI 0.53–0.84). Aerosolized surfactant have also been evaluated as a less invasive alternate route of surfactant administration and similar findings have been reported.[52]

Corticosteroids:

Inflammation in lungs has been known to be the major culprit of acute lung injury, so it only makes sense to use corticosteroids in the treatment of BPD. Antenatal corticosteroids are indicated for women at risk of preterm delivery as they decrease

the risk of RDS. Studies have shown that antenatal glucocorticosteroids have decreased the incidence of RDS by as high as 50%, but they have not impacted the incidence of BPD. This can be due to early lung maturation induced by these drugs, but no or deleterious effect on alveolarization. Animal studies have shown similar findings. Maternal glucocorticoid treatment has both an acute and a chronic effect on fetal monkey lung. A maternal dose of 0.3 mg/kg betamethasone before preterm delivery at 133 days gestation caused mesenchymal thinning and a large increase in maximal lung gas volumes, with minimal effect on surfactant phospholipids. When the fetuses were delivered close to term at 160 days gestation, however, the alveolar number, lung surface area and lung gas volume expressed per kilogram body weight were decreased.[53]

Postnatal corticosteroids: Systemic: Reviews have shown that dexamethasone facilitates extubation, reduces the combined endpoint of death or BPD at 28 days or 36 weeks PMA, and also reduces the incidence of PDA and ROP. However trials where glucocorticoids have been used early in life have also found a significant increase in adverse long term neurologic outcomes like cerebral palsy. There has however been no significant increase in long term neurologic outcomes detected with regard to moderately early and late administration of glucocorticoids some other studies state that moderately early administration of dexamethasone (7–14 days after birth) did not significantly increase the combined outcome of death or cerebral palsy and actually showed a dose dependent decrease (6.2%) in cerebral palsy with each incremental mg/kg increase in cumulative dexamethasone dose which was not demonstrated in delayed trials. These data illustrate the potential time sensitive effects of dexamethasone and the need for clinicians to balance the known impact on neurodevelopmental outcome associated with prolonged mechanical ventilation and the development of BPD with the risks/benefits of systemic glucocorticoid treatment.[54]

Other investigators have suggested that a primary cortisol deficiency in preterm infants increases the risk of BPD which may be amenable to early treatment with a less potent corticosteroid such as hydrocortisone. Infants who received hydrocortisone however did not demonstrate a significant reduction in mortality, BPD, or cerebral palsy and actually had a significant increase in the incidence of gastrointestinal perforation which occurred more often with concurrent indomethacin administration.[55]

Inhaled: Inhaled steroids have been suggested to promote respiratory benefits while also reducing systemic side effects. Studies examining the benefits of inhaled corticosteroids administered early or late have not been able to demonstrate any impact of inhaled corticosteroids respiratory status. Further, the potential for systemic absorption of inhaled steroids and subsequent side effects (e.g., growth, adrenal suppression, etc.) remains an issue. Further research is needed to evaluate the perfect strategy for inhaled steroid administration.[56]

Caffeine:

Caffeine is a mainstay of treatment in most NICUs, and is used to prevent apnea of permaturity and BPD. While its mechanism of action is not entirely known, it is said that it may have anti-inflammatory properties. The standard dose of caffeine citrate is 20 mg/kg for loading and 5–10 mg/kg for daily maintenance. It has been shown to increase pulmonary compliance and reducing airway resistance. Also, it infants show more diaphragm contractility and respiratory drive, which facilitates early extubation.[57] Also, the famous Caffeine for Apnea of Prematurity study showed that caffeine administration was associated with a significant reduction in BPD development and reduced neurodisability at 18 months of age.[58] Other studies have also shown similar findings, where infants in the treatment group had significantly less apnea of prematurity, and were also noted to have less BPD, patent ductus arteriosus (PDA), and cerebral palsy when followed out to 18–21 months corrected gestational age. However, these outcomes were limited to short term benefits.[59]

Further studies which compared the timing of administration of caffeine, showed improved outcomes with early caffeine therapy, with 25% of infants who received early caffeine developing the outcome of death or BPD compared to 53% of infants in the late caffeine group. Another study showed that administration of caffeine within the first 2 days of life seems to lead to a reduced risk of BPD compared to later administration (or 0.69; 95% CI 0.58–0.82; $p < 0.001$), although it was found to be associated with an increased risk of necrotizing enterocolitis (OR 1.41; 95% CI 1.04–1.91; $p = 0.027$). Present research thus concludes that caffeine should remain the mainstay of treatment especially when initiated within the first week of life for prevention of development of BPD.[60]

PDA Closure:

Studies have shown that presence of a PDA is

associated with the development of BPD, but it has not proven to be causative. The mechanism of left to right shunting observed across a patent ductusarteriosus can worsen pulmonary congestion and edema, further compromising alveolar development. Randomized controlled trials evaluating ductal closure however, have failed to show a reduction a risk of BPD.[61]

An RCT which was evaluating PDA closure with indomethacin or surgical ligation compared to no intervention, found lower rates of BPD in the later group ($p<0.05$) with no difference in mortality or morbidity. Another study examining ibuprofen treatment concluded on similar lines. These studies however, focus on treatment of BPD and not the prevention. Trials like the PDA-Tolerate trial compared the timing of PDA closure and its effect on BPD. It compared early with later conservative pharmacologic treatment of moderate to large PDA in infants who had on going respiratory support needs and had a moderate to large PDA, there was a higher incidence of BPD in those intubated >10 days (75%) compared to infants intubated <10 days (27%, $p<0.0001$). However, among the infants intubated greater than 10 days, prolonged exposure to moderate-to-large PDA was associated with increased risk of BPD ($p=0.04$). These findings suggest that an increased risk of BPD among infants with exposure to moderate-to-large PDA and receiving prolonged mechanical ventilation >10 days.[62]

Due to lack of definitive proof, most centres prefer non-intervetion and conservative management. However, it is prudent to note that a subset infants <28 weeks with moderate severe PDA might likely benefit from PDA closure as spontaneous closure is delayed and it can decrease the incidence and mortality associated with BPD.[63]

Diuretics:

Excessive intravenous fluids used to provide nutrition and hydration to preterm neonates, often results in pulmonary edema, which can warrant a need for external respiratory support and thus cause BPD. So, clinicians often use diuretics with the goal of decreasing pulmonary edema and the amount of respiratory support needed, thereby improving risk factors leading to the development of BPD. Various independent studies have shown that diuretics are associated with improved lung compliance and decreased resistance. Loop diuretics such as Furosemide are considered the treatment of choice. Several studies have demonstrated alternate day, daily, and even aerosolized furosemide improve clinical respiratory status, pulmonary mechanics, oxygenation, and facilitate weaning from mechanical ventilation. Furosemide also decreases interstitial edema and vascular resistance.[64] A study conducted on infants born at 23-29 weeks gestational age, who were exposed to diuretics between first 9 weeks of life, an increased exposure to furosemide therapy by 10% significantly reduced the incidence of BPD (4.6%; $p=0.001$) or death due to the same (3.7%; $p=0.01$). A review of 6 RCTs concluded that a decreased risk of failure to extubate within a week of furosemide usage and improvement in pulmonary compliance with a one-to-two-day course of furosemide was seen. However, long term benefits of this treatment have not yet been observed. So while the short term improvement is a plus, a number of side effects of long term use of diuretics like electrolyte disturbances, ototoxicity and azotemia are also known occur.[65] Also, an observational cohort (the Prematurity and Respiratory Outcomes Program) showed no association between diuretic use and change in respiratory outcomes. It is also pertinent to note that other classes of diuretics like Thiazides and Spironolactone have not been as extensively studied, and the small number of studies which have been performed have not shown any promising results in terms of duration of hospitalization or ventilation. So they are not recommended as treatment.[66]

As of now, there are no standard guidelines in place that suggest the chronic use of loop diuretics in preterm neonates with BPD, and studies comparing centres using diuretics verus those who don't use them, found no differences in mortality. So more studies need to be designed to establish protocol for diuretic therapy and clear the conflict related to benefits versus long term side effects.

Bronchodilators:

A majority of the clinical trials have been performed using inhaled bronchodilators like Salbutamol (inhaled Beta 2 agonist) and Ipratropium bromide (muscarinic antagonist), which produce bronchodilation and thus improve lung compliance and decrease airway resistance.

Salbutamol is indicated where strong reversible bronchospasm is present, where as ipratropium bromide has been recommended in chronically ventilated infants with BPD, either singly or in combination with salbutamol. However, while acute exacerbation of symptoms are managed effectivey by these agents, trials have failed to demonstrate any improvement in the severity or progression of BPD. Although a few studies have shown improvement in lung function with

Salbutamol, others have questioned its long-term efficacy and pointed out that tolerance develops with its prolonged use.[67]

Despite this data, hospitals prefer prescribing a trial of salbutamol with addition of ipratropium bromide if improvements are not seen in neonates who develop wheezing or severe BPD. The trend and manner of this exposure varies between centres however. This lack of conclusive evidence to strongly support inhaled bronchodilator use in hospitalized infants warrants more research.[68]

Nitric Oxide:

While the use of inhaled nitric oxide is common in the treatment of acute hypoxaemic respiratory failure and pulmonary hypertension in term neonates, its use in the prevention of BPD in preterm babies has proven to be unsuccessful. Studies which focused on administration of this gas early or later after birth have shown no significant effect, and so it is not a preferred modality for treatment when administered alone. However, when given alongside intramuscular injections of Vitamin A, a statistically significant reduction in not only mortality and neurocognitive morbidity but also incidence of BPD was observed in low birth weight preterm infants.[69]

Vitamin A:

Vitamin A or retinol plays a role in the normal development of epithelium of the respiratory tract as well as in promoting tissue repair. More over multiple studies showed that deficiency of Vitamin A in preterm LBW babies leads to more risk of BPD development. A recent meta-analysis of studies showed that preterm neonates treated with vitamin A had a lower risk of BPD. However, the reduction in risk was small and observed only in children weighing <1000 g. Vitamin A also does not reduce mortality or neurodevelopmental morbidity and the need for ventilation.[70]

Also, the best route of administration is not yet clear. As an exploration for alternate routes of administration, a recent RCT of 188 infants born less than 28 weeks gestation evaluated enterally administered vitamin A compared to intramuscular. While it was found that following enteral treatment plasma retinol levels increased, there was no improvement in severity of BPD. So, it was suggested that the administration of vitamin A to preterm infants should be done after considering both advantages and problems as intramuscular administration is painful and needs to be repeated multiple times which increases risk of sepsis.[71]

Antioxidants:

As discussed previously, due to immature antioxidant enzymes in preterm lungs, they are more prone to oxidative stress induced by reactive oxygen species. The concentration of these ROS is increased in premature lungs especially in the first week of life and results in chronic lung damage. These reactive oxygen species which are toxic to the lung tissue are not only produced by infection and inflammation, but the treatment modalities that we use like oxygen supplementation (results in hyperoxia), blood transfusion (reperfusion injury) and ventilation associated inflammation also contribute towards their production. A study conducted by Davis et al in 1997 and followed up in 2000, showed that antioxidant enzyme replacement therapy in high risk very low birth weight preterm neonates via intratracheal administration of recombinant human CUZN SOD is associated with lower levels of biomarkers of acute lung injury, but there is no difference in morbidity or mortality.[72] However, when a larger trial was later conducted, it showed a reduction in pulmonary morbidity in the treatment group as compared to the placebo group. This shows that more larger trials need to be conducted and the effect of antioxidant enzyme replacement on lung injury outcomes cannot be totally negated.[73]

Infection prevention and antibiotic stewardship:

As previously discussed, ureaplasma infection has been associated with the development of BPD. Macrolides not only treat the infection, but are also anti-inflammatory and so are thought to be a potential agent for both the prevention as well as management of BPD. However, trials with prophylactic azithromycin therapy have not found much effectiveness and an RCT including IV azithromycin therapy showed that ureaplasma can be eradicated from the respiratory tract, but it does not change the incidence of BPD. Further, it is known that antibiotics used to treat infections, can further increase the risk of development of BPD, as proven by a study where, early empiric antibiotic therapy of 4–7 days is associated with increased adjusted odds of BPD, and each additional day of antibiotics in the first 2 weeks of age significantly increases the risk of severe BPD (or 1.15, 95% CI 1.08–1.27).[74] Similar findings were seen in other studies evaluating antibiotic exposure and risk of BPD. These nosocomial infections that result in inflammatory mediators can easily be prevented by quality control and strict hand hygiene policies. Nosocomial infections reduce by 8% by simple quality control measures. Pros and cons of antibiotic use need to be weighed and

effective antibiotic stewardship policies need to be set in place. At present, larger trials need to be conducted to ascertain the efficacy of prophylactic antibiotic therapy, but until then, some centres report screening extremely premature infants for Ureaplasma soon after birth, and selectively treating those infants requiring prolonged mechanical ventilation with azithromycin.[75]

Role of nursing:

Close monitoring is important, as infants with BPD are susceptible to lower respiratory tract infections, hypertension and respiratory failure. Daily measurement of body weight, without clothes and with the same scales, is required in order to determine weight changes. Assessment of the child's respiratory and fluid status, skin color, breathing effort and abnormal sounds of breathing, chest retraction, capillary filling time, secretions, vital signs and edema every 1–4 hrs is important. Any deviation from the baseline is required to be reported. Fluid intake and output should be carefully monitored in order to maintain adequate hydration, along with regular assessment of electrolyte levels and an increased fluid intake, if no contraindications exist. Infants should be fed over a long time interval after which the infants need to be held in an upright position in order to enable them to burp. Feeding through a nasogastric (NG) tube, whenever required, particularly at night, and checking the placement of the NG tube prior to feeding to avoid aspiration are important care-taking steps in the management of BPD.

Chest physiotherapy is required every 4 h as tolerated, suction should be performed 4 times per day as and when required and oxygen should be administered if necessary. Chest physiotherapy and suctioning help to remove mucus from the airways and lungs. The condition of the skin surface should be monitored if required. Bronchodilators should be administered to increase the airflow to the alveoli and diuretics should be added to reduce the risk of fluid retention and pulmonary edema, thereby improving the respiratory function.Regular care of the child with regard to bathing, clearing the airways and maintaining the skin is important along with informing parents about the details of the treatment and care of the baby with follow-up instructions.[76]

Emerging areas of research

Stem cells

Evidence suggests that stem and progenitor cell impairment can favour BPD development. So it has been hypothesized that the use of exogenous stem or progenitor cells could protect or regenerate even a damaged lung as stem cells contribute to organogenesis and growth and also contribute to organ repair and regeneration throughout life. Mesenchymal stromal cells (MSCs) are the most extensively studied cells because of their ease of isolation and culture and their pleiotropic effects (anti-inflammatory, pro-angiogenic, anti-apoptotic, anti-oxidant, and anti-fibrotic activities). A great number of animal studies have used lung resident mesenchymal stem or progenitor cells (MSCs) in BPD model. Research suggests that MSCs are an important component of the parenchymal progenitor cell niche and orchestrate organ homeostasis and repair following injury.[77]

In animal models, treatment with MSCs was shown to reverse alveolar injury and improve lung functioning. MSC derived extracellular vesicles have pro-regenerative and immune modulating effects and have been shown to improve lung morphology, pulmonary function and suppress inflammation in animal models. Chang et al. assessed the safety and feasibility of a single, intratracheal transplant of human umbilical cord blood derived MSCs in preterm infants. Administration of both low and high doses of cells was well tolerated and the respiratory severity score measured after transplantation was significantly lower than in controls. MSCs were also found to be safe and well tolerated in adult patients. No evidence of pro-fibrotic and tumorigenic potential of MSCs was reported. These results of MSC administration are noteworthy but more clinical trials need to be perfomed for defining exact guidelines. Further larger scale MSC transplantation remains a challenge.[78]

IGF1:

Insulin like growth factor which rises during the third trimester of pregnancy is associated with vascular development. The levels of IGF-1 are low in preterm neonates. IGF-1 is upregulated by insulin and so hyperglycemia is common in preterm neonates. Due to lower levels of IGF-1, preterm babies are known to have less weight gain, increased respiratory distress, retinopathy of prematurity and necrotizing enterocolitis. Studies have shown that early insulin treatment during the first week of life induces a late increase in IGF-1 levels between days 7 and 28 of life, improved weight gain, and may improve the outcomes of these infants. Intravenous infusion of recombinant human IGF-1 complexed with its binding protein recombinant human IGFBP-3 (rhIGF-1/rhIGFBP-3) has been investigated as a therapy since IGF-

1 replacement in extremely preterm infants has been demonstrated to be safe and well tolerated. This potential needs to be better tapped into as a treatment option and more clinical trials need to be performedto draw conclusive evidence and create guidelines.[79]

Clara proteins

CC10 is a protein secreted by non-ciliated bronchiolar epithelial cells (club cells) and is one of the most abundant proteins within the fluid lining the lung epithelium.) is a major secretory protein 0CC10 binds to lipid components of the pulmonary surfactant such as phosphatidylcholine and phosphatidylinositol, suggesting that it may transport or protect these phospholipids from degradation. It also negatively regulates airway inflammatory responses and also regulates surfactant phospholipids catabolism. It also has anti-inflammatory properties is lower in tracheal aspirates of premature infants who subsequently died or developed BPD. Animal studies have demonstrated that administration of recombinant human CC10 (rhCC10) showed a significant rhCC10 dose dependent increase in respiratory compliance and ventilation efficiency index. Early intervention with rhCC10 up-regulates surfactant proteins and vascular endothelial growth factor expression. This finding suggests that CC10 can protect against hyperoxia and mechanical ventilation in the immature lung. Further larger scale studies and clinical trials in NICUs are warranted to determine its effectiveness in hospital settings.[80]

CONCLUSION

Despite advancement in technology and availability of a myriad of treatment options, the multifactorial nature of BPD makes it a persistently challenging disorder to treat and even more so to prevent. While the understanding of the pathogenesis of BPD has increased a lot, what continues to remain a challenge is reducing its incidence and thus the economic as well as social and physical burden on health systems and families.[81] While multiple therapies are used routinely either alone or in combination (potentially increasing drug–drug interactions and associated side effects), there is insufficient evidence supporting short and longer term use of many of these agents. In fact, no single therapy has been shown to have a significant impact on the incidence or severity of BPD. Many strategies which have proven to be effective on paper have not shown similar outcomes when applied to clinical settings. There is continued need for future meta-analyses and prospective randomized controlled studies designed to measure clinically meaningful outcomes, and an even greater need to design trials evaluating the safety, efficacy, and dosing of pharmacologic agents in this population. Also, Future research should be focused on establishing better biomarkers predictive of BPD and associated longer-term chronic respiratory morbidity, developing stratification models to identify high-risk infants early on, and applying a multimodal approach when studying various pharmacologic interventions. Stem cell treatment and other such innovative strategies may be the beginning of a new era in the treatment of BPD. New ways of preventing or modulating BPD are on the horizon, and will hopefully lead to continued improvement of long-term outcome of prematurely born infants.[82]

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