Retraction Notice

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Recent Advances in Bronchopulmonary Dysplasia Protection and Therapy

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Abstract

For preterm infants, bronchopulmonary dysplasia (BPD) is usually caused by abnormal lung development due to various factors during prenatal and postnatal process. One of the reasons for death and bad prognosis of preterm infants is to have BPD. Up to now, there are no unified strategies or drugs to treat BPD. In clinical, many intervention treatments have been applied to achieve BPD therapy, mainly including preterm protection, protective ventilation strategies, and delivery of corticosteroids, pulmonary vasodilators, and antioxidants. This review summarizes the current advances in BPD protection and treatment, and notes that gut microbiota and mesenchymal stem cells (MSCs) can be the promising strategy for protecting and treating BPD in the future.

Keywords

Bronchopulmonary Dysplasia, Preterm Infants, Protection and Therapy, Mesenchymal Stem Cells, Gut Microbiota

1. Introduction

Preterm birth belongs to chronic disease, and preterm infants are usually suffering from respiratory diseases after birth. BPD is the most common complication of preterm infants, which will increase the incidence rate of respiratory diseases in children and adolescents, severely affecting the health of preterm infants and adults. The incidence rate of BPD is 32% - 59%, and it often induces chronic respiratory diseases in infants, including recurrent respiratory tract infections and bronchial asthma [1] [2] [3]. Up to now, there is no unified consensus on the definition, pathogenesis, and therapeutics of BPD. The National Institutes of Health (NIH) proposed the NIH 2001 definition of BPD, which is widely used in clinical practice, detailed procedures include oxygen inhalation for more than 28 days and then grading [4], without lung imaging support. Lung imaging has

been incorporated into the NIH 2018 definition, making more accurate in BPD diagnosis [5] [6]. With the application of prenatal glucocorticoids and protective respiratory therapeutics, BPD shows novel pathological characteristics (called "new" BPD), mainly including abnormal development of lung tissue and pulmonary blood vessels [7]. These lung injuries are related to various factors, such as inflammation and oxidative stress [8], leading to the reconstruction of lung tissues and pulmonary blood vessels [9]. In addition, illogically assisted ventilation can also trigger lung inflammation [10]. There are many methods to protect and treat BPD, such as glucocorticoids and assisted ventilation. However, their usage and benefits are still controversial. This review will conclude the current strategies and new therapeutics for protecting and treating BPD (**Figure 1**).

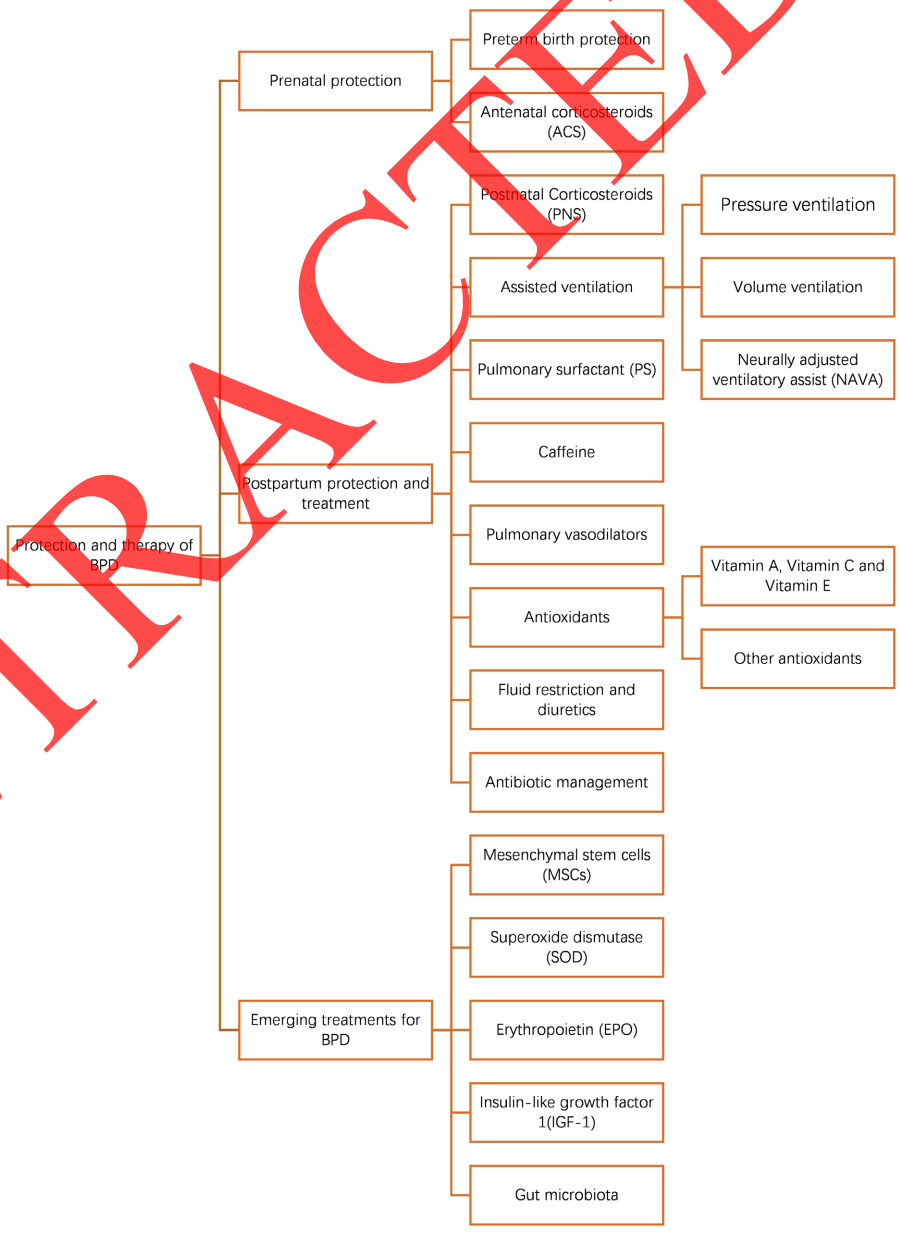

Figure 1. Various therapeutics for protecting and treating BPD.

2. Prenatal Protection

2.1. Preterm Birth Protection

BPD is negatively correlated with gestational age. Most BPD occurs in infants born before 32 weeks of gestation, the lung tissues present tubular (17 - 26 weeks gestation) or cystic [11]. BPD may still occur even under prenatal glucocorticoids and postpartum surfactant administration. Therefore, eliminating and avoiding risk factors of preterm birth in pregnant women is the key to controlling the occurrence of BPD. Some studies have shown that women who smoke in the first trimester of pregnancy not only significantly increase the risk of preterm birth, but also show a 20% increased risk of very early preterm birth (less than 28 weeks of gestation). Intrauterine infection-induced preterm births are 25% - 40% of preterm births at least. In addition, maternal diseases also increase the rate of preterm births, such as thyroid disease, diabetes, and hypertension. At the same time, women with serum iron, folic acid, or zinc deficiency are more likely to suffer from preterm birth [12] [13]. Controlling these premature birth-related risks can effectively reduce BPD.

2.2. Antenatal Corticosteroids (ACS)

In 1972, Liggins *et al.* first discovered that ACS can promote lung maturity and prevent respiratory distress syndrome (RDS) for preterm infants [14]. ACS administration improves respiratory function by promoting alveolar epithelial cells differentiation towards type II pneumocytes, increasing surfactant level, enhancing pulmonary blood flow via activating nitric oxide synthase, and opening sodium ion channels [15] [16] [17] [18]. It is reported that the number of infants with required mechanical ventilation and RDS is decreased by analyzing the impact of ACS on BPD in 1368 infants [19]. Thus, some cases used ACS for pregnant women with high risk factors of preterm infant. On the contrary, there are some relevant meta-analysis suggesting that prenatal use of ACS cannot reduce BPD incidence. Some studies even show that multiple courses of ACS could increase the incidence of BPD [20] [21]. In summary, the application of ACS can reduce RDS and mortality, but more research is needed to support the impact on the incidence of BPD.

3. Postpartum Protection and Treatment

3.1. Postnatal Corticosteroids (PNS)

Inflammation reactions at the lung tissue sites often trigger BPD. Anti-inflammatory glucocorticoids are usually applied in the protection and treatment of BPD through both intravenous and inhaled methods [22]. In 1985, Avery *et al.* [23] first examined the efficacy of intravenous infusion of PNS in preterm infants (2 - 6 weeks old). The results indicated that lung compliance was significantly improved after dexamethasone treatment. However, intravenous infusion of PNS induced systemic side effects for infants, such as neurodevelopmental

disorders, intestinal perforation, and so on. Recent studies revealed that the early (less than 8 days) intravenous infusion of PNS for infants could decrease BPD incidence and mortality, but the risk of intestinal perforation, hypertrophic cardiomyopathy, cerebral palsy, and major neurosensory dysfunction was increased. Compared with the infants with later administration, the infants with early PNS administration exhibited a higher BPD incidence and a relatively lower risks of cerebral palsy, retinopathy (ROP), and hypertension [24] [25]. Based on these side effects, using intravenous PNS should be cautious, and routinely intravenous infusion of PNS is not recommended.

Inhaled corticosteroids (ICS) are able to protect and treat BPD due to their anti-inflammatory capability at the lungs. In 1992, Yuskel *et al.* [26] reported that the cough and wheeze of infants were decreased and their lung function would be improved after 6 weeks of ICS treatment. Subsequently, Bassler *et al.* [27] found that, under no increased risks of neurodevelopmental disorders, the incidence of BPD of the ICS-treated group was significantly diminished. Moreover, Nelin *et al.* [28] showed that ICS had a positive effect on infants with BPD for a short time. According to a study about efficacy of ICS and intravenous infusion of PNS, Shah *et al.* [29] discovered that the incidence of BPD, neonatal necrotizing enterocolitis (NEC), ROP or neurodevelopment presented no differences at the corrected gestational age of 36 weeks. Owing to the short-term adverse effects of hormones (such as high blood pressure, hyperglycemia, gastrointestinal adverse reactions, etc.) and long-term neurological adverse consequences (such as cerebral palsy, learning disabilities, cognitive impairment, etc.), the classes selection and timing point of glucocorticoids usage in the clinical remains controversial. Therefore, the strategy of ICS to protect and treat BPD still needs more in-depth clinical research to clarify its efficacy.

3.2. Assisted Ventilation

One study showed that the infants suffered from BPD at an extremely high incidence (99%) when applied ventilators within 7 days [30], which was also affected by oxygen exposure. Thus, it's important to determine the optimal oxygen saturation. European guidelines recommend that the oxygen saturation should keep at 90% - 94% [31]. In order to ensure the optimal oxygen saturation, many respiratory support will induce lung damage and facilitate BPD occurrence. Thus, there still exists controversy about the determination of the ventilator mode for infants with developing or diagnostic BPD.

3.2.1. Pressure Ventilation

Barotrauma refers to lung damage caused by excessively stretching airways and alveoli when exposed to high positive pressure. Webb and Tierney first discovered that the severity of lung injury was positively correlated with the peak airway pressure [32]. However, overly low airway pressure will cause alveolar collapse and trigger lung injury. Appropriate positive airway pressure for maintaining proper alveoli expansion is essential. Airway pressure is currently ex-

amined by using esophageal pressure tests, which show inaccurately characteristic. Therefore, it is particularly important to propose a method to obtain accurate airway pressure results [33].

Compared with mechanical ventilation, non-invasive pressure ventilation mode can reduce the occurrence of BPD. According to some studies, continuous positive airway pressure (CPAP) would reduce the death or BPD incidence of preterm infants at a corrected gestational age of 36 weeks [34]. Some studies demonstrated that nasal intermittent positive pressure ventilation (NIPPV) was associated with a significantly decreased incidence of BPD [35] [36].

3.2.2. Volume Ventilation

Volume injury refers to lung damage caused by excessive alveolar expansion under high tidal volume (VT) conditions. Besides, volume injury is able to activate macrophages and neutrophils to induce lung inflammation reactions and secondary lung damage, which weaken the efficacy of surfactant [37] [38] [39]. The key factor on BPD occurrence is the lung volume at the end of inhalation. Lista *et al.* indicated that volume targeted ventilation (VTV) could relieve RDS and pulmonary inflammation for preterm infants [40], keeping lung compliance and resistance, and decreasing volume injury [41]. On the basis of one systematic review of 18 trials, VTV showed lower BPD incidence than pressure-limiting ventilation [42]. A meta-analysis from 2017 revealed that, compared with pressure limited ventilation (PLV), VTV could significantly lower BPD incidence. Meanwhile, pneumothorax, severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and average days of ventilation in preterm infants who applied VTV were also significantly lower than those of preterm infants using PLV [43]. Recently, Cannavo *et al.* highlighted that avoiding volume injury played a crucial role in decreasing lung damage and brain damage in newborns [44].

3.2.3. Neurally Adjusted Ventilatory Assist (NAVA)

NAVA can trigger breath through diaphragm electrical activity and maintain the breath of newborn by delivering the pressure with proportional to the electrical signals [45], and most preterm infants are still keeping the respiratory pressures and volumes within or below recommended ranges [46]. Compared with traditional ventilation, NAVA is capable of improving respiratory function [47]. From a study of 29 preterm infants, the oxygen saturation of 21 preterm infants with BPD improved significantly and meanwhile $PaCO_2$ was decreased from mechanical ventilation to NAVA [48]. A recent research enunciated that NAVA techniques decreased the failure rate of extubation and shortened invasive ventilation time, but there was no significant difference in BPD incidence between NAVA and conventional breath modes [49], which may be attributed to the small sample size. Overall, whether NAVA can become a ventilation model for BPD protection and treatment requires more research support.

3.3. Pulmonary Surfactant (PS)

PS synthesis can cause lung development disorders. At 15 weeks of gestation, the

RNA of pulmonary surfactant protein B (SP-B) and surfactant protein B (SP-C) could be measured, phospholipids and active SP-B were synthesized at 24 - 25 weeks, and PS increased rapidly at 35 weeks [50]. Therefore, the preterm infants less than 35 weeks gestational age are susceptible to suffering from BPD. A review from 1998 reported that surfactant therapy with intratracheal administration could reduce mortality rate and chronic lung diseases formation [51]. Simultaneously, early applied surfactants decreased BPD risks by analyzing six randomized controlled trials [52]. From the meta-analysis results, compared with standard surfactant administration, less invasive surfactant therapies (LIST) via an endotracheal tube exhibited lower BPD incidence (RR 0.71, 95% CI 0.52 - 0.99) and less time to need for invasive ventilation (RR 0.67, 95% CI 0.53 - 0.84) [53]. A recent randomized controlled trial of 457 infants at age of 23 - 41 weeks found that the infants (less than 12 hours) with nebulized surfactant treatment did not need to proceed later intubation and surfactant administration generally [54]. Although LIST and nebulization may be good for treating BPD and reducing the need of mechanical ventilation, more reliable data are needed to ensure their efficacy in BPD therapy.

3.4. Caffeine

In 1977, Aranda *et al.* [55] first discovered that caffeine showed sufficient efficacy on treating apnea of preterm infants. Caffeine improves pulmonary ventilation by increasing the influx of Ca^{2+} and the reactivity of central and peripheral chemoreceptors to CO_2, improving the contractile force of the diaphragm [56]. Moreover, it was reported that caffeine improved pulmonary ventilation for 16 preterm infants with BPD [57]. Through a trial on caffeine for apnea treatment in preemies, caffeine was able to decrease BPD incidence at a 36% reduction ($p < 0.001$). 78 infants with caffeine treatment could be successfully extubated at the early stage. Besides, those infants (less than 3 days) with early caffeine treatment possessed shorter respiratory support time than the infants without caffeine administration [58] [59]. Lodha *et al.* [60] demonstrated that the group with early caffeine treatment (less than 3 days) exhibited low mortality rate or BPD incidence characteristics. In conclusion, caffeine administration at the early stage can protect and treat BPD effectively for the infants.

3.5. Pulmonary Vasodilators

Generally, BPD infants with abnormal pulmonary vascular development increase vascular resistance to cause pulmonary hypertension, aggravates BPD to increase mortality [61]. Pulmonary vasodilators (including inhaled nitric oxide (NO) and sildenafil) can treat pulmonary hypertension through the NO-cyclic guanosine monophosphate (NO-cGMP) signal pathway, thereby protect and treat BPD [62].

NO promotes pulmonary vasodilation by increasing cGMP and decreasing intracellular Ca^{2+} [63]. Animal experiments indicated that inhaled NO could reduce lung inflammatory reactions and fibrosis [64]. In addition, the treatment of

NO inhalation could also improve PaO_2 in BPD [65]. According to one Cochrane review, there was no differences in the total mortality rate or BPD incidence of preterm infants at 36 weeks between the infants treated with inhaled NO and infants without NO treatment, fortunately, cerebral hemorrhage or retinopathy did not appear after NO inhalation [66], NO inhalation could also lessen the usage of bronchodilators, glucocorticoids, diuretics and oxygen inhalation [67]. Sildenafil can inhibit the degradation of cGMP and bring about pulmonary vasodilation. neonatal mice treated with sildenafil tests demonstrated that sildenafil could facilitate alveolar formation and angiogenesis, reduce lung inflammatory reactions and fibrosis, thereby reducing BPD incidence finally [68]. Furthermore, one meta-analysis results revealed that sildenafil could improve the pulmonary artery pressure of neonates without any serious adverse events appearance [69]. Although there is no direct evidence that pulmonary vasodilators can be used to treat BPD well, they may bring many benefits.

3.6. Antioxidants

3.6.1. Vitamin A, Vitamin C and Vitamin E

Immature antioxidant system is one of the factors of lung injury in preterm infants [70]. For BPD preterm infants, the number of retinol and retinol-binding proteins are less than normal infants. Vitamin A and its metabolite retinol are involved in the growth, differentiation, and regeneration of airway epithelial cells [71]. In 1985, Shenai *et al.* [72] had already discovered that the infants with BPD showed low vitamin A level within blood vessels of vitamin A, indicated that vitamin A played a protective role in the lungs. In a multicenter randomized trial, after experiencing vitamin A administration of 4 weeks for 807 infants with very low birth weight, the BPD incidence of infants decreased significantly ($p = 0.03$). Moreover, vitamin A administration showed sufficient efficacy (especially for the infants with low risks), including BPD incidence and mortality rate reduction of preterm infants [73] [74]. However, various studies demonstrated that vitamin A-treated infants presented a higher incidence of NEC, ROP, sepsis, and persistent patent ductus arteriosus [75], the safety of vitamin A still needed to be evaluated further.

Both Vitamin E and vitamin C can protect and treat BPD by removing reactive oxygen species and preventing lipid peroxidation. Vitamin E and vitamin C play a positive role in protecting the lungs. It was reported that preterm infants (less than 33 weeks of gestation) possessed low serum vitamin E levels, which were associated with the occurrence of BPD [76]. Vyas *et al.* [77] also found that the content of vitamin C within preterm infants was the lowest in comparison with other vitamins, but less evidence to demonstrate that vitamin E or vitamin C supplement can protect and treat BPD effectively.

3.6.2. Other Antioxidants

Trace elements like selenium (Se) and zinc (Zn) are the basis of endogenously and exogenously antioxidative performances in vivo and enhance lung matura-

tion [78] [79]. Se plays an important role in modulating immune response, redox, and inflammatory reactions, which can be used to produce selenoenzymes" to participate in various metabolisms [80]. Generally, preterm infants exhibit high risks of BPD incidence due to intestinal malabsorption and immature selenium metabolism. Mostafa-Gharehbaghi *et al.* [81] found that Se concentration in the BPD group was lower than that in the non-BPD group (38.5 ± 14.1: 45.4 ± 18.7 μg/L, p = 0.02). However, Peirovifar *et al.* [82] found that no significant differences in Se contents emerged between newborns and BPD newborns. Zn is mainly involved in basic metabolisms and the upgrowth of the brain, respiration and intestines. Some studies indicated that Zn supplement could reduce mortality rate for preterm infants, but it had little impact on the protection and treatment of BPD [83] [84]. Thus, more studies are essential to proceed to verify the function that Se and Zn enhance BPD protection and treatment through their antioxidative capability.

Melatonin can conduct antioxidative behavior through different pathways, it can scavenge reactive oxygen species, promote the production of antioxidant enzyme complexes, and reduce the levels of plasma inflammatory markers (such as IL-6, IL-8, and tumor necrosis factor) [85]. Animal experiments demonstrated that mice with melatonin supplement showed better lung structural maturity than common mice [86] [87]. Moreover, melatonin could reduce KL-6 (a marker of neonatal BPD) levels in serum, indicating that melatonin possessed the potential to reduce BPD incidence of newborns [88] [89]. Currently, no clinical studies have proven the efficacy of melatonin for BPD therapy.

3.7. Fluid Restriction and Diuretics

For preterm infants, the aim of fluid restriction is to reduce pulmonary edema incidence and the amount of required respiratory support, thereby decreasing BPD-related risk factors. BPD infants usually present poor tolerance to fluid burden, and fluid restriction is a common therapeutics. In one randomized controlled trial, no significant differences between BPD infants with fluid restriction and BPD infants in supplemental oxygen, mechanical ventilation, and length of hospital stay [90], and there still is no sufficient evidence to support the above results.

Diuretics can reduce pulmonary edema, improve airway compliance, and reduce airway resistance which are usually used in infants with BPD. According to 6 randomized controlled trials of Cochrane review, lung compliance improved after furosemide treatment for 1 - 2 days, but there was no more evidence to show the positive effects of diuretics in BPD infants [91]. Meanwhile, thiazides and spironolactone could improve lung compliance, but the number of patients included in the study were too small [92]. However, diuretics administration via oral and intravenous induced many side effects, such as nephrocalcinosis, electrolyte imbalance, osteopenia, and ototoxicity [93] [94], Thus local atomized diuretics administration is necessary to avoid systemic side effects. Besides, a sys-

tematic review summarized that nebulized diuretics with single dose applied in the BPD infants could temporarily improve respiratory mechanics, but there were no studies on long-term efficacy and long-term outcomes [95].

3.8. Antibiotic Management

Ureaplasma urealyticum (UU) infection is associated with BPD [96]. Wang *et al.* [97] indicated that the infants infected with UU showed higher BPD incidencce than that of the uninfected infants, appropriately 1.72 times. In addition, Ballard (2007) *et al.* [98] demonstrated that the infants treated with azithromycin presented less duration time of PNS treatment and respiratory support, the occurrence of BPD was not reduced. Furthermore, treating BPD with protectively azithromycin administration could decrease BPD incidence (RR 0.83, 95% CI 0.71 - 0.91) [99]. However, recent studies proved that the BPD infants at the corrected gestational age of 36 weeks with azithromycin treatment did not significantly improve BPD infants incidence or mortality rate [100].

Infection increases the risks of suffering from BPD which may be possibly associated with inflammatory mediators [101]. According to retrospective study results, infection significantly increased the risks of suffering from BPD (OR 2.74, 95% CI 2.54 - 2.94). With the infection rates decreased from 24.7% to 15%, the BPD incidence also decreased by 8% [102]. In addition, the time of antibiotic exposure for newborns was correlation with increased risks of BPD [103]. In clinical practice, strict hand hygiene, aseptic operation, disinfection, and medical waste management have been applied to prevent hospital infections and achieve BPD prevention and treatment, avoiding abuse of antibiotics.

4. Emerging Treatments for BPD

4.1. Mesenchymal Stem Cells

For preterm infants, abnormal alveolar upgrowth is associated with reduced MSCs [104]. MSCs are able to promote cell growth and angiogenesis, prevent oxidation and fibrosis, and inhibit inflammatory reactions [105]. The origin of MSCs is diverse, including embryonic tissue, umbilical cord blood, and placenta tissue. Among of these, umbilical cord-derived MSCs showed better effectiveness [106]. Neonatal rats with MSCs treatment experiments demonstrated that MSCs could reconstruct the structure and function of lung. No adverse reactions emerged during follow-up within 6 months, lung structure and exercise tolerance improved sustainedly during this process [107]. In recent years, some studies have evaluated the efficacy of BPD with MSCs treatment in clinical practice, Chang *et al.* conducted phase I study of MSCs treatment on 9 preterm infants. MSCs treatment could relieve inflammatory reactions and decrease the severity of BPD in comparison with the control group. During two years follow-up, none of the infants treated with MSCs went home to receive oxygen therapy, and no long-term respiratory complications (including wheezing and asthma) were observed [108] [109]. In order to further investigate the efficacy of MSCs on the

infants, 66 infants (23 - 28 weeks gestation) were randomly assigned to receive intratracheal MSCs or saline treatment. Results showed that the infants treated with MSCs possessed lower levels of endotracheal inflammatory markers and lower incidence of severe BPD in the infants at 23 - 24 weeks gestation, but the rates of mortality or severe/moderate BPD incidence exhibited similar trends between the two groups [110]. MSCs can improve lung function of the infants. However, these studies do not provide enough evidence to ensure that MSCs treatment can reduce BPD incidence, further research is ongoing in many countries, such as Spain, South Korea, and China.

4.2. Superoxide Dismutase (SOD)

SOD belongs to an antioxidative enzyme. Animal experiments proved that SOD could reduce BPD incidence [111]. Rosenfeld *et al.* [112] first discovered that the clinical symptoms of BPD would be reduced after proceeding SOD administration for the infants with severe RDS. However, a randomized controlled trial revealed that no differences in the occurrence of BPD in infants treated with SOD at 28 days or 36 weeks were observed. SOD treatment could be beneficial for reducing wheezing episodes and hospitalization rates of the infants at one year before corrected age [113]. SOD may improve the long-term prognosis of the BPD infants.

4.3. Erythropoietin (EPO)

EPO has anti-inflammatory and antioxidative properties and can improve alveolar structure and reduce lung fibrosis [114] [115]. Some studies suggested that EPO may reduce the BPD incidence of preterm infants, but a meta-analysis showed that no differences in the incidence of BPD between the infants-treated with EPO and placebo were observed [116]. Compared with single MSCs treatment, the combination of MSCs and EPO applied in neonatal mice significantly reduced lung injury and fibrosis [114], the combination therapeutic of EPO and MSCs is still applied in the clinical study.

4.4. Insulin-Like Growth Factor 1 (IGF-1)

IGF-1 is a growth factor involved in vascular development [117]. The woman at late pregnancy possesses high IGF-1 levels, which promote the growth and development of the infants. Compared with full-term infants, preterm infants have lower IGF-1 levels due to loss of IGF-1 from the mother and postpartum malnutrition. Some studies demonstrated that IGF-1 in the serum kept at low levels in BPD infants, indicating that IGF-1 could be a potential therapeutic target for BPD by improving vascular development [118].

4.5. Gut Microbiota

Gut microbiota may influence BPD through the gut-lung axis [119]. Gut microbiota disorder can induce inflammatory reactions and lung damage [120]. Pre-

term infants have less microbiota diversity than full-term infants [121]. BPD infants showed lung flora imbalance characteristic [122]. In addition, Klebsiella and Salmonella were significantly reduced in the BPD infants, and the number and type of gut microbiota also decreased after 28 days of birth [123] [124]. Meanwhile, some studies directly or indirectly proved that the BPD infants showed gut microbiota disorder behavior. The risk of death or suffering from BPD was significantly increased for infants at very low birth weight with antibiotic administration after two weeks of birth [125]. The relationship between gut microbiota and BPD still exists in the primary exploration stage, more studies are proceeding to prove the viability and safety of gut microbiota in preventing and treating BPD.

5. Prospectives

BPD is the most common long-term adverse outcome in preterm infants which is closely associated with chronic respiratory diseases, finally causing abnormal lung function, this process will last into adulthood usually. The high-risk factors of having BPD are complex, even many current studies indicated that the effects of the same factor on BPD showed different results. Further large-sample and multi-center studies are needed to provide sufficient evidence on these controversial factors. Currently, most drugs used to prevent and treat BPD still have not been supported by clinical practice completely, and meanwhile lack evaluation about their side effects. Thus, more research, and exploration are essential to investigate the risks of these drugs. For example, when intravenous infusion of glucocorticoids is applied, the long-term effects on the patient's nervous system and respiratory system need to be considered; whether glucocorticoids inhalation can effectively prevent long-term complications and decrease side effects. In addition, more powerful evidence is necessary to measure the efficacy of vasodilators on BPD-related pulmonary hypertension. MSCs can be a promising strategy for preventing/treating BPD in the future. Because of lacking effective therapeutics for BPD, perinatal and neonatal medicine should focus on how to avoid or reduce the adverse effects caused by high-risk factors for newborns, especially for preterm infants. Besides, well clinical protection in a "point-to-point" manner should be provided, which will significantly reduce BPD incidence and enhance prognosis improvement. Simultaneously, with the increasing of infants with BPD, favorable ventilation modes will establish the optimal respiratory support mode for these BPD infants. Above all, the prevention and treatment of BPD require more diversified responses and clinical research support to find the optimal strategy to prevent and treat BPD due to BPD coincidence caused by multiple factors.

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Conflicts of Interest

The authors declare no competing financial interest.

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