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Review

Upper Airway Manifestations and Otolaryngologic Management of Bronchopulmonary Dysplasia in Preterm Infants: A Systematic Review

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Abstract: Bronchopulmonary dysplasia (BPD) is a complex chronic lung disorder that affects extremely premature infants, particularly those born before 30 weeks of gestation or weighing less than 1500 g at birth. This systematic review aimed to evaluate the effectiveness of pharmacological interventions for BPD and to explore otolaryngologic manifestations and management strategies. A comprehensive literature search was conducted in the PubMed, Scopus, and Web of Science databases, yielding five studies that met the inclusion criteria. The studies investigated the effects of corticosteroids (prednisolone, hydrocortisone, and dexamethasone), erythropoietin, and diuretics on BPD outcomes. Prednisolone showed minimal short-term benefits, whereas hydrocortisone did not significantly reduce the incidence of BPD. However, extended dexamethasone regimens have been shown to improve survival rates without increasing complications. Early erythropoietin treatment reduced the incidence of BPD but did not affect hospital readmission rates. Diuretic use varied widely across centers, without clear survival or discharge benefits. Preterm infants with severe BPD requiring prolonged mechanical ventilation are at a high risk of subglottic stenosis, tracheomalacia, and vocal cord paralysis. Early diagnosis through airway endoscopy and multidisciplinary

management, including tracheostomy for severe cases, are crucial for optimizing outcomes. BPD survivors may experience long-term respiratory impairment, exercise intolerance, and developmental delays, necessitating close monitoring and intervention. Future research should focus on developing standardized, evidence-based management protocols and exploring novel therapies to improve long-term respiratory and neurodevelopmental outcomes in this vulnerable population group.

Keywords: Bronchopulmonary Dysplasia; Subglottic Stenosis; Airway Obstruction; Neonatal Intubation; Laryngoscopy; Corticosteroids

1. Introduction

Extremely premature infants, particularly those born at 23–24 weeks of gestation, frequently suffer from bronchopulmonary dysplasia (BPD), a chronic lung condition [1,2]. This complication arises from an imbalance between lung damage and repair in the developing respiratory system [3]. BPD is characterized by impaired alveolar and pulmonary vascular growth, leading to a simplified lung structure that compromises gas exchange and increases cardiopulmonary morbidity and mortality rates [4].

An understanding of the pathophysiology of BPD has evolved. While traditionally linked to postnatal injury from ventilator use and oxygen therapy, current research indicates that factors before and during birth contribute to disrupted lung development in extremely preterm infants [4]. Sepsis and conditions triggering systemic inflammatory responses are crucial risk factors for BPD, underscoring the interplay between the elements involved in its onset [5].

Infants born prematurely with BPD experience long-lasting respiratory impairments and physical limitations from infancy to adulthood [6]. This disorder is linked to an increased risk of respiratory infections, pulmonary hypertension, and delayed neurodevelopment [7]. Despite improvements in perinatal care, leading to increased survival rates for extremely preterm infants, BPD remains a challenge, with few effective treatment options.

BPD, a long-term lung condition in preterm babies, is associated with numerous risk factors. Maternal factors, such as young age, hypertensive disorders, antepartum bleeding, and clinical chorioamnionitis, are associated with a higher risk of BPD [8,9]. Infant-related factors include male sex, non-Jewish ethnicity, congenital anomalies, small gestational age, and early gestational age [8,9]. Post-birth factors, such as delivery room resuscitation, mechanical ventilation, and management of patent ductus arteriosus, significantly influence BPD development [8–10].

BPD onset stems from intricate interactions between various pre- and postnatal factors [11]. The early detection of high-risk infants using predictive models incorporating these risk factors may enable targeted preventive approaches [11,12]. Strategies to protect the lungs, optimal nutrition, and medical treatments have shown potential in lowering BPD risk; however, their long-term effects remain unclear [13].

Premature infants with BPD often require extended intubation and mechanical ventilation in severe cases. Patients with severe BPD require prolonged positive pressure ventilation [14]. Extended mechanical ventilation increases the risk of BPD and related health issues [15]. Infants with severe BPD experience longer endotracheal ventilation periods. Noninvasive respiratory support techniques are gaining focus, with noninvasive support preferred as initial support in extremely preterm infants [15]. Early continuous positive airway pressure and surfactant administration protects against severe BPD. While extended intubation remains common in severe cases, mechanical ventilation beyond seven days is the primary risk factor [16]. Strategies to reduce prolonged intubation may improve outcomes.

Subglottic stenosis commonly occurs due to extended intubation, particularly in newborns and children, and is a leading cause of stridor in infants after prolonged mechanical ventilation [16]. Among infants intubated for 3–50 days, subglottic stenosis occurred in 0.4%, with low-birth-weight infants (<1,500g) being more susceptible to laryngeal injuries [17]. Tracheomalacia is also associated with extended mechanical ventilation, with higher mean airway pressure and lower gestational age being clinical indicators in premature infants [18]. Vocal cord paralysis can result from prolonged intubation or surgery near the recurrent laryngeal nerves [19]. ENT specialists diagnose these conditions through airway endoscopy and implement treatments such as posterior cricoid grafts or CO2 laser techniques [20,21]. Prolonged mechanical ventilation requires ENT expertise for airway care, and early detection

and intervention are crucial for patient outcomes. Bush et al. note that neonates with BPD are prone to developing airway pathology, particularly for patients who require intubation and positive-pressure ventilation [22].

The recommended therapeutic approach emphasizes prevention, as BPD affects multiple organ systems. Prevention and treatment strategies include antibacterial and anti-inflammatory medications using systemic corticosteroids, such as Dexamethasone or Hydrocortisone, and intrapulmonary corticosteroids, such as Budesonide and Fluticasone. It may also involve ventilatory techniques, avoiding orotracheal intubation and promoting noninvasive ventilation methods.

Corticosteroids enhance fetal lung development and reduce risks such as perinatal mortality, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and systemic infections [23]. They aid in extubation and decrease BPD. However, prolonged use can lead to neurological and metabolic issues, potentially causing growth problems. Dexamethasone improves lung function and reduces extubation failure [24]. The recommended dose is 0.25 mg/kg/dose every 8 hours for five days. Extending to seven days may cause side effects and is advised only for infants on mechanical ventilation for over two weeks [25]. Hydrocortisone shows fewer adverse effects and is recommended at low doses (0.15 mg/kg/day) during the first 7–14 days after birth. Although hyperglycemia is a notable side effect [26], it shows promise in preventing BPD. Prednisolone has a temporary positive effect and is linked to changes in infants' linear growth [24].

Administering corticosteroids within the first four days promotes extubation and reduces BPD risk but is associated with complications. Corticosteroids administered between days 7 and 14 had lower mortality and BPD without affecting neurological development. A regimen three weeks after birth reduces death rates and BPD, but more research is needed for optimal timing [22,27].

Inhaled corticosteroids have been developed to avoid systemic complications. Budesonides and fluticasone were commonly used. Inhaled Budesonide within 24 h of birth helps prevent BPD, but increases mortality at 18 months. Thus, inhaled corticosteroids are not recommended for routine use. However, Budesonide with exogenous surfactant administered via intratracheal injection reduces BPD-related mortality [25,27].

A study of 1,285 newborns treated within the first two weeks showed a decreased incidence of BPD (relative risk: 0.86, 95% CI: 0.75–0.99; $p = 0.04$), but was linked to higher mortality (relative risk: 0.76; 95% CI: 0.63 – 0.93; $p = 0.005$) [27]. A study examining 265 infants administered budesonide with intratracheal surfactants found no difference in mortality rates [27].

Bronchodilators are justified in treating individuals with BPD because of their ability to expand the small airways and decrease airway resistance. Research on inhaled salbutamol has shown no significant impact on mortality (relative risk: 10.8; 95% CI, 0.50–2.31) or BPD incidence (relative risk: 1.03; 95% CI, 0.78–1.37). However, B2-agonists increase the heart rate in newborns [28].

Alveolization relies on pulmonary angiogenesis, and factors influencing this process are linked to BPD. Angiogenic factors, such as erythropoietin, may aid in alveolar restoration. Erythropoietin, used to treat anemia in premature infants, also exhibits anti-inflammatory, anti-apoptotic, and neuroprotective properties. It can mobilize endothelial progenitor cells and promote angiogenesis. Studies have shown that erythropoietin is linked to lower BPD incidence and fewer hospital readmissions [29].

Although surfactant administration reduces oxygen requirements within 24 h, no substantial benefits have been observed regarding BPD. Consequently, this medication is not routinely prescribed [30].

Nitric oxide plays a crucial role in alveolar and vascular development. In BPD, insufficient production and signaling lead to pulmonary and vascular damage. It has been proposed to enhance pulmonary angiogenesis and to reduce inflammation, oxidative stress, and apoptosis. Studies show that administering nitric oxide as prophylaxis and rescue therapy in premature neonates with respiratory issues decreases BPD-related mortality (relative risk: 0.77; 95% CI: 0.65–0.91) [31].

Sildenafil, a selective phosphodiesterase inhibitor, promotes pulmonary vasodilation and alveolar maturation, reduces lung inflammation, alleviates pulmonary hypertension, and minimizes hyperoxia-induced lung damage. Studies in newborns have reported improved right ventricular function and decreased BPD-associated mortality. However, the FDA cautions against prescribing sildenafil to children aged 1–17 years due to inadequately studied side effects [31].

BPD increases the susceptibility to interstitial pulmonary edema caused by enhanced capillarity and permeability due to oxygen pressure-induced lung damage. Diuretics, particularly loop diuretics, target this pathway.

However, extended use may result in side effects, such as electrolyte imbalances, nephrocalcinosis, ototoxicity, and delayed ductus arteriosus closure [32].

Furosemide is widely used because of its effectiveness in reducing edema and improving respiratory mechanics, lung function, and distensibility. It is favored for premature infants with fluid overload, as its use is associated with a lower BPD risk, fewer days on mechanical ventilation, and shorter hospital stays. However, its use is not universally endorsed due to the development of tolerance, necessitating dose increases, which amplify adverse effects, particularly metabolic and renal complications, potentially extending the hospitalization duration [33].

Recent research has identified chorioamnionitis as an indirect contributing factor to BPD. This condition involves inflammatory cells, primarily neutrophils, infiltrating the chorion, amnion, and the placenta. Elevated levels of interleukin 8 (IL-8), a cytokine that promotes neutrophil movement, have been observed in tracheal aspirates of intubated newborns. Neutrophil elastase is believed to damage the interstitium and pulmonary alveoli in BPD. Sivelestat administration at high doses decreased IL-8 levels. However, a study of 1,031 preterm infants treated with Sivelestat showed no improved survival rates (odds ratio: 0.83; 95% CI 0.53–1.30) [34].

Studies using mesenchymal stem stromal cells for BPD prevention and treatment have shown that these cells' properties can improve repaired lung tissue, affect pulmonary artery remodeling, and protect against BPD-induced pulmonary hypertension. However, these therapies remain in experimental animal models [35,36]. An initial study involving nine extremely preterm infants born between 23 and 29 weeks of gestation, weighing 500–1250 g, administered a single dose of stem cells via the trachea within 5–14 days of mechanical ventilation. The results showed no immediate adverse effects on the respiratory function or neurodevelopment.

Tracheostomy is a crucial option for infants with severe BPD requiring prolonged mechanical ventilation. The decision-making process varies between centers, and universal guidelines are lacking [37]. Anatomical upper airway obstruction and BPD are common reasons for neonatal tracheostomy [38]. The procedure typically occurs at 168 days and 48 weeks of postmenstrual age [39]. Although tracheostomy can be life-saving, it poses significant mortality risks, especially for infants who are small for gestational age or with pulmonary hypertension [39,40]. Despite the risks, tracheostomy aids in ventilation weaning and decannulation. By age 5, 97% of survivors achieve ventilation independence, and 79% undergo decannulation, although half require airway reconstruction [40]. The decision requires weighing the benefits against the complications, hospitalization risks, and impacts on development and caregivers [41].

Infants with BPD are at a higher risk of intermittent hypoxemia, characterized by a capillary oxygen saturation below 92%, particularly during sleep and feeding. Hypoxemic conditions are associated with growth deficits, necessitating supplemental oxygen for most of the discharged newborns. However, most infants overcome this requirement by two years of age. Given the need for home oxygen supplementation, it is essential to establish protocols to determine the optimal timing of oxygen weaning. The proposed criteria included maintaining a minimum oxygen saturation of 95% during sleep. Alternatively, pediatric pulmonology specialists recommend conducting polysomnography to rule out episodes of hypoxemia [32,42,43].

After leaving the neonatal unit, infants with BPD face an increased likelihood of returning to the hospital due to vulnerability to viral infections, lung deterioration, declining respiratory function, and an elevated risk of respiratory illnesses. These children may experience poor nutritional status or neurological developmental issues, leading to more frequent medical care. Healthcare providers and parents must monitor disease progression and implement treatment to minimize the effects of chronic respiratory conditions [44].

Exercise intolerance is a primary consequence of BPD that triggers bronchoconstriction and disrupts gas exchange, leading to structural alterations in the lungs. This may result in right ventricular dysfunction that worsens during physical exertion. Chemoreceptor abnormalities can cause inadequate response to hypoxia and predispose patients to central airway disorders. Pulmonary arterial hypertension, occurring in up to 39% of patients, is a significant adverse effect, increasing mortality rates and the risk of right ventricular dysfunction, manifesting as an increased need for respiratory support and extended hospital stays [6,45]. This study aimed to describe updated therapeutic protocols for BPD in premature newborns through a systematic review. This review also explores otolaryngologic manifestations of bronchopulmonary dysplasia, including upper airway obstruction, vocal cord dysfunction, and tracheal anomalies, with a focus on diagnostic strategies and surgical management.

2. Methods

This systematic review followed the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses [46].

This comprehensive review was conducted through an extensive literature search across multiple databases including Scopus, Web of Science, and PubMed, encompassing publications from 2016 to 2022. The search used a combination of Medical Subject Headings terms and keywords, such as premature newborns, neonatal intensive care unit, respiratory distress in neonates, and BPD, along with Boolean operators (AND, OR, and NOT) to refine the results. The reference lists of key studies and reviews were manually examined to identify additional relevant articles.

The inclusion criteria for this review were as follows: (1) studies focusing on pharmacological management of BPD in premature infants, particularly those born before 30 weeks of gestation or weighing less than 1500 g at birth; (2) quantitative, analytical, or experimental research designs, including randomized controlled trials (RCTs), cohort studies, meta-analyses, or systematic reviews; (3) peer-reviewed, indexed journal publications between 2016 and 2022; (4) clear reporting of treatment methodologies, sample sizes, and outcomes related to BPD incidence, severity, or neonatal respiratory health; and (5) studies published in English. Priority was given to studies evaluating corticosteroids, erythropoietin, diuretics, or other pharmacological interventions with well-defined efficacy and safety outcomes.

The exclusion criteria were as follows: (1) non-pharmacological interventions; (2) qualitative methodologies, case reports, book chapters, letters to the editor, or conference abstracts; (3) lack of a control group or well-defined comparison of pharmacological treatments; (4) absence of explicit data on treatment efficacy, safety, or patient outcomes; (5) non-English-language publications; and (6) incomplete, inconclusive, or anecdotal evidence without rigorous methodological validation. Studies reporting outdated treatments or lacking statistical analyses were also excluded.

A team of experts in neonatology, pharmacology, and systematic review methodologies independently conducted the literature screening, data extraction, and quality assessment. Standardized tools, such as the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for observational studies, were used for quality assessment. The reviewers collaborated to synthesize the findings and draft the final report, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Discrepancies were resolved through group discussion and consensus-based decisions.

This review focused on pharmacological treatments subjected to scientifically rigorous research and robust methodologies. Data extraction was performed systematically, capturing essential variables, such as study design, sample size, intervention type, primary and secondary outcomes, and statistical significance. The emphasis was on identifying treatments that demonstrated clinically meaningful benefits in reducing BPD incidence, improving pulmonary function, and mitigating associated complications.

A thorough risk of bias assessment was performed for studies in a systematic review evaluating six areas: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (masking outcome assessment), attrition bias (completeness of outcome data), reporting bias (reporting all prespecified outcomes), and other biases (additional risks, such as funding bias or study-specific issues). Each study was rated as low risk of bias (1), unclear risk of bias (2), or high risk of bias (3), according to the Cochrane Handbook for Systematic Reviews of Interventions. The ROBINS-I Tool was used for non-RCTs, focusing on confounding factors, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurements, and reporting bias. The assessment process involved two independent reviewers, and any disagreements were resolved through discussion or consultation with a third reviewer. This thorough approach ensured a transparent and reliable evaluation of the study.

This review did not involve human participants or confidential patient data, and thus did not require ethical approval. Ethical standards were maintained through accurate representation of findings, proper attribution, and plagiarism avoidance. Constraints included potential publication bias towards positive results and exclusion of non-English studies. Variations in study design, interventions, outcomes, and patient populations have limited generalizability. Incomplete reporting in some studies could affect the quality and bias assessment.

3. Results

The initial literature search yielded 122 results, with 101 articles excluded because they did not meet the inclusion criteria. After excluding 15 articles due to insufficient data or conclusions, 21 articles were thoroughly examined. Full-text access for one of the remaining six studies was unattainable despite multiple attempts, leaving five studies for a systematic review [24,26,29,33,47]. **Figure 1** illustrates the selection process and **Table 1** lists the five studies included.

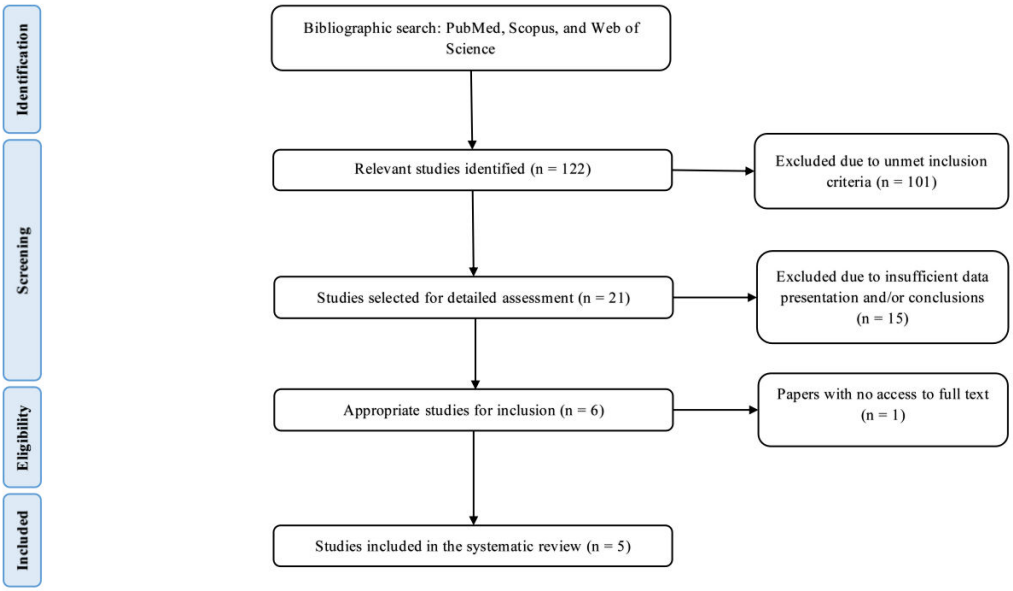

Figure 1. Flow Diagram of Literature Search and Study of Selection for Systematic Review (PRISMA Flow Chart).

Table 1. Characteristics of Selected Studies on Evaluating Treatments Used in Premature Newborns with BPD.

Study details	Study objectives	Study design	Sample size	Intervention	Outcome measures	Main findings
Linafelter et al. [24]	To assess prolonged prednisolone effects in severe BPD.	Retrospective cohort	43 infants	Prolonged prednisolone use	Pulmonary severity score, growth parameters	Slight short-term pulmonary improvement (p = 0.03), but no long-term benefits. Potential growth impairment.
Onland et al. [26]	To evaluate the impact of hydrocortisone on mortality and BPD prevention.	Randomized controlled trial	372 infants	Hydrocortisone therapy	Mortality rate, BPD incidence, hyperglycemia risk	No significant reduction in BPD (p = 0.31). Lower mortality (p = 0.048), increased hyperglycemia.
Bui et al. [29]	To evaluate the role of erythropoietin in reducing BPD incidence and hospital readmission.	Retrospective cohort	1,821 infants	Erythropoietin administration	BPD incidence, hospital readmission rates	Erythropoietin reduced BPD incidence at 36 weeks (18.8% vs. 25.9%, p < 0.01). No effect on readmission.
Bamat et al. [33]	To examine variability in loop diuretic use across centers and its outcomes.	Retrospective cohort	3,252 infants	Loop diuretic variability	Diuretic exposure variation, mortality, discharge timing	Diuretic use varied widely (7.3%–49.4% of days, p < 0.0001). No clear survival or discharge benefits.
Marr et al. [47]	Compare long-term vs. short-term dexamethasone regimens on BPD outcomes.	Retrospective cohort	59 infants	42-day vs. 9-day dexamethasone regimen	Ventilation duration, transfusions, survival at school age	Longer dexamethasone use led to shorter ventilation duration, fewer transfusions, and higher intact survival at school age (p < 0.005).

BPD: Bronchopulmonary dysplasia.

This systematic review incorporated five studies that investigated the impact of different pharmacological treatments on BPD in premature infants. The research designs varied, with four retrospective cohort studies and one RCT. The number of participants in these studies ranged from 59 to 3,252 infants, primarily those born before 30 weeks of gestation and weighing less than 1,500 g at birth.

3.1. Effects of Prednisolone on Severe BPD

A single-center retrospective cohort study by Linafelter et al. examined the effects of prolonged prednisolone administration in infants with severe BPD [24]. The study included 43 neonates with an average birth weight of 729 g and mean gestational age of 26 weeks. The results showed a slight short-term improvement in the pulmonary severity score after one week of treatment (mean difference: 0.19; 95% CI: 0.01 to 0.37; $p = 0.03$). However, continued therapy did not lead to a further reduction in pulmonary severity score. Over a four-week period, the length z-scores decreased (mean difference: 0.6; 95% CI: 0.01 to 1.1; $p = 0.04$), while weight and head circumference remained unchanged. These outcomes indicate that extended prednisolone use may not offer lasting respiratory benefits, and could potentially hinder linear growth.

3.2. Hydrocortisone Therapy in Extremely Premature Infants

A multicenter RCT by Onland et al. evaluated the effects of hydrocortisone administration in mechanically ventilated preterm infants 7–14 days after birth [26]. The study involving 372 infants found no significant difference in the primary outcome of mortality or BPD at 36 weeks' postmenstrual age between the hydrocortisone and placebo groups (70.7% vs. 73.7%; $p = 0.54$). Although hydrocortisone reduced mortality at 36 weeks of postmenstrual age (15.5% vs. 23.7%; $p = 0.048$), it did not significantly affect the incidence of BPD (55.2% vs. 50.0%; $p = 0.31$). The hydrocortisone group had a higher rate of hyperglycemia requiring insulin therapy (18.2% vs. 7.9%). Based on these results, routine use of hydrocortisone for BPD prevention is not recommended.

3.3. Erythropoietin and BPD Risk Reduction

Bui et al. examined the effects of erythropoietin (Epo) on BPD occurrence and hospital readmission rates in premature infants [29]. The study involved 1,821 preterm babies, with 928 receiving Epo treatment and 893 untreated infants. Results showed that Epo therapy was linked to a reduced BPD incidence at 36 weeks postmenstrual age (18.8% compared to 25.9%, $p < 0.01$). The most pronounced advantage was noted when Epo administration began before two weeks of age. Nevertheless, no significant difference was found in the rehospitalization rates between the two groups during the first year. These results indicate that early Epo treatment may help decrease BPD occurrence but does not impact the likelihood of long-term hospital readmissions.

3.4. Variability in Loop Diuretic Use and Outcomes

A retrospective cohort study by Bamat et al. examined the variation in loop diuretic use among preterm infants with severe BPD across different medical centers [33]. The analysis, which included 3,252 infants from 43 centers, revealed substantial differences in diuretic exposure, ranging from 7.3% to 49.4% of the days ($p < 0.0001$). Despite this variability, no significant differences were found in the mortality rates (adjusted OR, 0.98; 95% CI: 0.62–1.53; $p = 0.92$) or postmenstrual age at discharge (47.3 vs. 47.4 weeks; $p = 0.96$). These results indicate considerable variation in treatment approaches without clear evidence of improved survival or earlier discharge.

3.5. Dexamethasone Regimens and Long-Term Outcomes

Marr et al. compared the effects of a 42-day versus 9-day dexamethasone protocol in extremely preterm infants with BPD requiring ventilatory support [47]. A study involving 59 infants found that those on a longer regimen experienced reduced ventilation time (25 vs. 37 days; $p < 0.005$), fewer blood transfusions (2 vs. 3.5; $p < 0.01$), and earlier initiation of enteral feeding (40 vs. 46 days; $p < 0.05$). Long-term assessment revealed a higher rate of intact survival at school age in the 42-day group (75% vs. 34%, $p < 0.005$). These findings indicate that an extended dexamethasone taper may enhance survival outcomes without increasing complications.

Studies of various corticosteroid therapies (prednisolone, hydrocortisone, and dexamethasone) for preterm infants have yielded diverse results. Prednisolone showed minimal advantages, while hydrocortisone did not significantly lower BPD risk. However, extended dexamethasone protocols have improved the survival rates. Erythropoietin therapy demonstrated a protective effect against BPD, especially when initiated early. The use of loop diuretics showed considerable variation without clear advantages. These outcomes highlight the importance of developing standardized evidence-based protocols for managing BPD in preterm infants.

The included studies focused on pharmacological treatments, and the clinical literature indicates high rates of

airway injuries in preterm infants with severe BPD [24,26,29,33,47]. Subglottic stenosis, a narrowing below the vocal cords, causes stridor in infants after prolonged intubation, affecting up to 0.4% of intubated infants, particularly those weighing < 1,500 g at birth. Tracheomalacia, characterized by weakened tracheal walls that cause airway collapse, is correlated with a lower gestational age and extended ventilation. Vocal cord paralysis can occur due to trauma or inflammation affecting the recurrent laryngeal nerve during intubation or surgery. Diagnosis requires flexible or rigid airway endoscopy by ENT specialists.

Treatment ranges from observation for mild cases to airway stenting, tracheostomy, or surgeries such as posterior cricoid split with grafting. Outcomes depend on severity, diagnosis timing, and lung health, with early ENT involvement improving the long-term results. These findings emphasize the importance of interdisciplinary care in BPD management, where ENT monitoring and intervention are crucial for addressing airway obstruction and optimizing respiratory outcomes.

This visual representation offers a comprehensive look at the methodological quality of each study included in the systematic review. The Cochrane Risk of Bias Tool was used to assess RCTs, while the ROBINS-I tool was used to evaluate non-randomized studies. Six primary areas were examined: selection, performance, detection, attrition, reporting, and other biases. **Figure 2** displays the risk of bias evaluation for the included studies across various domains using a color-coded system where green indicates low risk, yellow suggests some concerns, and red denotes high risk.

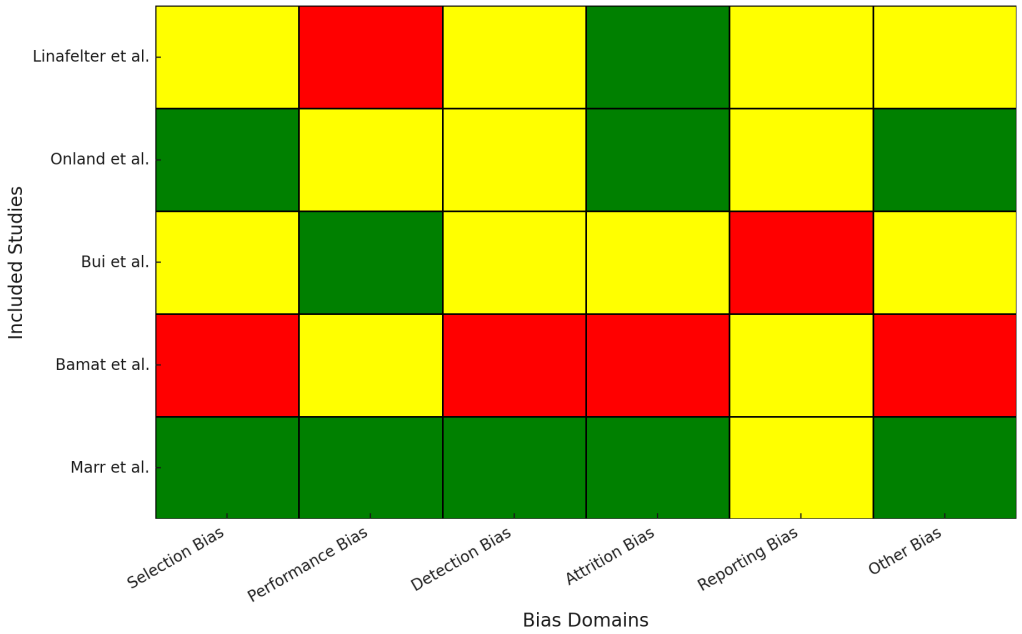

Figure 2. Risk of Bias Assessment in Systematic Review.

Of the five studies analyzed, Onland et al. was the sole RCT [26], with the other four (Linafelter et al., Bui et al., Bamat et al., and Marr et al.) being retrospective cohort studies [24,29,33,47]. Selection bias was minimal in Onland et al. and Marr et al., which was attributed to their stringent selection criteria [26,47]. However, Bamat et al. showed a high risk of selection bias owing to significant differences in treatment exposure across centers [33].

Performance bias levels varied among the studies. Marr et al. exhibited low risk owing to consistent treatment protocols [47], while Linafelter et al. demonstrated high risk due to extended prednisolone exposure without a standardized approach [24]. The remaining studies raised some concerns, mainly because of the absence of participant and clinician blinding.

The detection bias was low in studies by Onland et al. and Marr et al., who employed blinded outcome assessments [26,47]. Conversely, Bamat et al. showed a high detection bias risk due to inconsistent outcome definitions across study sites [33], potentially affecting the reliability. Other studies have raised concerns in this regard.

Most studies showed low attrition bias, although Bui et al. raised some concerns owing to missing data that

could have impacted the final analysis [29]. Reporting bias was evident in Bui et al., where secondary outcomes were incompletely reported, resulting in a high risk of bias [29]. Bamat et al. and Marr et al. raised some concerns regarding selective outcome reporting [33,47].

Regarding other potential biases, Bamat et al. showed a high risk due to possible funding bias and center-based treatment variations, potentially limiting the generalizability of the results [33]. Other studies have raised some concerns, particularly when controlling for potential confounding factors.

Marr et al. demonstrated the lowest overall bias risk, indicating relatively high methodological quality [47]. In contrast, Bamat et al. showed the highest risk of bias due to substantial treatment practice variations and reporting inconsistencies [33]. These findings underscore the importance of cautious result interpretation, as certain methodological limitations may have influenced the systematic review's overall conclusions.

4. Discussion

BPD is identified in newborns requiring extra oxygen for > 28 days or remaining oxygen dependent beyond 36 weeks of gestation. The diagnosis considers signs of respiratory distress and the clinical and imaging indicators of abnormalities. The symptoms include rapid breathing, chest retraction, and wheezing. Imaging studies may reveal fluid in the lungs, areas of condensation, overinflation, or emphysema [19,32,48]. Premature infants are at risk for BPD, with mortality rates reaching 30% in those delivered at 32 weeks. The major complications include high blood pressure in the lungs, obstructive lung disease, and neurological developmental issues that affect growth [49]. Treatment approaches include antimicrobial therapies, anti-inflammatory treatments with systemic corticosteroids, such as Dexamethasone or Hydrocortisone, and intrapulmonary corticosteroids, such as Budesonide and Fluticasone. Ventilation strategies emphasize avoiding orotracheal intubation and promoting non-invasive ventilation systems that deliver positive airway pressure through masks. Other approaches include caffeine, vitamin A, surfactants, inhaled nitric oxide, diuretics, and emerging therapies using stem cells [20,21,38].

This systematic review examined five studies on pharmacological interventions for BPD in preterm infants. Linafelter et al. found minor short-term improvements with prednisolone in severe BPD, but no lasting benefits and possible growth effects [24]. Onland et al.'s RCT showed hydrocortisone in ventilated preterm infants did not decrease BPD occurrence but lowered mortality rates while increasing hyperglycemia risk [26]. Bui et al. found Epo treatment reduced BPD incidence when started early, though hospital readmission rates remained unchanged [29]. Bamat et al.'s study showed treatment variation without improved outcomes [33]. Marr et al. found that extended dexamethasone tapering led to better ventilation outcomes and survival rates [47]. Overall, although prednisolone and hydrocortisone showed limited benefits, extended dexamethasone and early erythropoietin demonstrated more promising BPD outcomes.

A meta-analysis by Bassler et al. showed that inhaled corticosteroids led to lower prevalence rates, mortality, and neurological development decline without increasing the risk of cerebral palsy [28]. Doyle et al.'s study found similar effects for Budesonide and Dexamethasone, improving the quality of life [27].

Diuretics are another pharmacological approach for managing BPD. Bamat et al. demonstrated effectiveness of furosemide showing improved survival rates [33]. Greenberg et al. confirmed this, reporting reduced incidence and mortality rates when administered from postnatal day 7 [50]. Bui et al.'s retrospective study of Epo administration revealed a significant reduction in BPD at 36 weeks, the only recent evidence supporting its benefits [29].

Lodha et al. performed a retrospective cohort study showing that caffeine decreased BPD prevalence [51]. Jensen et al. confirmed these findings and stated that it improved survival without neurological impairment [52].

Subramaniam et al. studied early-onset continuous positive airway pressure as an alternative to conventional mechanical ventilation, showing reduced mortality and need for mechanical ventilation and surfactant [41]. Darlow et al. confirmed that ventilatory methods protect against and decrease the risk of BPD [53].

In preterm infants with BPD, prolonged endotracheal intubation can cause laryngeal and subglottic stenosis through mucosal damage and inflammation [54]. Subglottic stenosis occurs in 2–11% of intubated preterm infants, with higher rates in those with longer intubation [54]. The susceptibility and halted development of immature airways lead to smaller, flexible airways that are prone to tracheomalacia and stenosis [54,55]. Risk factors include low gestational age, prolonged intubation, traumatic tubes, and gastroesophageal reflux [54,56]. Flexible and rigid endoscopy provide direct airway visualization for diagnosis, whereas CT and MRI help evaluate multilevel disease [54,55]. Bronchoscopy differentiates between fixed stenosis and dynamic airway collapse [54,57]. Management

includes conservative monitoring for mild cases, balloon laryngoplasty for moderate stenosis, and adjunctive therapies such as proton pump inhibitors and steroids [54]. Severe stenosis requires surgical reconstruction, and outcomes are affected by pulmonary comorbidities [54].

In infants, ENT consultation is recommended for persistent stridor after extubation, difficulty reducing ventilation without a clear pulmonary cause, and signs of upper airway obstruction during feeding or sleep [54, 57]. Management requires collaboration among neonatology, ENT, pulmonology, gastroenterology, and rehabilitation specialists. Complex cases may require triple endoscopy. Prompt ENT referral aids timely diagnosis [54,57].

Tracheostomy trends remain stable in preterm infants with BPD, indicating persistent airway conditions [55, 58]. The indications for tracheostomy include severe airway obstruction, extended ventilation needs, and pulmonary hypertension [54,55,58,59]. Endoscopic balloon laryngoplasty is an effective treatment for mild-to-moderate stenosis. Open reconstruction procedures are used for severe stenosis, with success depending on comorbidities [54,58]. Tracheomalacia, which is common in BPD infants, shows >50% tracheal collapse on bronchoscopy. Management is supportive, with severe cases requiring intervention [54,55,57].

Voice disorders caused by vocal fold immobility affect BPD survivors [54]. Assessment should include multiple methods with therapeutic referrals. Oropharyngeal dysphagia is caused by neuromotor issues and intubation effects [54]. Instrumental assessments are crucial because of the risk of aspiration. BPD survivors experience breathing problems due to restrictive and obstructive causes [56, 60]. Exercise intolerance and airway issues require long-term monitoring [54,57,60]. Multidisciplinary care and long-term follow-up are essential for optimizing outcomes [54,55,61].

Bassler et al. employed bronchodilators for their effectiveness in dilating small airways with muscle-layer hypertrophy and reducing airway resistance [28]. Studies using inhaled salbutamol have shown no reduction in mortality or BPD incidence. B2-agonists have been found to increase heart rates in neonates.

This review highlights diverse approaches for managing BPD. Systemic corticosteroids, especially dexamethasone, reduce BPD severity and enhance survival but are debated due to possible neurodevelopmental impacts. Extended dexamethasone regimens may be more effective than brief regimens; however, personalized treatment is crucial.

Epo therapy has the potential to lower BPD occurrence, especially when initiated early. Its role in regulating inflammation and fostering lung development warrants further investigation. Caffeine therapy reduces the prevalence of BPD and improves survival without increasing the incidence of neurological complications.

Non-drug interventions, such as improved ventilation strategies and early continuous positive airway pressure, are linked to better respiratory outcomes. Surfactant therapy remains fundamental in decreasing neonatal mortality and air leakage. Diuretics have limited advantages in terms of survival and long-term outcomes.

Novel therapies, including stem cell-based treatments and nutritional interventions such as parenteral fish oil lipid emulsions, show promise in reducing BPD severity. Comprehensive clinical trials are necessary to confirm the effectiveness and safety of these drugs.

The risk of bias assessment revealed variability in methodological quality across the included studies, highlighting both strengths and limitations in their design and execution. The Cochrane Risk of Bias Tool and the ROBINS-I tool were used to systematically evaluate six key bias domains: selection, performance, detection, attrition, reporting, and other biases. The findings indicate that while some studies were methodologically robust, others exhibited significant concerns that could influence the interpretation of results [24,26,29,33,47].

Onland et al. and Marr et al. managed selection bias using stringent criteria and randomization [26,47]. However, Bamat et al. showed a high risk of selection bias due to treatment exposure differences across centers [33]. Performance bias varied across the studies. Marr et al. showed a low risk by following standardized protocols [47], while Linafelter et al. demonstrated a high risk due to inconsistent prednisolone exposure [24]. Detection bias was significant in Bamat et al. due to varying outcome definitions [33], while Onland et al. and Marr et al. maintained a low risk through blinded assessments [26,47]. Most studies had low attrition bias, except for Bui et al., which showed concerns due to missing data [29]. Reporting bias was noted by Bui et al. [29], while Bamat et al. and Marr et al. showed concerns due to selective reporting [33,47]. Other biases were present, with Bamat et al. showing a high risk of funding bias and protocol variations [33], while the remaining studies had concerns regarding confounding factors.

The risk of bias assessment indicated that Marr et al. had the lowest risk and was methodologically the most

robust [47], whereas Bamat et al. had the highest risk due to variability in treatment practices and reporting inconsistencies [33]. These findings highlight the importance of methodological rigor in studies that evaluate pharmacological treatments for bronchopulmonary dysplasia. Future research should prioritize randomized controlled trial designs, standardized treatment protocols, and comprehensive outcome reporting to enhance the reliability and applicability of these findings.

5. Limitations

This systematic review has several important limitations. With only five studies included and only one RCT, the evidence base is limited in terms of robustness and generalizability. Most studies were retrospective cohort studies, which are more susceptible to bias than RCTs. Significant variability in study designs, protocols, outcomes, and populations prevented meta-analysis and limited firm conclusions. Inconsistencies in treatment exposure and assessment methods introduced selection and detection bias risks, while the lack of blinding and incomplete outcome reporting increased performance and reporting bias.

Several studies had incomplete follow-up data or lacked long-term outcome assessments, particularly regarding neurodevelopmental effects beyond infancy. This limits the evaluation of treatment safety and effectiveness. The review's inclusion of only English-language publications may have led to publication bias favoring positive results. Additionally, the focus on pharmacological treatments excluded the evaluation of non-pharmacological interventions and multidisciplinary care strategies that are important for managing BPD complications.

6. Conclusions

BPD is a complex disorder with multiple factors that impact the survival and long-term health of extremely preterm infants. This review highlights the limitations of current drug treatments, including corticosteroids, erythropoietin, and diuretics, which show inconsistent effectiveness in decreasing the incidence and severity of BPD. Although dexamethasone and early erythropoietin show potential advantages, concerns regarding neurodevelopmental safety and inconsistent protocols highlight the need for personalized, evidence-based management strategies.

Non-drug approaches, such as early continuous positive airway pressure and careful ventilation techniques, are vital for reducing lung damage and invasive support needs. Otolaryngologic issues, especially subglottic stenosis, tracheomalacia, and vocal cord paralysis, are common in severe BPD cases requiring extended mechanical ventilation and should lead to early ENT assessment and multidisciplinary collaboration.

New therapies, such as stem cell treatment, nutritional adjustments, and biomarker-guided interventions, offer promise but require validation through clinical trials. Standardizing protocols, enhancing early diagnostic models, and ensuring long-term follow-up are crucial for improving respiratory and developmental outcomes in this vulnerable population.

Author Contributions

Conceptualization, M.A., S.A., and N.A.; methodology, F.A., A.A., and W.A.; validation, H.A., S.A., and K.H.; formal analysis, D.A., and H.A.-Q.; resources, A.F., and A.A.; data curation, M.A., and M.K.; writing—original draft preparation, M.A., S.A., and N.A.; writing—review and editing, F.A., A.A., W.A., H.A., S.A., and K.H.; supervision, D.A., H.A.-Q., A.F., A.A., M.A., and M.K.. All authors have read and agreed to the published version of the manuscript.

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