

Prevention of bronchopulmonary dysplasia in extremely low gestational age neonates: current evidence

Christian F Poets, Laila Lorenz

Department of Neonatology,
University Children's Hospital,
Tübingen, Germany

Correspondence to

Professor Christian F Poets,
Department of Neonatology,
University Children's Hospital,
Tübingen 72076, Germany;
christian-f.poets@med.uni-tuebingen.de

Received 25 October 2017

Revised 8 January 2018

Accepted 8 January 2018

Published Online First

23 January 2018

ABSTRACT

Bronchopulmonary dysplasia (BPD) is one of the most frequent complications in extremely low gestational age neonates, but has remained largely unchanged in rate. We reviewed data on BPD prevention focusing on recent meta-analyses. Interventions with proven effectiveness in reducing BPD include the primary use of non-invasive respiratory support, the application of surfactant without endotracheal ventilation and the use of volume-targeted ventilation in infants requiring endotracheal intubation. Following extubation, synchronised nasal ventilation is more effective than continuous positive airway pressure in reducing BPD. Pharmacologically, commencing caffeine citrate on postnatal day 1 or 2 seems more effective than a later start. Applying intramuscular vitamin A for the first 4 weeks reduces BPD, but is expensive and painful and thus not widely used. Low-dose hydrocortisone for the first 10 days prevents BPD, but was associated with almost twice as many cases of late-onset sepsis in infants born at 24–25 weeks' gestation. Inhaled corticosteroids, despite reducing BPD, were associated with a higher mortality rate. Administering dexamethasone to infants still requiring mechanical ventilation around postnatal weeks 2–3 may represent the best trade-off between restricting steroids to infants at risk of BPD while still affording high efficacy. Finally, identifying infants colonised with ureaplasma and treating those requiring intubation and mechanical ventilation with azithromycin is another promising approach to BPD prevention. Further interventions yet only backed by cohort studies include exclusive breastmilk feeding and a better prevention of nosocomial infections.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most frequent complications in extremely low gestational age neonates (ELGANs; gestational age <28 weeks) affecting around 22% to 38% of them.^{1,2} It is also an important predictor of neurodevelopmental impairment.³ Various definitions for BPD exist, the most precise is probably the room-air challenge at 36 weeks postmenstrual age (PMA).⁴ The increasing use of high-flow nasal cannulae at fraction of inspired oxygen (FiO₂) 0.21 in recent years might hamper this, so that initiatives at finding a new definition are underway.^{5,6} BPD likely results from the effects of non-physiologic stimuli (inflammation, ventilator-induced lung injury, high oxygen levels) on a structurally and functionally immature lung with underdeveloped defence mechanisms.⁷ In the

past, interventions to avoid BPD mainly focused on reducing inflammation using steroids. This policy was drastically curtailed after data emerged linking dexamethasone use with the subsequent development of cerebral palsy (CP),⁸ leading to a resurgence in BPD.⁹ Exogenous surfactant, particularly if given soon after intubation, has been another first major step in reducing BPD.^{10,11} In recent years, new approaches to respiratory care and steroid use have evolved. This review provides a personal view on strategies likely to reduce death/BPD, or BPD alone (tables 1–3), defined as oxygen requirement at 36 weeks PMA, based on current evidence.

Avoidance of mechanical ventilation via an endotracheal tube

The lungs of ELGANs are uniquely susceptible to injury. Experiments in lambs have shown that already a few large-volume breaths (eg, during bagging) may induce volutrauma leading to long-lasting structural lung injury.¹² It thus seems logical to avoid mechanical ventilation (MV) via an endotracheal tube altogether. This may be achieved by using nasal continuous positive airway pressure (NCPAP) and, if needed, by applying surfactant without MV, for example, through INSURE (intubate, surfactant, extubate) or the less/minimally invasive surfactant administration/therapy (LISA, MIST). The effectiveness of these strategies in preventing BPD has been addressed in several meta-analyses.

The first included four randomised controlled trials (RCT) in infants <32 weeks PMA evaluating the effect of NCPAP compared with MV±surfactant. NCPAP showed a significant benefit for the combined outcome death/BPD, but no effect on BPD alone.¹³

Another meta-analysis compared NCPAP±LISA (LISA used in 3 of 7 studies) vs MV±INSURE in infants <30 weeks PMA. There was a 17% reduction in death/BPD in the NCPAP±LISA group.¹⁴

A third meta-analysis included *only* studies with NCPAP+LISA in the intervention group in infants <34 weeks PMA. Control group infants received MV and, in four of six RCT, surfactant via INSURE. Death/BPD was reduced by 25%, BPD alone by 28%.¹⁵

The most comprehensive meta-analysis included 30 trials on different ventilation strategies for spontaneously breathing infants <33 weeks PMA. One study compared LISA with MV; LISA halved the risk of death/BPD.¹⁶ A similar, although smaller,



To cite: Poets CF, Lorenz L.
Arch Dis Child Fetal Neonatal
Ed 2018;**103**:F285–F291.

Review

Table 1 Summary of randomised controlled trial data on the effects of various respiratory support strategies on death and/or BPD (including selected complications)

Intervention: different modes of respiratory support	Outcome	N studies	N patients	Intervention group	Control group	RR	95% CI
NCPAP vs MV ¹³	Death/BPD	4	2782	532/1296	641/1486	0.91	0.84 to 0.99
	BPD	4	2536	383/1182	461/1354	0.91	0.82 to 1.01
NCPAP±LISA vs MV±INSURE ¹⁴	Death/BPD	4	3289	614/1552	737/1737	0.83	0.71 to 0.96
NCPAP+LISA vs MV±INSURE ¹⁵	Death/BPD	6	895	90/447	121/448	0.75	0.59 to 0.94
	BPD	6	814	56/410	77/404	0.72	0.53 to 0.97
NCPAP+LISA vs MV ¹⁶	Death/BPD	1	189	n.p.	n.p.	0.49*	0.30 to 0.79
INSURE vs MV ¹⁶	Death/BPD	2	419	n.p.	n.p.	0.71*	0.50 to 0.98
NCPAP vs MV ¹⁶	Death/BPD	3	2085	n.p.	n.p.	0.58*	0.35 to 0.93
NIPPV vs NCPAP ¹⁶	Death/BPD	5	775	n.p.	n.p.	0.82*	0.53 to 1.24
NIPPV vs NCPAP ¹⁷	BPD	9	899	60/450	77/449	0.78	0.58 to 1.06
sNIPPV vs NCPAP ¹⁸	BPD	3	181	26/93	38/88	0.64	0.44 to 0.95
VTV vs pressure-limited MV ²²	Death/BPD	4	224	53/114	67/110	0.79	0.62 to 1.01
	BPD	9	909	74/325	102/295	0.68	0.53 to 0.87
	PVL/grade 3–4 IVH	6	441	17/227	35/214	0.47	0.27 to 0.80
VTV vs pressure-limited MV ²³	BPD	9	596	58/310	89/286	0.61	0.46 to 0.82
	Grade 3–4 IVH	11	707	n.p.	n.p.	0.55	0.39 to 0.79
HFOV vs pressure-limited MV ²⁵	Death/BPD	17	3329	678/1659	756/1679	0.90	0.84 to 0.97
	BPD	17	2768	421/1392	485/1394	0.86	0.78 to 0.96
	Air leaks	13	2854	392/1615	337/1439	1.19	1.05 to 1.34
Early vs delayed surfactant for respiratory distress syndrome ¹⁰	Death/BPD	3	3040	447/1519	543/1531	0.83	0.75 to 0.91
	BPD	3	3040	117/1519	170/1531	0.69	0.55 to 0.87

*OR.

BPD, bronchopulmonary dysplasia; HFOV, high frequency oscillatory ventilation; INSURE, intubate, surfactant, extubate; IVH, intraventricular haemorrhage; LISA, less-invasive surfactant administration; MV, mechanical ventilation; NCPAP, nasal continuous positive airway pressure; n.p., not provided; PVL, periventricular leucomalacia; RR, relative risk; sNIPPV, synchronised nasal intermittent positive pressure ventilation; VTV, volume-targeted ventilation.

effect was seen when INSURE was compared with MV, but not if LISA was compared with NCPAP without surfactant.¹⁶ Comparing individual effects of the different strategies on the various outcomes investigated, the authors concluded that ‘LISA was the best strategy among all strategies for all outcomes assessed’, and that INSURE ranked second best in this analysis; the quality of the evidence, however, was low.

There are various techniques to provide non-invasive respiratory support and the question arises whether nasal intermittent positive pressure ventilation (NIPPV) is more effective than NCPAP in preventing BPD. For the use of NIPPV vs NCPAP as primary respiratory support, no difference in BPD was seen.^{16 17} For postextubation use, results were similar if all NIPPV techniques were analysed together.¹⁸ However, subgroup analysis on synchronised NIPPV (sNIPPV) versus NCPAP did show a reduction in BPD using sNIPPV.¹⁸ Unfortunately, only few commercially available ventilators offer this mode of respiratory support.

Avoiding invasive mechanical ventilation via LISA (or INSURE) with NCPAP, followed by sNIPPV postextubation (if needed), appears to be a promising respiratory support strategy for reducing BPD, although definite data from large well-designed (blinded) trials on the effectiveness of this approach are missing. Nonetheless, in the authors’ unit ELGANs receive LISA followed by NCPAP or sNIPPV.

A note of caution must be added here. In a longitudinal follow-up study from Victoria (Australia) comparing respiratory function of ELGANs over three periods (1991/1992, 1997 and 2005), mean duration of NCPAP increased from 5 to 31.5 days, while duration of MV decreased from 21 to 10 days. Despite this increased use of NCPAP, the proportion of infants with BPD increased from 46% to 56% over time. Whether this

disappointing trend towards *more* BPD points to an overuse of non-invasive respiratory support, or is due to a 50% reduction in postnatal steroid use or more severely ill infants surviving in recent years remains unanswered.¹⁹

Alternatives to pressure-limited MV

Despite the increasing use of LISA, many infants with respiratory distress syndrome (RDS) still require MV. What is the best ventilation strategy to avoid BPD in these infants? Given the detrimental effects of volutrauma on the developing lung,^{12 20} the volume applied with each breath should be limited. As lung compliance changes rapidly during RDS and its treatment, this is best achieved by using volume-targeted ventilation (VTV).²¹ A Cochrane review reported a 21% reduction in death/BPD and a 53% reduction in periventricular leucomalacia/grade 3–4 intraventricular haemorrhage (IVH) for VTV compared with pressure-limited MV.²² Another meta-analysis found that VTV reduced BPD by 40% and almost halved grade 3–4 IVH.²³ Most studies, however, were small (<50 patients/group), the intervention was not blinded and BPD not the primary outcome. This, combined with recent animal data suggesting that VTV might not eliminate lung injury during spontaneous breaths,²⁴ raises questions whether the evidence that VTV is superior to other forms of respiratory support can already be regarded conclusive.

An alternative to conventional MV that might also reduce volutrauma is high-frequency oscillatory ventilation (HFOV). A Cochrane review on elective use of HFOV, that is, soon after intubation, showed a significant reduction in death/BPD at 36–37 weeks PMA or discharge and in BPD alone.²⁵ All but one study applied a high-volume strategy, where mean airway

Table 2 Summary of randomised controlled trial data on the effects of corticosteroids on death and/or BPD (including selected complications)

Intervention: corticosteroids	Outcome	N studies	N patients	Events	Control group	RR	95% CI
Early dexamethasone vs placebo ²⁸	Death/BPD	15	2481	538/1248	615/1233	0.87	0.80 to 0.94
	BPD	15	2484	247/1249	350/1235	0.70	0.61 to 0.81
	Severe ROP	8	1507	90/762	115/745	0.77	0.60 to 0.99
	GI perforation	9	1936	70/968	40/968	1.73	1.20 to 2.51
	Hypertension	10	1943	211/978	115/965	1.84	1.53 to 2.21
	Hypertrophic cardiomyopathy	1	50	13/25	3/25	4.33	1.40 to 13.37
Early hydrocortisone vs placebo ²	Cerebral palsy	7	921	75/472	40/449	1.75	1.20 to 2.55
	Survival w/o BPD	1	523	153/256	136/267	1.48*	1.02 to 2.16
Late dexamethasone vs placebo ³²	BPD	1	523	55/256	70/267	0.82*	0.58 to 1.16
	Death/BPD	9	535	159/272	204/263	0.76	0.68 to 0.85
	BPD	9	535	128/272	166/263	0.76	0.66 to 0.88
	Severe ROP	12	558	93/285	65/273	1.38	1.07 to 1.79
	Hypertension	14	1175	58/588	29/587	2.12	1.45 to 3.10
	Hypertrophic cardiomyopathy	4	238	23/119	8/119	2.76	1.33 to 5.74
Early inhaled steroids vs placebo ³⁵	Cerebral palsy	14	631	60/322	53/309	1.05	0.75 to 1.47
	Death/BPD	6	1285	227/649	256/636	0.86	0.75 to 0.99
	BPD	7	1168	149/581	192/587	0.77	0.65 to 0.91
Inhaled steroids (<2 weeks) vs placebo ³⁶	Death/BPD	6	1285	227/649	256/636	0.86	0.77 to 0.99
	BPD	5	429	31/212	33/217	0.97	0.62 to 1.52
Inhaled budesonide vs placebo ^{1 38}	Death/BPD	1	863	175/437	194/419	0.86	0.75 to 1.00
	BPD	1	863	101/363	138/363	0.74	0.60 to 0.91
	Death	1	863	74/437	57/419	1.37	1.01 to 1.86
	Neurodevelopmental disability	1	629	148/308	165/321	0.93	0.80 to 1.09
Intratracheal budesonide+SF vs SF ³⁹	Death/BPD	1	265	55/131	89/134	0.58	0.44 to 0.77

*OR.

BPD, bronchopulmonary dysplasia; chorio, chorioamnionitis; GI, gastrointestinal; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; SF, surfactant.

pressure is initially set a few cmH₂O above that used with conventional MV, and FiO₂ is reduced first during weaning, before reducing mean airway pressure. Importantly, most studies showing superiority of HFOV are rather old, and the comparison group received pressure-limited MV; thus, the benefits seen with HFOV may not hold up if comparing the latter against VTV. Recent data in adults questioning benefits of lung recruitment strategies might have an impact on ventilation strategies in preterm infants.²⁶

Corticosteroids

With inflammation playing a key role in the pathophysiology of BPD, suppressing inflammation is a logical consequence. Traditionally, this has been achieved by systemic corticosteroids using three different approaches: early (postnatal week 1), late (postnatal week 2) and very late administration (after week 3). The last option is used for treating instead of preventing BPD and thus beyond the focus of this review. Early administration of steroids has the advantage that the pathophysiology leading

Table 3 Summary of data from randomised controlled trials and observational studies on the effects of various other strategies for BPD prevention on death and/or BPD (including lung function data)

Intervention: others	Outcome	N studies	N patients	Events	Control group	RR	95% CI
Azithromycin vs placebo ⁴⁵	Death/BPD	3	363	106/186	118/177	0.86	0.77 to 0.97
	BPD	3	310	81/161	90/149	0.83	0.71 to 0.97
Vitamin A intramuscular vs placebo ⁵³	Death/BPD	3	935	222/469	248/466	0.90	0.81 to 1.01
	BPD	4	886	190/442	224/444	0.85	0.74 to 0.98
Caffeine vs placebo ⁴⁸	BPD	1	2006	350/1006	447/1000	0.64*	0.52 to 0.78
Caffeine vs placebo ⁴⁹	FVC z-score <5th centile	1	142	8/74	19/68	0.31*	0.12 to 0.77
Caffeine vs placebo ⁵⁰	BPD	1	822	111/396	190/426	0.48*	0.36 to 0.65
Early—postnatal days ≤3							
Caffeine vs placebo ⁵⁰	BPD	1	1095	239/567	257/528	0.77*	0.61 to 0.98
Late—postnatal days >3							
Early vs late caffeine ⁵¹	Death/BPD	1	29070	3681/14 535	4591/14 5365	0.74*	0.69 to 0.80
Exclusive formula vs exclusive breastmilk ⁵⁶	BPD	1	462	n.p.	n.p.	2.56*	1.33 to 5.04
Exclusive breastmilk ⁵⁷	BPD	1	254	n.p.	n.p.	0.91*	0.82 to 0.99

*OR.

BPD, bronchopulmonary dysplasia; FVC, forced vital capacity; n.p., not provided; RR, relative risk.

Review

to BPD is interrupted soon after birth, yet the disadvantage that many infants at low risk of developing BPD are exposed to a toxic drug. Unfortunately, most models for the early prediction of BPD have been assessed as poor,²⁷ so that targeted prevention remains difficult.

Early administration of systemic corticosteroids

The Cochrane review on early systemic corticosteroids to prevent BPD found a lower risk of death/BPD, patent ductus arteriosus (PDA) and severe retinopathy of prematurity (ROP) using dexamethasone. Short-term side effects included gastrointestinal perforation, hypertension and hypertrophic cardiomyopathy. Most important, however, was an increased risk of CP²⁸ at 2-year follow-up. Thus, the benefits of early postnatal dexamethasone may not outweigh its adverse effects.

The early use of low-dose hydrocortisone, however, increased survival without BPD with fewer side effects.²⁹ ELGANs with a birth weight \geq 3rd percentile were randomised to 2×0.5 mg/kg/day hydrocortisone on days 1–7 followed by 3 days with 1×0.5 mg/kg/day, or placebo. Survival without BPD was present in 60% in the treatment versus 51% in the placebo group; death occurred in 18 vs 23%. There was no difference in pulmonary haemorrhage, insulin treatment, gastrointestinal perforation, sepsis and BPD alone between groups. Post hoc analysis showed a stronger effect of hydrocortisone in infants born in the context of chorioamnionitis and a higher rate of sepsis in the most immature infants (24–25 weeks PMA; 40 vs 23%). The 2-year follow-up, done in 93% of survivors, showed no difference in revised Brunet-Lézine test results or in the proportion of infants with moderate-to-severe neurodevelopmental impairment or CP. Although the data on neurodevelopment are reassuring, it remains unclear whether all ELGANs should be exposed to hydrocortisone early after birth or whether a more selective approach is preferable; this decision may be influenced by an individual centre's BPD rate.³⁰

Late (>1 week) systemic corticosteroids

The administration of systemic corticosteroids in the second or third postnatal week may allow for a better identification of infants at risk of BPD. For example, an ELGAN with birth weight <1000 g who still requires MV with $\text{FiO}_2 \geq 0.3$ at 14 days of age has a <60% chance of surviving without BPD.³¹ In such infants, the beneficial effects of dexamethasone outweigh the potential risk of CP.³⁰

In a Cochrane review on late systemic steroids, >75% of infants were started on study drug (almost always dexamethasone) between 1 and 3 weeks of age.³² Death/BPD was reduced by 24%, as was BPD alone. Adverse events included hypertension, hypertrophic cardiomyopathy and severe ROP, but there was no significant increase in the risk of gastrointestinal perforation or CP. These data suggest that administering dexamethasone to ELGANs who still require MV in their second to third postnatal week may help avoiding BPD without an increased risk of CP.

An important issue with postnatal steroid use is the cumulative dose administered to achieve optimal efficacy with minimal long-term sequelae. A meta-analysis of RCTs comparing different doses of dexamethasone in ventilated infants <30 weeks and >7 days of age found an increased risk of BPD and also of abnormal neurodevelopment with a moderate (2 mg/kg) compared with a high-dose regimen (>4 mg/kg cumulative dose); however, the quality of the evidence was assessed as low or very low.³³ These data are important as they raise the question whether a

low cumulative dexamethasone dose, compared with higher doses, although intuitively preferable, is indeed the safest way to prevent BPD. In the author's unit, infants receiving systemic steroids are started on the low dose corticosteroid regime used in the Dexamethasone: A Randomized Trial (DART) study.³⁴ If extubation after 3 days is unrealistic or unsuccessful, the dose will be increased to 0.3 mg/kg/day for 3 days followed by the DART regime.

Early or late administration of topical corticosteroids

With the emergence of data suggesting an increased risk of CP and gastrointestinal perforation following systemic steroids, interest in topical, for example, inhaled routes of administration resurged. A meta-analysis comparing inhaled steroids versus placebo for the prevention or treatment of BPD found a reduction in death/BPD and BPD alone.³⁵ The relevant Cochrane analysis focused on inhaled steroids before 14 days of age versus placebo and also found a reduction in death/BPD but not for BPD alone.³⁶

A recent large RCT on early (<24 hours) inhaled budesonide for BPD prevention in ELGANs found a reduction in death/BPD.¹³⁷ Mortality at 2 years of age, however, was increased (19.9% vs 14.5%), while neurodevelopmental disability, which could be assessed in 94% of survivors, was no different.³⁸ Although no specific cause of death could be identified explaining this mortality signal, prophylactic administration of budesonide to all ELGANs will be difficult to justify.

An alternative to inhalation is the intratracheal administration of budesonide combined with exogenous surfactant. This approach has been investigated in a three-centre study enrolling infants with a birth weight <1500 g with RDS and $\text{FiO}_2 \geq 0.50$ within 4 hours of birth.³⁹ Intervention group infants received 100 mg/kg surfactant (Survanta) mixed with 0.25 mg/kg budesonide, controls received only surfactant; up to five repeat doses were allowed every 8 hours. Primary outcome was death/BPD, which occurred in 42% of intervention and 66% of control group infants. Two-year to three-year follow-up data obtained in 85% of survivors showed no difference in growth, neuromotor dysfunction or Bayley II test results.³² Given the high baseline rate for death/BPD in this study, these data await confirmation in other settings before this approach can be recommended.

Eradication of ureaplasma urealyticum

Ureaplasma urealyticum is a genitourinary tract commensal in females that can invade the intra-amniotic fluid causing inflammation. It is the most common organism isolated in chorioamnionitis and associated with an increased risk for preterm labour and neonatal morbidity in ELGANs.⁴⁰ Its role in developing BPD is controversial.^{41–42} *Ureaplasma* may not by itself cause BPD, but if combined with other stimuli like MV or exposure to high oxygen levels.⁴³ It still remains unclear if eradication of ureaplasma may prevent BPD. An early Cochrane analysis on erythromycin found no effect on BPD or death.⁴⁴ A broader meta-analysis on the effects of macrolides on BPD reported a reduction in death/BPD and BPD alone for azithromycin.⁴⁵ Given these data, the approach chosen in the authors' institution is to screen ELGANs for ureaplasma in tracheal aspirates soon after birth and treat those infants still receiving MV and colonised with ureaplasma with azithromycin (10 mg/kg/day for 7 days). The dosage used is based on the above-mentioned meta-analysis.⁴⁵ Pharmacokinetic data, however, suggest that a 3-day course of 20 mg/kg/day might be more effective in eradicating

ureaplasma.⁴⁶ Whichever regime is used, evidence for using macrolides for BPD prevention is rather weak.

Caffeine citrate

Given that caffeine stimulates breathing, reducing the need for MV, and has diuretic effects and exerts anti-inflammatory properties in the developing lung,⁴⁷ it is not surprising that its use led to a 36% reduction in BPD in the Caffeine for Apnea of Prematurity (CAP) trial.⁴⁸ Encouragingly, this effect on BPD in the neonatal period continued to translate into better lung function results at 11 years of age in Australian former CAP study participants. Expiratory flows were improved by 0.5 SD in children randomised to caffeine, and 11 vs 28% had forced vital capacity values below the fifth centile.⁴⁹ Post hoc subgroup analysis of the CAP data showed that postnatal age at onset of treatment influenced the effect of caffeine: BPD was reduced by 52% in those with treatment started on postnatal days 1–3 (early), whereas it was reduced by only 23% if started after day 3 (late).⁵⁰ Subsequent cohort studies confirmed this finding: in an analysis of data from the Pediatrix network, death/BPD occurred in 28% of infants with early caffeine start, but in 34% of those started late.⁵¹ Similar data were also reported from the Canadian Neonatal Network.⁵² Such post hoc analyses or cohort study data, however, are only hypothesis-generating.

Vitamin A

Vitamin A is important for lung growth and differentiation, and benefits of intramuscular vitamin A administration (usually 3×5000 IE/week intramuscular over 4 weeks) have been confirmed in meta-analysis: BPD was reduced by 13% in infants <1000 g birth weight receiving vitamin A compared with placebo, but there was no effect on the combined outcome death/BPD.⁵³ Clinical uptake of these data has been limited, possibly because it is costly and intramuscular administration is reported to be painful. One smaller study tested the effect of oral vitamin A showing no effect on BPD.⁵⁴

Exclusive breastmilk feeding and nosocomial infection—cohort studies

Exclusive breastmilk

Breastmilk feeding has been associated with less necrotising enterocolitis and ROP,⁵⁵ but there are no RCT data whether it prevents BPD. Data from the German Neonatal Network, however, showed that exclusively formula-fed infants had 2.6-times the risk of developing BPD in multivariate analysis than exclusively breastmilk-fed infants.⁵⁶ In another cohort study, multivariable analysis showed a 9.5% reduction in the odds of BPD for every 10% increase in expressed breastmilk.⁵⁷ These data further encourage the use of breastmilk instead of formula in ELGANS.

Avoidance of nosocomial infections

Nosocomial infection (NI) has been associated with the development of BPD, but whether BPD can be avoided through better infection control is unknown. In a cohort study from the California Perinatal Quality Care Collaborative database involving 22 967 very low birthweight infants <30 weeks PMA from 129 hospitals, NI rates declined from 25% to 15% between 2006 and 2013, while BPD fell from 35% to 30%. Adjusted individual hospital rates of BPD correlated positively with those for NI. The authors estimated that

Box 1 Possible strategies for bronchopulmonary dysplasia prevention in extremely low gestational age neonates (ELGANS)

- ▶ Using nasal continuous positive airway pressure (NCPAP) instead of intubation and mechanical ventilation as primary respiratory support.
- ▶ Applying exogenous surfactant via less/minimal invasive administration via a thin tracheal catheter/nasogastric tube or via the INSURE method.
- ▶ Using volume instead of pressure targeted ventilation in infants requiring mechanical ventilation.
- ▶ Using synchronised intermittent positive pressure ventilation instead of NCPAP after extubation
- ▶ Starting caffeine on postnatal days 1–3 instead of later.
- ▶ Applying vitamin A intramuscularly for the first four postnatal weeks.
- ▶ Considering low-dose intravenous hydrocortisone for the first 10 postnatal days in any infant born with a birth weight above the third percentile.
- ▶ Considering intravenous dexamethasone in infants who require mechanical ventilation at the end of their second postnatal week.
- ▶ Test tracheal aspirates of all ELGANS requiring mechanical ventilation after birth for ureaplasma, consider intravenous azithromycin in those tested positive.

this 8% fall in BPD rates was attributable to the reductions in NI.⁵⁸ Implementing quality improvement bundles for NI prevention may thus be a yet underused approach to reducing BPD.

Conclusions and outlook

Effective BPD prevention continues to be challenging. Although meta-analyses of RCTs are considered the highest level of evidence, their results may not be generalisable to other settings. Given the evidence summarised above, some personal recommendations may be given (box 1).

There are also other interventions, such as the use of antenatal steroids, inhaled nitric oxide, cyclooxygenase inhibitors for PDA closure or lower versus higher oxygen target ranges we did not review, as meta-analyses either showed an increased risk⁵⁹ or no significant/inconsistent effects on BPD.^{10 60–63} The most important approach, however, is to avoid preterm birth. Here, we yet seem far away from an effective intervention, which would likely require closer collaboration with our obstetrical colleagues.

Acknowledgements The authors are grateful to Monika Osfolk for carefully constructing Tables 1–3.

Contributors CFP wrote the first draft and critically revised the manuscript, LL critically revised the draft for important intellectual input.

Funding LL was supported by an Intramural Habilitation Program (TÜFF; 2459-0-0).

Competing interests CFP has received speaker honoraria from Chiesi Farmaceutici.

Patient consent Obtained.

Provenance and peer review Commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

Review

REFERENCES

- Bassler D, Plavka R, Shinwell ES, *et al.* Early Inhaled Budesonide for the prevention of bronchopulmonary dysplasia. *N Engl J Med* 2015;373:1497–506.
- Baud O, Maury L, Lebaill F, *et al.* Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. *Lancet* 2016;387:1827–36.
- Schmidt B, Asztalos EV, Roberts RS, *et al.* Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA* 2003;289:1124–9.
- Walsh MC, Wilson-Costello D, Zadell A, *et al.* Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. *J Perinatol* 2003;23:451–6.
- Poindexter BB, Feng R, Schmidt B, *et al.* Comparisons and limitations of current definitions of bronchopulmonary dysplasia for the prematurity and respiratory outcomes program. *Ann Am Thorac Soc* 2015;12:1822–30.
- Jobe AH, Bancalari EH. Controversies about the definition of bronchopulmonary dysplasia at 50 years. *Acta Paediatr* 2017;106:692–3.
- Jobe AH. Mechanisms of lung injury and bronchopulmonary dysplasia. *Am J Perinatol* 2016;33:1076–8.
- Yeh TF, Lin YJ, Huang CC, *et al.* Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics* 1998;101:E7.
- Yoder BA, Harrison M, Clark RH. Time-related changes in steroid use and bronchopulmonary dysplasia in preterm infants. *Pediatrics* 2009;124:673–9.
- Bahadur FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2012;11:CD001456.
- Singh N, Halliday HL, Stevens TP, *et al.* Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2015:CD010249.
- Björklund LJ, Ingimarsson J, Curstedt T, *et al.* Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997;42:348–55.
- Schmölzer GM, Kumar M, Pichler G, *et al.* Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ* 2013;347:f5980.
- Fischer HS, Bühner C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013;132:e1351–60.
- Aldana-Aguirre JC, Pinto M, Featherstone RM, *et al.* Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2017;102:F17–23.
- Isayama T, Iwami H, McDonald S, *et al.* Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA* 2016;316:611–24.
- Lemyre B, Laughon M, Bose C, *et al.* Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. *Cochrane Database Syst Rev* 2016;12:CD005384.
- Lemyre B, Davis PG, De Paoli AG, *et al.* Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev* 2017;2:CD003212.
- Doyle LW, Carse E, Adams AM, *et al.* Ventilation in extremely preterm infants and respiratory function at 8 years. *N Engl J Med* 2017;377:329–37.
- Perlman JM, Goodman S, Kreusser KL, *et al.* Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. *N Engl J Med* 1985;312:1353–7.
- Scopesi F, Calevo MG, Rolfe P, *et al.* Volume targeted ventilation (volume guarantee) in the weaning phase of premature newborn infants. *Pediatr Pulmonol* 2007;42:864–70.
- Klingenberg C, Wheeler KI, McCallion N, *et al.* Volume-targeted versus pressure-limited ventilation in neonates. *Cochrane Database Syst Rev* 2017;10:CD003666.
- Peng W, Zhu H, Shi H, *et al.* Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F158–65.
- Yoshida T, Nakahashi S, Nakamura MAM, *et al.* Volume-controlled ventilation does not prevent injurious inflation during spontaneous effort. *Am J Respir Crit Care Med* 2017;196:590–601.
- Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2015:CD000104.
- Cavalcanti AB, Suzumura EA, Laranjeira LN, *et al.* Effect of lung recruitment and titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2017;318:1335–45.
- Onland W, Debray TP, Laughon MM, *et al.* Clinical prediction models for bronchopulmonary dysplasia: a systematic review and external validation study. *BMC Pediatr* 2013;13:207.
- Doyle LW, Ehrenkranz RA, Halliday HL. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2014:CD001146.
- Baud O, Trousson C, Biran V, *et al.* Association between early low-dose hydrocortisone therapy in extremely preterm neonates and neurodevelopmental outcomes at 2 years of age. *JAMA* 2017;317:1329–37.
- Doyle LW, Halliday HL, Ehrenkranz RA, *et al.* An update on the impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk of bronchopulmonary dysplasia. *J Pediatr* 2014;165:1258–60.
- Laughon MM, Langer JC, Bose CL, *et al.* Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. *Am J Respir Crit Care Med* 2011;183:1715–22.
- Doyle LW, Ehrenkranz RA, Halliday HL. Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2014:CD001145.
- Onland W, De Jaegere AP, Offringa M, *et al.* Systemic corticosteroid regimens for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev* 2017;1:CD010941.
- Doyle LW, Davis PG, Morley CJ, *et al.* Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. *Pediatrics* 2006;117:75–83.
- Shinwell ES, Portnov I, Meerpohl JJ, *et al.* Inhaled corticosteroids for bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2016;138:e20162511.
- Shah VS, Ohlsson A, Halliday HL, *et al.* Early administration of inhaled corticosteroids for preventing chronic lung disease in very low birth weight preterm neonates. *Cochrane Database Syst Rev* 2017;1:CD001969.
- Bassler D, Halliday HL, Plavka R, *et al.* The Neonatal European Study of Inhaled Steroids (NEUROSIS): an eu-funded international randomised controlled trial in preterm infants. *Neonatology* 2010;97:52–5.
- Bassler D, Shinwell ES, Hallman M, *et al.* Long-term effects of inhaled budesonide for bronchopulmonary dysplasia. *N Engl J Med* 2018;378:148–57.
- Yeh TF, Chen CM, Wu SY, *et al.* Intratracheal administration of budesonide/surfactant to prevent bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2016;193:86–95.
- Kallapur SG, Kramer BW, Jobe AH. Ureaplasma and BPD. *Semin Perinatol* 2013;37:94–101.
- Zheng XD, Li D, Yang DH, *et al.* Association of Ureaplasma urealyticum colonization with development of bronchopulmonary dysplasia: a systemic review and meta-analysis. *J Huazhong Univ Sci Technolog Med Sci* 2014;34:265–9.
- Viscardi RM. Ureaplasma species: role in neonatal morbidities and outcomes. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F87–92.
- Inatomi T, Oue S, Ogihara T, *et al.* Antenatal exposure to Ureaplasma species exacerbates bronchopulmonary dysplasia synergistically with subsequent prolonged mechanical ventilation in preterm infants. *Pediatr Res* 2012;71:267–73.
- Mabanta CG, Pryhuber GS, Weinberg GA, *et al.* Erythromycin for the prevention of chronic lung disease in intubated preterm infants at risk for, or colonized or infected with Ureaplasma urealyticum. *Cochrane Database Syst Rev* 2003:CD003744.
- Nair V, Loganathan P, Soraisham AS. Azithromycin and other macrolides for prevention of bronchopulmonary dysplasia: a systematic review and meta-analysis. *Neonatology* 2014;106:337–47.
- Merchan LM, Hassan HE, Terrin ML, *et al.* Pharmacokinetics, microbial response, and pulmonary outcomes of multidose intravenous azithromycin in preterm infants at risk for Ureaplasma respiratory colonization. *Antimicrob Agents Chemother* 2015;59:570–8.
- Köroğlu OA, MacFarlane PM, Balan KV, *et al.* Anti-inflammatory effect of caffeine is associated with improved lung function after lipopolysaccharide-induced amnionitis. *Neonatology* 2014;106:235–40.
- Schmidt B, Roberts RS, Davis P, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;354:2112–21.
- Doyle LW, Ranganathan S, Cheong JLY. Neonatal caffeine treatment and respiratory function at 11 years in children under 1,251 g at birth. *Am J Respir Crit Care Med* 2017;196:1318–24.
- Davis PG, Schmidt B, Roberts RS, *et al.* Caffeine for apnea of prematurity trial: benefits may vary in subgroups. *J Pediatr* 2010;156:382–7.
- Dobson NR, Patel RM, Smith PB, *et al.* Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. *J Pediatr* 2014;164:992–8.
- Lodha A, Seshia M, McMillan DD, *et al.* Association of early caffeine administration and neonatal outcomes in very preterm neonates. *JAMA Pediatr* 2015;169:33–8.
- Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants. *Cochrane Database Syst Rev* 2011:CD000501.
- Wardle SP, Hughes A, Chen S, *et al.* Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F9–13.
- Zhou J, Shukla VV, John D, *et al.* Human milk feeding as a protective factor for retinopathy of prematurity: a meta-analysis. *Pediatrics* 2015;136:e1576–86.

- 56 Spiegler J, Preuß M, Gebauer C, *et al.* Does breastmilk influence the development of bronchopulmonary dysplasia? *J Pediatr* 2016;169:76–80.
- 57 Patel AL, Johnson TJ, Robin B, *et al.* Influence of own mother's milk on bronchopulmonary dysplasia and costs. *Arch Dis Child Fetal Neonatal Ed* 2017;102:F256–61.
- 58 Lapcharoensap W, Kan P, Powers RJ, *et al.* The relationship of nosocomial infection reduction to changes in neonatal intensive care unit rates of bronchopulmonary dysplasia. *J Pediatr* 2017;180:105–9.
- 59 Jones LJ, Craven PD, Attia J, *et al.* Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F45–52.
- 60 Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2017;1:CD000509.
- 61 Roberts D, Brown J, Medley N, *et al.* Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2017;3:CD004454.
- 62 Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2011:CD004213.
- 63 Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. *Neonatology* 2014;105:55–63.



Prevention of bronchopulmonary dysplasia in extremely low gestational age neonates: current evidence

Christian F Poets and Laila Lorenz

Arch Dis Child Fetal Neonatal Ed 2018 103: F285-F291 originally published online January 23, 2018
doi: 10.1136/archdischild-2017-314264

Updated information and services can be found at:
<http://fn.bmj.com/content/103/3/F285>

These include:

References

This article cites 56 articles, 13 of which you can access for free at:
<http://fn.bmj.com/content/103/3/F285#ref-list-1>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>