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Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Neonates

An Umbrella Review of Systematic Reviews and Meta-analyses

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IMPORTANCE Bronchopulmonary dysplasia (BPD) has multifactorial etiology and long-term adverse consequences. An umbrella review enables the evaluation of multiple proposed interventions for the prevention of BPD.

OBJECTIVE To summarize and assess the certainty of evidence of interventions proposed to decrease the risk of BPD from published systematic reviews.

DATA SOURCES MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and Web of Science were searched from inception until November 9, 2020.

STUDY SELECTION Meta-analyses of randomized clinical trials comparing interventions in preterm neonates that included BPD as an outcome.

DATA EXTRACTION AND SYNTHESIS Data extraction was performed in duplicate. Quality of systematic reviews was evaluated using Assessment of Multiple Systematic Reviews version 2, and certainty of evidence was assessed using Grading of Recommendation, Assessment, Development, and Evaluation.

MAIN OUTCOMES AND MEASURES (1) BPD or mortality at 36 weeks' postmenstrual age (PMA) and (2) BPD at 36 weeks' PMA.

RESULTS A total of 154 systematic reviews evaluating 251 comparisons were included, of which 110 (71.4%) were high-quality systematic reviews. High certainty of evidence from high-quality systematic reviews indicated that delivery room continuous positive airway pressure compared with intubation with or without routine surfactant (relative risk [RR], 0.80 [95% CI, 0.68-0.94]), early selective surfactant compared with delayed selective surfactant (RR, 0.83 [95% CI, 0.75-0.91]), early inhaled corticosteroids (RR, 0.86 [95% CI, 0.75-0.99]), early systemic hydrocortisone (RR, 0.90 [95% CI, 0.82-0.99]), avoiding endotracheal tube placement with delivery room continuous positive airway pressure and use of less invasive surfactant administration (RR, 0.90 [95% CI, 0.82-0.99]), and volume-targeted compared with pressure-limited ventilation (RR, 0.73 [95% CI, 0.59-0.89]) were associated with decreased risk of BPD or mortality at 36 weeks' PMA. Moderate to high certainty of evidence showed that inhaled nitric oxide, lower saturation targets (85%-89%), and vitamin A supplementation are associated with decreased risk of BPD at 36 weeks' PMA but not the competing outcome of BPD or mortality, indicating they may be associated with increased mortality.

CONCLUSIONS AND RELEVANCE A multipronged approach of delivery room continuous positive airway pressure, early selective surfactant administration with less invasive surfactant administration, early hydrocortisone prophylaxis in high-risk neonates, inhaled corticosteroids, and volume-targeted ventilation for preterm neonates requiring invasive ventilation may decrease the combined risk of BPD or mortality at 36 weeks' PMA.

Supplemental content

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With improved survival of neonates born at less than 28 weeks' gestation, the number of survivors with bronchopulmonary dysplasia (BPD) is increasing.[1] Large cohort studies have indicated that BPD is associated with poor long-term neurological outcomes.[2] The etiopathogenesis of new BPD is predominantly due to the arrest of lung development at the alveolar phase.[3] Multiple other factors such as chorioamnionitis, ventilation-induced lung injury, oxygen toxicity, inflammation secondary to infections, pulmonary edema secondary to patent ductus arteriosus, and inadequate nutrition result in additional injury to the developing lung.[4] Because BPD is a disease of multifactorial etiology, an umbrella review evaluating multiple interventions studied in systematic reviews and meta-analyses may provide clinicians with a comprehensive approach for its prevention.[5] Hence, this umbrella review was undertaken with an aim to evaluate published systematic reviews with meta-analyses of interventions that have been proposed for decreasing the risk of BPD, assess the quality of these systematic reviews using the Assessment of Multiple Systematic Reviews version 2 (AMSTAR 2) tool, and assess the certainty of evidence (COE) of the effect estimates for these interventions using Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) working group recommendations.

Key Points

Question What interventions are effective for preventing bronchopulmonary dysplasia (BPD) or mortality at 36 weeks' postmenstrual age in preterm neonates, as evaluated in systematic reviews with meta-analyses?

Findings In this umbrella review of 154 systematic reviews with 251 comparisons, a high certainty of evidence was found indicating that delivery room continuous positive airway pressure, early selective surfactant therapy, early inhaled corticosteroids, early systemic hydrocortisone, avoiding invasive ventilation, and volume-targeted ventilation were associated with decreased risk of BPD or mortality at 36 weeks' postmenstrual age.

Meaning A multipronged approach including the above interventions may decrease the risk of BPD or mortality; inhaled nitric oxide, lower saturation targets, or vitamin A supplementation are not recommended as BPD prevention strategies owing to the possibility of increased risk of mortality.

Methods

The protocol for the umbrella review was registered with PROSPERO (CRD42020216148).[6]

Inclusion Criteria

All systematic reviews with meta-analyses of randomized clinical trials (RCTs) that appraised interventions performed in preterm neonates (born at <37 weeks' gestation) and reported BPD as a primary or a secondary outcome were eligible for inclusion. Systematic reviews that pooled RCTs with nonrandomized trials were excluded. Interventions that were initiated during the antenatal or postnatal period and were compared with an alternative intervention, placebo, or no intervention were evaluated.

Outcomes

Primary outcomes were (1) BPD or mortality at 36 weeks' postmenstrual age (PMA) and (2) BPD at 36 weeks' PMA. Secondary outcomes included (1) BPD at 28 days of life and (2) BPD or mortality at 28 days of life.

Literature Search and Data Extraction

MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and Web of Science were searched from inception until November 9, 2020. The search strategy is provided in eTable 1 in the Supplement. Among systematic reviews that evaluated the same research question, the most recent high-quality systematic review with the maximum number of RCTs was chosen for inclusion. Four authors (T.A., V.V.R., T.B., and N.B.S.), in pairs of 2, independently screened the titles and abstracts of all identified systematic reviews using QCRI software (Rayyan)[7] and assessed the full-text of potentially eligible systematic reviews for inclusion. Four authors (T.A., T.B., S.H.S., and N.B.S.), in pairs of 2, independently extracted data in duplicate from included systematic reviews.

COE Assessment

Using GRADE methodology, the COE of the effect estimates reported in the included meta-analyses was assessed independently and in duplicate by 2 authors (V.V.R. and T.A.).[8] The COE was ranked as high, moderate, low, or very low. A brief description of GRADE methodology is provided in eAppendix 1 in the Supplement.

Quality Appraisal of Systematic Reviews

Using the AMSTAR 2 tool, 2 authors (T.A. and T.B.) independently assessed the quality of the included systematic reviews.[9] The overall confidence in the results of a systematic review was rated as high, moderate, low, or critically low. The AMSTAR 2 tool is described in eAppendix 2 in the Supplement.

Results

Of 16 025 titles and abstracts screened, 876 full-text articles were assessed, and 154 systematic reviews evaluating 251 different research questions were included in the final umbrella review (eFigure 1 in the Supplement).[10-163] The characteristics of the included systematic reviews are shown in eTable 2 in the Supplement.

AMSTAR 2 Assessment of Included Systematic Reviews

Using the AMSTAR 2 tool, 110 systematic reviews (71.4%) were rated as high quality. While none were evaluated as moderate, 24 (15.6%) were low quality, and 14 (9%) were very low quality. Six systematic reviews (3.9%) used individual patient data meta-analysis and therefore were not evaluated by AMSTAR 2.[17,38,69,124,130,132] The AMSTAR 2 assessment of included systematic reviews is provided in eTable 3 in the Supplement.

GRADE Assessment of Interventions

Primary Outcome: BPD or Mortality at 36 Weeks' PMA

Twelve comparisons had high COE, indicating significant benefit of an intervention in preventing BPD or mortality at 36 weeks' PMA. Of 23 comparisons that had moderate COE, 8 indicated benefit of an intervention and 15 showed no difference between interventions. Of 20 comparisons with a low or very low COE for the effect

estimates, 2 showed benefit of one intervention over the other. The AMSTAR 2 quality assessments and the COE for effect estimates of interventions for the primary outcome of BPD or mortality at 36 weeks' PMA are given in the **Table**.

Primary Outcome: BPD at 36 Weeks' PMA

Eight comparisons had a high COE, indicating statistically significant differences between the interventions for preventing BPD at 36 weeks' PMA. Of 60 comparisons that had a moderate COE, 14 indicated a benefit of an intervention and 46 indicated no difference. None of the 89 comparisons with a low or very low COE for the effect estimates showed statistically significant differences between the interventions. The AMSTAR 2 quality assessments and the COE for the effect estimates of interventions for the prevention of BPD at 36 weeks' PMA are given in eTable 4 in the Supplement. The GRADE and AMSTAR 2 results for the secondary outcomes are given in eTables 5-8 in the Supplement.

Primary Outcome: BPD or Mortality at 36 Weeks' PMA

Delivery Room CPAP

High COE indicated that initiation of continuous positive airway pressure (CPAP) in the delivery room compared with routine intubation with or without surfactant administration was associated with a lower risk of BPD or mortality at 36 weeks' PMA in preterm neonates of any gestational age (relative risk [RR], 0.80 [95% CI, 0.68-0.94]; AMSTAR 2 rating, high), extreme preterm neonates (RR, 0.78 [95% CI, 0.66-0.93]), and when initiated at CPAP of at least 5 cm H_2O (RR, 0.89 [95% CI, 0.81-0.98]).[148]

Surfactant Therapy

High COE showed that prophylactic surfactant was associated with an increased risk of BPD or mortality when compared with stabilization receiving CPAP with selective surfactant administration (RR, 1.12 [95% CI, 1.02-1.23]; AMSTAR 2 rating, high).[122] Similarly, high COE indicated that early (within 3 hours) selective surfactant administration compared with delayed surfactant therapy was associated with a lower risk of BPD or mortality (RR, 0.83 [95% CI, 0.75-0.91]; AMSTAR 2 rating, high).[18]

Moderate COE suggested that surfactant therapy using less invasive surfactant administration (LISA) was associated with lower risk of BPD or mortality at 36 weeks when compared with the intubate-surfactant-extubate (INSURE) technique (RR, 0.75 [95% CI, 0.59-0.95]; AMSTAR 2 rating, low).[14] For the type of surfactant, moderate COE suggested that porcine surfactant used at a dose of more than 100 mg/kg, compared with bovine lung surfactant, was associated with decreased risk of BPD or mortality (RR of bovine vs porcine >100 mg/kg, 1.39 [95% CI, 1.08-1.79]; AMSTAR 2 rating, high).[140] The effect estimates were not significant for the other comparisons on types of surfactant.

Inhaled Corticosteroids Initiated in the First 2 Weeks of Life

High COE suggested that inhaled corticosteroids administered in the first 2 weeks of life were associated with decreased risk of BPD or mortality at 36 weeks' PMA (RR, 0.86 [95% CI, 0.75-0.99]; AMSTAR 2 rating, high).[136] Different inhaled corticosteroids, including budesonide, beclomethasone, and fluticasone, were studied by the included RCTs of this systematic review. Moderate COE showed inhaled or intratracheal instillation of corticosteroids (RR, 0.80 [95% CI, 0.68-0.94]; AMSTAR 2 rating, high) was associated with decreased risk of BPD or mortality.[44] Subgroup analyses showed intratracheal instillation of corticosteroids using surfactant as a vehicle (RR, 0.64 [95% CI, 0.53-0.77]) and inhaled/intratracheal budesonide (RR, 0.79 [95% CI, 0.65-0.96]) was associated with decreased risk; however, the effect estimates were not significant for either beclomethasone or fluticasone.[44]

Systemic Corticosteroids

Early Systemic Steroids (Started ≤7 Days) | Moderate COE showed that early systemic steroids (dexamethasone or hydrocortisone) were associated with decreased risk of BPD or mortality (RR, 0.88 [95% CI, 0.83-0.93]; AMSTAR 2 rating, high).[46]

High COE showed that early systemic dexamethasone was associated with decreased risk of BPD or mortality at 36 weeks' PMA (RR, 0.87 [95% CI, 0.80-0.94]; AMSTAR 2 rating, high).[46] The dexamethasone regimens used, including the day of initiation, cumulative dose, and the duration of therapy, varied between the included RCTs. The comparisons on different dexamethasone dosage regimens did not show significant differences.

High COE suggested that hydrocortisone initiated within the first week for varying reasons, such as prophylaxis for adrenal insufficiency, catecholamine resistant shock, and high respiratory support, was associated with decreased risk of BPD or mortality in infants born at less than 32 weeks (RR, 0.90 [95% CI, 0.82-0.99]; AMSTAR 2 rating, high)[46] and in neonates with extremely low gestational age exposed to chorioamnionitis (RR, 0.52 [95% CI, 0.34-0.79]; AMSTAR 2 rating, low).[163] Furthermore, high COE from an individual-patient meta-analysis indicated that early low-dose hydrocortisone as a prophylactic intervention to prevent adrenal insufficiency was associated with decreased risk of BPD or mortality at 36 weeks (RR, 0.69 [95% CI, 0.52-0.91]; unable to assign AMSTAR 2 score).[132]

Late Systemic Steroids (Started >7 Days) | Moderate COE showed that late systemic steroids (dexamethasone or hydrocortisone) was associated with less risk of BPD or mortality (RR, 0.77 [95% CI, 0.69-0.85]; AMSTAR 2 rating, high).[47] Of the RCTs synthesized in this meta-analysis, only 1 RCT evaluated systemic hydrocortisone.

Ventilation Strategies

Avoiding Endotracheal Intubation for Surfactant Administration | High COE showed that avoiding intubation for prophylactic surfactant administration by stabilizing preterm newborns less than 30 weeks' gestation receiving CPAP in the delivery room and using LISA instead of INSURE for selective surfactant administration was associated with decreased risk of BPD or mortality (RR, 0.90 [95% CI, 0.82-0.99]; AMSTAR 2 rating, low).[52]

Volume-Targeted Ventilation vs Pressure-Limited Ventilation | When compared with pressure-limited ventilation, volume-targeted ventilation was associated with decreased risk of BPD or mortality at 36 weeks' PMA with a high COE (RR, 0.73 [95% CI, 0.59-0.89]; AMSTAR 2 rating, high).[78] This effect estimate was a synthesis of 2 subgroups analyzed by the meta-analysis: (1) strict studies in which both the groups received invasive ventilation using similar modes

Table. Certainty of Evidence for Various Interventions Reported by Systematic Reviews on the Outcome: BPD or Mortality at 36 Weeks' Postmenstrual Age

Source	Intervention	Comparison	No. of RCTs	No. with BPD or death/total No.	Estimate (95% CI)	GRADE self-assessment	Reasons for downgrading	AMSTAR 2 rating
Noninvasive respiratory support								
Subramaniam, et al,[148] 2016	Delivery room CPAP	Invasive ventilation	3	1042/2358	OR, 0.8 (0.68-0.94)	High	NA	High
	Delivery room CPAP, <28 wk	Invasive ventilation	3	991/2126	OR, 0.78 (0.66-0.93)	High	NA	High
	Delivery room CPAP, ≥28 wk	Invasive ventilation	1	51/232	OR, 1.04 (0.56-1.94)	Low	Very serious imprecision	High
	Delivery room CPAP at 5 cm H_2O	Invasive ventilation	2	820/1748	0.89 (0.81-0.98)	High	NA	High
	Delivery room CPAP at 8 cm H_2O	Invasive ventilation	1	222/610	0.87 (0.7-1.07)	Moderate	Serious imprecision	High
	Delivery room CPAP	Supportive care (oxygen by cannula/hood)	1	42/256	0.69 (0.4-1.19)	Moderate	Serious imprecision	High
Surfactant therapy								
Isayama et al,[73] 2015	INSURE at birth (early INSURE) extubated within 1 h to CPAP	CPAP alone at birth	6	399/1250	0.88 (0.76-1.02)	Moderate	Serious imprecision	High
Bahadue et al,[18] 2012	Early selective surfactant (within 3 h of life)	Delayed selective surfactant (after development of established RDS)	3	990/3050	0.83 (0.75-0.91)	High	NA	High
Rojas-Reyes et al,[122] 2012	Prophylactic surfactant	Selective surfactant (with or without routine CPAP)	3	N = 1866	1.12 (1.02-1.23)	High	NA	High
Aldana-Aguirre et al,[14] 2017	Surfactant administration via a thin endotracheal catheter (LISA)	Endotracheal intubation for surfactant administration (INSURE)	6	211/895	0.75 (0.59-0.95)	Moderate	Serious imprecision	Low
Singh et al,[140] 2015	Bovine lung lavage surfactant	Modified bovine minced lung surfactant	5	825/2009	0.95 (0.86-1.06)	Moderate	Serious imprecision	High
	Bovine minced lung surfactant	Porcine minced lung surfactant	3	187/448	1.3 (1.04-1.64)	Moderate	Serious imprecision	High
	Modified bovine minced lung surfactant	Porcine minced lung (≤100 mg/kg) surfactant	1	82/175	1.04 (0.76-1.43)	Moderate	Serious imprecision	High
	Modified bovine minced lung surfactant	Porcine minced lung (>100 mg/kg) surfactant	3	148/363	1.39 (1.08-1.79)	Moderate	Serious imprecision	High
Ardell et al,[15] 2015	Animal-derived surfactant	Protein-free synthetic surfactant	5	1557/3332	0.97 (0.9-1.04)	Moderate	Serious imprecision	High
Pfister et al,[116] 2009	Protein-containing synthetic surfactant	Protein-free synthetic surfactant	1	N = 1036	0.88 (0.77-1.01)	Moderate	Serious imprecision	High
Postnatal steroids: pulmonary application								
Shah et al,[136] 2017	Inhaled steroids started within 2 wk of life	No steroids	6	483/1285	0.86 (0.75-0.99)	High	NA	High

(continued)

Table. Certainty of Evidence for Various Interventions Reported by Systematic Reviews on the Outcome: BPD or Mortality at 36 Weeks' Postmenstrual Age (continued)

Source	Intervention	Comparison	No. of RCTs	No. with BPD or death/total No.	Estimate (95% CI)	GRADE self-assessment	Reasons for downgrading	AMSTAR 2 rating
Delara et al,[44] 2019	Inhaled/intratracheal instillation of steroids in infants with RDS	No steroids	8	741/1716	0.8 (0.68-0.94)	Moderate	Serious indirectness	High
	Intratracheal instillation of steroids using vehicle in infants with RDS	No steroids	2	210/381	0.64 (0.53-0.77)	Moderate	Serious ROB	High
	Intratracheal instillation of steroids in infants with RDS	No steroids	1	66/86	1.01 (0.8-1.28)	Low	Serious ROB, serious imprecision	High
	Inhaled/intratracheal budesonide in infants with RDS	No steroids	5	664/1350	0.79 (0.65-0.95)	Moderate	Serious inconsistency	High
	Inhaled/intratracheal beclomethasone in infants with RDS	No steroids	2	59/313	1.01 (0.64-1.6)	Low	Serious ROB, serious imprecision	High
	Inhaled/intratracheal fluticasone in infants with RDS	No steroids	1	18/53	0.48 (0.21-1.09)	Very low	Serious ROB, very serious imprecision	High
Onland et al,[110] 2017	Late (≥7 d) inhalational steroids	No steroids	1	21/30	1.1 (0.74-1.63)	Very low	Serious ROB, very serious imprecision	High
Shah et al,[135] 2017	Inhaled steroids started within 7 d of life	Systemic steroids started within 7 d of life	1	153/278	1.09 (0.88-1.35)	Low	Serious ROB, serious imprecision	High
Postnatal steroids: systemic application								
Doyle et al,[46] 2017	Early (≤7 d) systemic steroids (dexamethasone or hydrocortisone)	No steroids	25	1973/3960	0.88 (0.83-0.93)	Moderate	Publication bias	High
	Early (≤7 d) systemic steroids (only dexamethasone)	No steroids	16	1214/2581	0.87 (0.8-0.94)	High	NA	High
	Early (≤7 d) systemic steroids (only hydrocortisone)	No steroids	9	759/1379	0.9 (0.82-0.99)	High	NA	High
Doyle et al,[47] 2017	Late (>7 d) systemic steroids (dexamethasone or hydrocortisone)	No steroids	11	398/580	0.77 (0.7-0.86)	Moderate	Serious inconsistency	High
Zhou et al,[163] 2021	Systemic hydrocortisone in first week for neonates exposed to chorioamnionitis	No steroids	3	208/427	0.52 (0.34-0.79)	High	NA	Low
	Systemic hydrocortisone in first week for neonates not exposed to chorioamnionitis	No steroids	3	192/373	0.88 (0.59-1.33)	Moderate	Serious imprecision	Low
Shaffer et al,[132] 2019	Early hydrocortisone prophylaxis (initiated at <7 d)	No steroids	4	483/979	OR, 0.69 (0.52-0.9)	High	NA	NA
Onland et al,[109] 2017	Lower cumulative dose of dexamethasone	Higher cumulative dose dexamethasone	6	77/209	1.09 (0.82-1.44)	Low	Serious ROB, serious imprecision	High
	Later initiation of dexamethasone	Earlier initiation of dexamethasone	3	193/391	1.06 (0.87-1.29)	Low	Serious ROB, serious imprecision	High
	Pulse dexamethasone	Continuous dexamethasone	2	91/197	1.38 (1.02-1.88)	Low	Serious ROB, serious imprecision	High
	Individual tailored dexamethasone regimen	Continuous tapered dexamethasone regimen	2	56/109	1.17 (0.83-1.66)	Low	Serious ROB, serious imprecision	High
Invasive ventilation								
Fischer and Bührer,[52] 2013	Avoiding invasive ventilation (CPAP with or without surfactant by LISA)	Invasive ventilation with or without surfactant by INSURE	7	1351/3289	OR, 0.83 (0.71-0.96)	High	NA	Low
Klingenberg et al,[78] 2017	Volume-targeted ventilation	Pressure-limited ventilation	8	230/584	0.73 (0.59-0.89)	High	NA	High

(continued)

Table. Certainty of Evidence for Various Interventions Reported by Systematic Reviews on the Outcome: BPD or Mortality at 36 Weeks' Postmenstrual Age (continued)

Source	Intervention	Comparison	No. of RCTs	No. with BPD or death/total No.	Estimate (95% CI)	GRADE self-assessment	Reasons for downgrading	AMSTAR 2 rating
Greenough et al,[58] 2016	SIMV or SIMV with PS	HFOV	1	58/356	2.38 (1.41-4.03)	Low	Serious imprecision and serious ROB	High
Cools et al,[34] 2015	Elective HFOV	Conventional ventilation	17	1434/3329	0.9 (0.84-0.97)	Low	Serious ROB	High
Barrington et al,[20] 2017	iNO started within 3 d based on oxygenation	No iNO	8	695/958	0.94 (0.87-1.01)	Moderate	Serious imprecision	High
	iNO started after 3 d based on BPD risk	No iNO	3	689/1075	0.92 (0.85-1.01)	Moderate	Serious imprecision	High
	iNO started routinely	No iNO	4	1024/1924	0.94 (0.87-1.02)	Moderate	Serious imprecision	High
Davies and Woodgate,[41] 2002	Continuous tracheal gas insufflation for dead space washout during conventional ventilation	Conventional ventilation alone	1	17/34	0.53 (0.24-1.17)	Very Low	Serious ROB, very serious imprecision	High
Caffeine								
Vliegenthart et al,[154] 2018	High dose (loading + maintenance) caffeine in <32 wk	Standard-dose caffeine in <32 wk	3	191/430	0.89 (0.65-1.21)	Low	Serious imprecision, Serious inconsistency	Critically low
	High dose (loading + maintenance) caffeine in <32 wk, started >14 d	Standard-dose caffeine in <32 wk, started >14 d	2	145/356	0.76 (0.59-0.98)	Low	Serious imprecision, Serious inconsistency	Critically low
Other								
Darlow et al,[40] 2016	Vitamin A supplementation, enteral or parenteral	Placebo/no treatment	4	651/1089	0.92 (0.84-1.01)	Moderate	Serious imprecision	High
Soghier and Brion,[141] 2006	IV N-acetyl cysteine with cysteine containing TPN	Cysteine containing TPN	1	194/391	1.04 (0.85-1.27)	Moderate	Serious imprecision	High
Howlett et al,[67] 2019	Inositol supplementation for infants at risk or have RDS; repeat doses any amount, any duration of treatment	Placebo	2	357/666	1 (0.87-1.14)	Moderate	Serious imprecision	High
	Inositol supplementation for infants at risk or have RDS; IV initially followed by enteral (repeat dose 80 mg/kg/d) in <30 wk	Placebo	2	343/616	1.01 (0.87-1.16)	Moderate	Serious imprecision	High
Schulzke et al,[131] 2014	Pentoxifylline, nebulized	No pentoxifylline	1	57/100	0.73 (0.51-1.03)	Low	Very serious imprecision	High
Shah and Ohlsson,[133] 2001	α-1 Proteinase inhibitor from first week to prevent BPD	No treatment	2	66/195	0.95 (0.61-1.49)	Very Low	Serious ROB, serious inconsistency, serious imprecision	High
Mabanta et al,[88] 2003	Prophylactic erythromycin in intubated neonates	Placebo	1	36/75	1.06 (0.66-1.69)	Low	Very serious imprecision	High
	Erythromycin in urea plasma-positive intubated babies	Placebo	1	19/28	0.9 (0.54-1.5)	Low	Very serious imprecision	High
Meyer et al,[93] 2018	Heated humidified gas during resuscitation and transport	Cold air during resuscitation and transport	2	205/476	0.91 (0.74-1.12)	Low	Very serious imprecision	Critically low

Abbreviations: AMSTAR 2, Assessment of Multiple Systematic Reviews version 2; BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; GRADE, Grading of Recommendation, Assessment, Development, and Evaluation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; INSURE, intubate-surfactant-extubate; IV, intravenous; LISA, less invasive surfactant administration; NA, not applicable; OR, odds ratio; PS, pressure support; RCTs, randomized clinical trials; ROB, risk of bias; RDS, respiratory distress syndrome; SIMV, synchronized intermittent mandatory ventilation; TPN, total parenteral nutrition.

and ventilators, with volume-targeted ventilation being the only difference, and (2) hybrid studies where different ventilators and modes were used for the 2 groups with volume-targeted ventilation being one of the parameters that was different.

Elective High-Frequency Oscillatory Ventilation vs Conventional Mechanical Ventilation | Low COE suggested that elective high-frequency oscillatory ventilation was associated with decreased risk of BPD or mortality at 36 weeks' PMA when compared with conventional mechanical ventilation (RR, 0.90 [95% CI, 0.84-0.97]; AMSTAR 2 rating, high).[34] Although the event rate and the sample size were adequate, COE of the effect estimate was downgraded by 1 level each for risk of bias and inconsistency.

High-Dose Caffeine

High-dose caffeine (40-80 mg/kg loading dose + 20 mg/kg maintenance dose) compared with standard dose (20 mg/kg loading dose + 5-10 mg/kg maintenance dose) in neonates less than 32 weeks' gestation and older than 14 days of life was associated with decreased risk of BPD or mortality at 36 weeks' PMA (RR, 0.76 [95% CI, 0.59-0.98]; AMSTAR 2 rating, high).[154] The COE was low, downgraded by 1 level each for imprecision and indirectness related to the classification of intervention.

Other Interventions

The effect estimates for BPD or mortality at 36 weeks' gestation were not significant for other interventions. **Figure 1** depicts the various comparisons where interventions had a significant impact on decreasing BPD or mortality at 36 weeks' PMA, organized according to the COE of the effect estimates.

Primary Outcome: BPD at 36 Weeks' PMA

The interventions that had a statistically significant impact on BPD at 36 weeks' PMA are depicted in **Figure 2**. Most of the interventions that were effective in decreasing the risk of the combined outcome of BPD or mortality, such as practices related to CPAP, surfactant administration, inhaled or systemic corticosteroids, ventilation strategies, and caffeine therapy had moderate to high COE in decreasing the risk of BPD at 36 weeks' PMA as well.

The interventions that were associated with significant decrease in BPD at 36 weeks' PMA (Figure 2) with moderate to high COE but not the combined outcome of BPD or mortality with moderate COE (eFigure 2 in the Supplement) included vitamin A supplementation, targeting lower oxygen saturation targets (85%-89%), and inhaled nitric oxide (iNO) use (routine use or within 3 days for hypoxic respiratory failure or after 3 days for decreasing the risk of BPD).[16,17,40,160]

Number Needed to Treat for Benefit or Harm

We calculated the number needed to treat for benefit (NNTB) and number needed to treat for harm (NNTH) (with 95% CI) post hoc for interventions that showed significant reduction in BPD or mortality and BPD at 36 weeks' PMA. These are depicted in Figure 1 and Figure 2.

Interventions That Did Not Show a Significant Effect Estimate

Those comparisons where the interventions did not show a significant effect estimate in decreasing the risk of BPD or mortality at 36 weeks' PMA and BPD at 36 weeks' PMA with moderate COE are shown in eFigures 2 and 3 in the Supplement. Moderate COE showed some of the commonly used interventions such as INSURE at birth followed by extubation to CPAP within 1 hour vs CPAP alone, noninvasive ventilation vs CPAP for primary respiratory support, noninvasive ventilation or heated humidified high-flow nasal cannula for postextubation respiratory support when compared with CPAP, opioids for neonates receiving invasive ventilation, prophylactic methylxanthines, low (≤30%) vs high (≥60%) fraction of inspired oxygen (FIO_2) to initiate resuscitation, exclusive human milk feeding, prophylactic intravenous indomethacin, cord blood transfusion strategies, and restrictive transfusion thresholds were not associated with reduced risk of BPD at 36 weeks' PMA.

BPD and BPD or Mortality at 28 Days

The effect estimates and the COE for the various comparisons that showed a significant impact on the secondary outcomes of BPD at 28 days and BPD or mortality at 28 days are depicted in eFigures 4 and 5 in the Supplement.

Discussion

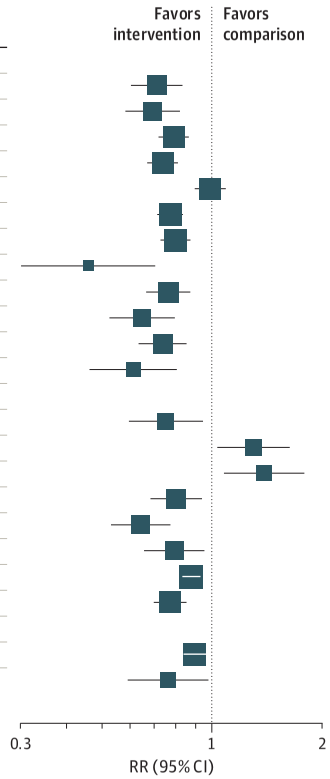
This umbrella review evaluated published systematic reviews with meta-analyses that studied the effectiveness of multiple interventions for decreasing the risk of BPD or mortality at 36 weeks' PMA and BPD at 36 weeks' PMA. To our knowledge, this is the only umbrella review on the prevention of BPD.

High COE indicated that delivery room CPAP, early selective surfactant therapy, inhaled corticosteroids initiated within 2 weeks, early systemic dexamethasone or hydrocortisone, avoiding endotracheal intubation by using delivery room CPAP and administering surfactant with LISA, and volume-targeted ventilation were associated with decreased risk of BPD or mortality at 36 weeks' PMA. However, early dexamethasone has been shown to be associated with long-term adverse neurological outcomes.[164] Hence, there is international consensus against its use in neonates during the first week of life.[165-167] Similarly, among the inhaled steroids, budesonide has been associated with a possible increased risk of mortality in a 2021 network meta-analysis.[168] The Canadian Pediatric Society 2020 guidelines also gave a moderate strength of recommendation against the use of early inhaled budesonide.[167] The network meta-analysis indicated a moderate COE suggesting that early inhaled fluticasone might be a safer alternative option. Future trials should evaluate inhaled fluticasone as a BPD prevention strategy.

Moderate COE suggested that surfactant administration by LISA, use of porcine surfactant, intratracheal administration of corticosteroids, and late systemic steroids (dexamethasone or hydrocortisone) are beneficial in decreasing the risk of BPD or mortality at 36 weeks' PMA. Of these interventions, late initiation of hydrocortisone had no benefit in a large multicentric RCT.[169] Although late dexamethasone (beyond the first week of life) has been associated with decreased risk of BPD or mortality, the appropriate day of initiation, cumulative dosage, and the treatment duration could not be assessed with good certainty in this umbrella review. International advisory bodies suggest a cumulative dose of 1 to 2 mg/kg of dexamethasone administered over 7 to 10 days; however, further RCTs

Figure 1. Primary Outcome of Composite of Bronchopulmonary Dysplasia (BPD) or Mortality at 36 Weeks' Postmenstrual Age: Comparisons With Significant Effect Estimates Collated According to the Certainty of Evidence

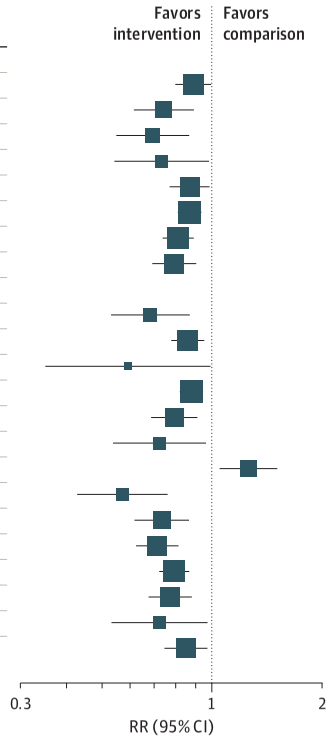
Study	Intervention	Comparison	NNTB/NNTH (95% CI)	RR (95% CI)
High				
Subramaniam et al,[148] 2016	Delivery room CPAP	Invasive ventilation ± surfactant	18 (11-46)	0.80 (0.68-0.94)
Subramaniam et al,[148] 2016	Delivery room CPAP, <28 wk	Invasive ventilation ± surfactant	17 (11-41)	0.78 (0.66-0.93)
Subramaniam et al,[148] 2016	Delivery room CPAP, started at 5 cm H_2O	Invasive ventilation ± surfactant	18 (10-58)	0.89 (0.81-0.98)
Bahadue et al,[18] 2012	Early selective surfactant (<3 h)	Delayed surfactant	17 (12-28)	0.83 (0.75-0.91)
Rojas-Reyes et al,[122] 2012	Prophylactic surfactant	CPAP followed by selective surfactant	No data	1.12 (1.02-1.23)
Doyle et al,[46] 2017	Early (≤7 d) systemic dexamethasone	No steroids	14 (10-27)	0.87 (0.80-0.94)
Doyle et al,[46] 2017	Early (≤7 d) systemic hydrocortisone	No steroids	17 (10-88)	0.90 (0.82-0.99)
Zhou et al,[163] 2021	Systemic hydrocortisone, first week, in chorioamnionitis	No steroids	12 (6-118)	0.52 (0.34-0.79)
Shah et al,[136] 2017	Inhaled steroids started within 2 wk	No steroids	19 (11-91)	0.86 (0.75-0.99)
Klingenberg et al,[78] 2017	Volume-targeted ventilation	Pressure-limited ventilation	8 (5-15)	0.73 (0.59-0.90)
Fischer and Bührer,[52] 2013	Avoiding invasive ventilation (DR CPAP ± LISA)	Invasive ventilation ± INSURE	35 (18-500)	0.83 (0.71-0.97)
Shaffer et al,[132] 2019	Early low-dose hydrocortisone prophylaxis	Placebo	13 (7-43)	0.69 (0.52-0.91)
Moderate				
Aldana-Aguirre et al,[14] 2017	Surfactant by LISA	Surfactant by INSURE	15 (9-34)	0.75 (0.59-0.95)
Singh et al,[140] 2015	Bovine minced lung surfactant	Porcine minced lung surfactant	11 (6-54)	1.30 (1.04-1.63)
Singh et al,[140] 2015	Modified bovine minced lung surfactant	Porcine minced (>100 mg/kg) surfactant	8 (5-24)	1.39 (1.08-1.79)
Delara et al,[44] 2019	Inhaled/intratracheal steroids within 2 wk	No steroids	11 (8-18)	0.80 (0.68-0.94)
Delara et al,[44] 2019	Intratracheal steroids using vehicle within 2 wk	No steroids	4 (3-6)	0.64 (0.53-0.77)
Delara et al,[44] 2019	Inhaled/intratracheal budesonide within 2 wk	No steroids	9 (6-15)	0.79 (0.65-0.96)
Doyle et al,[46] 2017	Early (≤7 d) systemic steroids, any	No steroids	15 (11-25)	0.88 (0.83-0.93)
Doyle et al,[47] 2017	Late (>7 d) systemic steroids, any	No steroids	5 (4-9)	0.77 (0.69-0.85)
Low				
Cools et al,[34] 2015	Elective HFOV	Conventional ventilation	23 (14-60)	0.90 (0.84-0.97)
Vliegenthart et al,[154] 2018	High-dose (loading + maintenance) caffeine (<32 wk, >14 d)	Standard-dose caffeine	9 (5-28)	0.76 (0.59-0.98)



CPAP indicates continuous positive airway pressure; DR, delivery room; HFOV, high-frequency oscillatory ventilation; INSURE, intubate-surfactant-extubate; LISA, less invasive surfactant administration; NNTB, number needed to treat for benefit; NNTH, number needed to treat for harm; RR, relative risk.

Figure 2. Primary Outcome of Bronchopulmonary Dysplasia (BPD) at 36 Weeks' PMA: Comparisons With Significant Effect Estimates Collated According to the Certainty of Evidence

Study	Intervention	Comparison	NNTB/NNTH (95% CI)	RR (95% CI)
High				
Subramaniam et al,[148] 2016	Delivery room CPAP	Invasive ventilation ± surfactant	24 (13-99)	0.89 (0.80-1.00)
Delara et al,[44] 2019	Inhaled steroids	No steroids	13 (9-24)	0.74 (0.61-0.89)
Bahadue et al,[18] 2012	Early selective surfactant (<3 h)	Delayed surfactant	29 (21-49)	0.69 (0.55-0.87)
Shaffer et al,[132] 2019	Early low-dose hydrocortisone prophylaxis	Placebo	No data	0.73 (0.54-0.98)
Darlow et al,[40] 2016	Vitamin A	No treatment	15 (8-83)	0.87 (0.77-0.99)
Askie et al,[16] 2017	Lower SpO_2 target (85%-89%)	Higher SpO_2 target (91%-95%)	17 (12-28)	0.87 (0.81-0.94)
Askie et al,[17] 2018	Lower SpO_2 target, <28 wk (85%-89%)	Higher SpO_2 target (91%-95%)	19 (13-30)	0.81 (0.73-0.89)
Askie et al,[17] 2018	Lower SpO_2 target, <28 wk, revised software (85%-89%)	Higher SpO_2 target (91%-95%)	14 (9-31)	0.79 (0.69-0.91)
Moderate				
Klingenberg et al,[78] 2017	Volume-targeted ventilation	Pressure-limited ventilation	8 (6-15)	0.68 (0.53-0.87)
Cools et al,[34] 2015	Elective HFOV	Conventional ventilation	22 (14-53)	0.86 (0.78-0.95)
Bhuta and Henderson-Smart,[24] 2000	Elective HFJV	Conventional ventilation	7 (4-22)	0.59 (0.35-0.99)
Yang et al,[160] 2016	Inhaled nitric oxide, any use	No inhaled nitric oxide	25 (15-72)	0.88 (0.82-0.95)
Chen et al,[30] 2018	High-maintenance caffeine (10-20 mg/kg)	Low-dose caffeine (5-10 mg/kg)	11 (7-20)	0.79 (0.68-0.91)
Vliegenthart et al,[154] 2018	High-dose (loading + maintenance) caffeine (<32 wk, >14 d)	Standard-dose caffeine	9 (5-25)	0.72 (0.54-0.96)
Lloyd et al,[83] 2003	Higher SpO_2 target (96%-99%) in prethreshold ROP	Normal SpO_2 target (89%-94%)	10 (6-32)	1.26 (1.05-1.51)
Delara et al,[44] 2019	Intratracheal steroids using vehicle within 2 wk	No steroids	5 (4-8)	0.57 (0.43-0.76)
Delara et al,[44] 2019	Inhaled/intratracheal steroids within 2 wk	No steroids	10 (8-15)	0.73 (0.61-0.87)
Doyle et al,[46] 2017	Early (≤7 d) systemic dexamethasone	No steroids	12 (9-16)	0.71 (0.62-0.81)
Doyle et al,[46] 2017	Early (≤7 d) systemic steroids, any	No steroids	15 (11-21)	0.79 (0.72-0.87)
Doyle et al,[47] 2017	Late (>7 d) systemic steroids, any	No steroids	6 (4-11)	0.77 (0.67-0.88)
Aldana-Aguirre et al,[14] 2017	Surfactant by LISA	Surfactant by INSURE	20 (12-73)	0.72 (0.53-0.97)
Askie et al,[17] 2018	Lower SpO_2 target, <28 wk, original software (85%-89%)	Higher SpO_2 target (91%-95%)	28 (17-92)	0.85 (0.74-0.97)



CPAP indicates continuous positive airway pressure; HFOV, high-frequency oscillatory ventilation; HFJV, high-frequency jet ventilation; LISA, less invasive surfactant administration; NNTB, number needed to treat for benefit; NNTH, number needed to treat for harm; ROP, retinopathy of prematurity; RR, relative risk; SpO_2, oxygen saturation as measured by pulse oximetry.

are warranted.[166,167] There was low COE to suggest that high-dose caffeine might decrease the risk of BPD or mortality at 36 weeks' PMA.[154] Further trials are required to improve the COE for this intervention.

We calculated NNTB/NNTH post hoc for the interventions that showed significant reduction in BPD or mortality and BPD at 36 weeks' PMA. Intratracheal steroids (using vehicle) within 2 weeks and late systemic steroids initiated beyond 7 days of life had the lowest NNTB with narrow 95% CIs. However, the NNTB/NNTH values need to be interpreted in the light of various factors such as adverse effects, cost of the intervention, and others.

iNO, lower oxygen saturation targets (85%-89%), and vitamin A supplementation were associated with decreased risk of BPD but not the competing outcome of BPD or mortality at 36 weeks' PMA.[16,17,40,160] This suggests that they might be associated with an increased risk of mortality. Of these, there are existing recommendations against the use of iNO and lower saturation targets by various advisory bodies.[170-172] Although the American Academy of Pediatrics gave a strong recommendation based on level A evidence against the use of iNO in preterm neonates younger than 34 weeks' gestation, some authors make a valid argument that a subset of preterm neonates who are born at less than 34 weeks and have pulmonary hypertension, a history of prolonged rupture of membranes, and received antenatal corticosteroids might benefit from iNO use.[172] However, the evidence for the beneficial effect of iNO are based on nonrandomized studies only and these subgroups of preterm neonates have not been evaluated separately in RCTs. Neonatal vitamin A supplementation has also been a subject of controversy.[173] The World Health Organization sponsored multicentric RCTs enrolling 99 938 term newborns from low- and middle-income countries in whom high-dose vitamin A (50 000 IU within 72 hours of life) was administered showed mixed results.[174-176] While RCTs from India showed a survival benefit for this strategy,[174] those from Tanzania and Ghana indicated a possibility of increased risk of mortality.[175,176] The dosage of vitamin A used in preterm neonates was different from that used in these studies. However, because the COE indicating the possibility of increased risk of mortality was moderate to high for this intervention, its use for BPD prevention cannot be recommended at this time.

Moderate COE suggested little difference between some interventions in decreasing the risk of BPD or mortality at 36 weeks' PMA. Of these, CPAP with early INSURE was not different from CPAP alone followed by delayed rescue surfactant. It should be noted that the RCTs included in this meta-analysis used varying threshold levels for deciding on early INSURE as well as for the comparator delayed rescue surfactant in the case of CPAP failure.[73] The appropriate threshold FIO_2 or CPAP level for early rescue surfactant administration among preterm newborns with RDS who are stabilized while receiving CPAP is yet to be determined with reasonable certainty. Reflecting the paucity of evidence, threshold recommendations of international advisory bodies also vary.[166,177]

The other important aspect of respiratory care in preterm newborns with RDS is the type of noninvasive respiratory support. We found moderate COE to suggest that noninvasive positive pressure ventilation was not significantly different from CPAP for BPD or mortality at 36 weeks' PMA. However, a recent network meta-analysis showed that noninvasive positive pressure ventilation as primary respiratory support was associated with lower risk of the combined outcome of BPD or mortality when compared with CPAP, with the COE being low.[178] This discrepancy between the findings of the present umbrella review and the network meta-analysis might be owing to the fact that this umbrella review derived its effect estimates for the primary outcome measures from traditional pairwise meta-analyses. In addition, the network meta-analysis had included some recent trials evaluating noninvasive positive pressure ventilation vs CPAP as primary respiratory support that had not been included in the meta-analysis included in this review.

Although inadequate nutrition is considered one of the causative factors in the etiopathogenesis of BPD, none of the interventions studied, such as higher amino acids or early lipids in total parenteral nutrition, inositol, N-acetyl cysteine or iodine supplementation, or use of exclusive human milk feeds were found to be effective. Adequately powered RCTs on nutritional interventions to assess the outcome of BPD or mortality are required. Similarly, there is a paucity of evidence for interventions related to oxidative stress-induced lung injury such as initial FIO_2 for preterm resuscitation. Further, although chorioamnionitis and neonatal infection-induced inflammation may exacerbate lung injury, moderate COE found no benefit from either antepartum or postnatal antibiotics in decreasing the risk of BPD. Given the biologic plausibility of these interventions, modifications of the treatment scheme or identification of the appropriate subgroup of preterm newborns who may benefit needs to be explored further. We could not evaluate interventions that had not been studied in the context of a systematic review of clinical trials, many of which are either in the early phases of use in human trials or have not been studied at all for their potential role in BPD prevention. One emerging intervention that seems to be promising is stem cell therapy. A recent meta-analysis of 25 preclinical studies showed that therapy with mesenchymal stem cells or their conditioning medium significantly improved alveolarization and ameliorated the inflammation and fibrosis in the lungs in rodent models of hyperoxia-induced BPD.[179] Also, there are multiple ongoing trials on assessing stem cell therapy in BPD (NCT02443961, NCT03392467, and NCT03558334). However, many aspects of stem cell therapy such as the optimal source of stem cells, the dosage regimen, route of administration, and timing of therapy need to be explored. Further, the long-term safety of stem cell therapy needs to be proven before it can be translated to routine clinical use.

Limitations

There were limitations in this umbrella review. We could not include systematic reviews based on network meta-analyses as the approach to interpreting the results from a network meta-analysis alongside the results from pairwise meta-analyses is unclear. Umbrella reviews are limited by the number of outcomes that could be assessed. Hence, adverse outcomes related to many of the interventions that could be beneficial in decreasing the risk of BPD could not be assessed. Specifically, although the combined outcome of BPD or mortality at 36 weeks' PMA was assessed, the critical outcome of mortality alone was not assessed in this umbrella review. Further, the interventions that had not been evaluated in a systematic review and meta-analysis could not be appraised in this umbrella review.

Conclusions

High COE indicated that delivery room CPAP, early selective surfactant therapy, inhaled corticosteroids initiated within 2 weeks, early systemic hydrocortisone, avoiding endotracheal tube placement, and volume-targeted ventilation were associated with decreased risk of the primary outcome of BPD or mortality at 36 weeks' PMA. Moderate COE suggested that surfactant administration by LISA, use of porcine surfactant, intratracheal administration of corticosteroids, and late systemic steroids are associated with decreased BPD or mortality at 36 weeks. Moderate to high COE suggest iNO, low oxygen saturation targets (85%-89%), and vitamin A supplementation are associated with decreased risk of BPD at 36 weeks' PMA but not the combined outcome of BPD or mortality, suggesting that they might be associated with an increased risk of mortality. Future multicenter trials that are adequately powered to assess the outcome of BPD or mortality at 36 weeks' PMA for interventions such as noninvasive respiratory support modes, initial FIO_2 for preterm resuscitation, infection control, and nutrition-related interventions are required.

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