Lung Health Working Group

"BPD Bundle" Revision

Initial Doses of Surfactant

Brooke Read

Currently in the BPD Bundle

Surfactant administration	Exact timing controversial: • If baby requires intubation for resuscitation – consider surfactant • If oxygen requirement becomes higher than 30% - 50% on nCPAP • Early-selective surfactant	1a and physiological sense to avoid lung injury 1a
	Avoid aggressive hand ventilation for administering surfactant	Physiological sense, no evidence

Previous Literature Search: Surfactant and BPD

- Jon Wong conducted search earlier this year evaluating repeat doses of surfactant
- Search Terms:
  - PUBMED: Surfactant, bronchopulmonary dysplasia
    (if added repeat = 0 results)
  - Limit: humans, newborn, English, date

  - EMBASE: surfactant
  - Limit: humans, English, clinical trial, date
- Databases:
  - Cochrane, MEDLINE, EMBASE
- Overall, no new data regarding the use of surfactant and outcomes, specifically BPD
- CPS and AAP recommendations used for repeat doses of surfactant used in revised BPD bundle

Canadian Pediatric Society Position Statement: Recommendations for neonatal surfactant therapy

Davis and Barrington 2005 Updated Jan 2015, Reaffirmed 2017

Recommendation

- Intubated infants with RDS should receive exogenous surfactant therapy (grade A).

Recommendation

- Infants who are at a significant risk of RDS should receive prophylactic natural surfactant therapy as soon as they are stable within a few minutes after intubation (grade A)

Canadian Pediatric Society Position Statement Recommendations for neonatal surfactant therapy *Addendum*

- **How should surfactant be used in preterm infants initially managed with nasal continuous positive airway pressure (CPAP)?**
- Preterm neonates who receive treatment with nasal CPAP as their initial method of respiratory support should be provided with exogenous surfactant treatment if exhibiting clinical signs of RDS with a demonstrated need for escalating or sustained levels of supplemental oxygen to maintain adequate arterial oxygen saturation (Grade B recommendation).
- Treatment with surfactant **should not** be withheld if the FiO_2 requirements exceed **0.5** (Grade A recommendation).

American Academy of Pediatrics: Surfactant Replacement Therapy for Preterm and Term Neonates With Respiratory Distress (Polin & Carol Committee of Fetus and Newborn,2014)

- Preterm infants born at <30 weeks' gestation who need mechanical ventilation because of severe RDS should be given surfactant after initial stabilization (Strong Recommendation).
- Using CPAP immediately after birth with subsequent selective surfactant administration should be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants (Strong Recommendation).

European Consensus Guidelines on the Management of RDS -2019 Update

Sweet et al, 2019 Neonatology

- Babies who require intubation for stabilization should be given surfactant (**B1**).
- A policy of early rescue surfactant should be standard (**A1**), but there are occasions when surfactant should be given in the delivery suite, such as when intubation is needed for stabilization (**A1**).
- Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies who are worsening when FiO_2 >0.30 on CPAP pressure of at least 6 cm H2O (**B2**).
  - FiO2 of > .30 was found to be a predictor of CPAP failure in infants 25-32 weeks (Dargaville et al, 2013)
- GRADE system was used

Summary of Recommendations

Revised

- Preterm infants with clinical or radiological evidence of RDS who require **intubation** for initial stabilization or early in the neonatal period should be given surfactant
- Preterm infants with RDS who are managed with non-invasive respiratory support as an initial mode should receive early selective surfactant at a FiO_2 threshold of greater than 0.3 and no later than 0.5

Previous

Exact timing controversial:

- If baby requires intubation for resuscitation – consider surfactant
- If oxygen requirement becomes higher than 30% - 50% on nCPAP
- Early-selective surfactant

Clarification of recommendations

- Do we need to define infants at high risk of RDS? Less than 29 weeks?
- Do we need to define a time period for surfactant administration early in the neonatal period? 72 hours?
- Should the term prophylactic surfactant be used for infants who are intubated?

Canadian Pediatric Society Position Statement: Recommendations for neonatal surfactant therapy

Level of evidence	
1a	Systematic review (with homogeneity) of randomized controlled trials
1b	Individual randomized controlled trial (with narrow CI)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (or low-quality randomized controlled trial, eg, <80% follow-up)
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or ‘first principles’

Canadian Pediatric Society Position Statement: Recommendations for neonatal surfactant therapy

Updated: Jan 30 2015 | **Reaffirmed:** Jan 30 2017

Grade of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies
C	Level 4 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

References

1. Davis DJ, Barrington KJ; Canadian Paediatric Society, Fetus and Newborn CommitteeRecommendations for neonatal surfactant therapy. Paediatr Child Health. 2005 Feb;10(2):109-16. PubMed PMID: 19668609; PubMed Central PMCID: PMC2722820.
2. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2012 Mar 14;(3):CD000510. doi: 10.1002/14651858.CD000510.pub2.Review. PubMed PMID: 22419276.
3. Polin RA, Carlo WA; Committee on Fetus and Newborn; American Academy of Pediatrics. Surfactant replacement therapy for preterm and term neonates with respiratory distress. Pediatrics. 2014 Jan;133(1):156-63. doi: 10.1542/peds.2013-3443. Epub 2013 Dec 30. PubMed PMID: 24379227.
4. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, Plavka R, Roehr CC, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GHA, Halliday HL. European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2019 Update. Neonatology. 2019;115(4):432-450. doi: 10.1159/000499361. Epub 2019 Apr 11. PubMed PMID: 30974433; PubMed Central PMCID: PMC6604659.
5. Dargaville PA, Aiyappan A, De Paoli AG, Dalton RG, Kuschel CA, Kamlin CO, Orsini F, Carlin JB, Davis PG. Continuous positive airway pressure failure in preterm infants: incidence, predictors and consequences. Neonatology. 2013;104(1):8-14. doi: 10.1159/000346460. Epub 2013 Apr 4. PubMed PMID: 23595061.

Lung Health Working Group

"BPD Bundle" Revision

INSURE Literature Review

Brooke Read, MHS, RRT

Clinical Question

- In preterm infants with respiratory distress syndrome requiring surfactant therapy, does use of the INSURE (Intubation, Surfactant, Extubate) Method compared to surfactant therapy followed by ongoing mechanical ventilation improve respiratory outcomes?

Search Strategy (Search terms and databases)

- Initial search performed by a librarian
- Search Terms
  - Newborn (preterm or infant or baby or newborn)
  - Surfactant
  - Mechanical Ventilation (Respiration, Artificial)
  - INSURE (transient intubation, brief ventilation, rapid extubation)
- Limits: newborn, humans, english
- Databases:PubMed/ Cochrane

List of exclusion criteria

- Abstract only results

Results of Search Strategy

- Total number of articles identified:64
- Articles remaining after screening of titles/abstracts: 25
- Articles included after full text review:10
- Additional articles identified (e.g. from references):11
- Final number of articles in this review: 21
  - *5 additional articles* identified that compared prophylactic or early INSURE to later INSURE, additional summary

Summary of Evidence

Evidence Supporting Clinical Question

Good (most/all on list*)	Rojas et al, 2009 Stevens et al, 2007 Tooley et al, 2003		Perez et al, 2014 Geary et al, 2008		
Fair (some on list)			Ji Wong Koh, 2018 Read et al, 2016 Leone et al, 2013 Bohlin et al, 2007 Alba et al, 1995	Tagare et al, 2014 Naseh et al, 2014 Kirsten et al, 2012 Tsakalidis et al, 2011 Dani et al , 2010 Blennow et al, 1999	
Poor (few on list)	Nayeri et al, 2013	Najafian et al 2014			
***See last page for list of "Quality Items"**	**1** **Randomized Controlled Trials (or meta-analyses of RCTs)**	**2** **Studies using concurrent controls non-randomized (or meta-analyses of such studies)**	**3** **Studies using retrospective controls**	**4** **Studies without a control group (e.g. case series)**	**5** **Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models)**
Level of evidence					

Evidence Neutral to Clinical Question

Good	Dunn et al , 2011				
Fair	Nakhshab et al, 2015 So et al, 2004				
Poor					
***See last page for list of "Quality Items"**	**1 RCT (or meta-analyses)**	**2 Concurrent controls NR (or meta-analyses)**	**3 Retrospective controls**	**4 No control group (e.g. case series)**	**5 Indirect studies**
Level of evidence					

Secondary Clinical Question

- In preterm infants, does prophylactic or early INSURE when compared to NCPAP with selective or late INSURE improve respiratory outcomes?

Summary of Evidence

Evidence Supporting Clinical Question

Good (most/all on list*)	Kandraju et al, 2012 Verder et al, 1999				
Fair (some on list)					
Poor (few on list)					
***See last page for list of "Quality Items"**	**1** **Randomized Controlled Trials (or meta-analyses of RCTs)**	**2** **Studies using concurrent controls non-randomized (or meta-analyses of such studies)**	**3** **Studies using retrospective controls**	**4** **Studies without a control group (e.g. case series)**	**5** **Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models)**
Level of evidence					

Evidence Neutral to Clinical Question

Good	Sandri et al, 2010				
Fair			Saianda et al, 2010		
Poor	Okulu et al, 2015				
***See last page for list of "Quality Items"**	**1 RCT (or meta-analyses)**	**2 Concurrent controls NR (or meta-analyses)**	**3 Retrospective controls**	**4 No control group (e.g. case series)**	**5 Indirect studies**
Level of evidence					

Reviewer's final comments and assessment based on available literature

- **INSURE versus surfactant and MV: 21 total**
  - 7 LOE 1, 1 LOE 2, 7 LOE 3, 6 LOE 4
  - When early or prophylactic INSURE is compared to later surfactant administration with continued MV, the use of MV, the risk of BPD, and air leaks is reduced.
  - When prophylactic INSURE is compared to prophylactic surfactant and MV, the reduction in air leaks and BPD is no longer evident in RCT's, only the reduction in the use of MV.
  - Observational/ Case series studies of NICU's that implemented use of the INSURE method who previously treated infants who required surfactant with ongoing MV found a reduction in the use of invasive MV No studies found an increased risk in adverse outcomes with use of the INSURE method.

Reviewer's final comments and assessment based on available literature

- **Prophylactic or early INSURE compared to NCPAP and later surfactant via INSURE: 5 total**
  - 4 LOE 1, 1 LOE 3:
  - Prophylactic INSURE is not superior to NCPAP + early selective surfactant with INSURE with a low FiO2 threshold > .40 on NCPAP
  - Early INSURE (FiO2 > 0.4 on NCPAP) is superior to NCPAP + late surfactant with INSURE or ongoing mechanical ventilation at FiO2 (> .60) at reducing the need for subsequent mechanical ventilation

Additional Comments

Limitations of the Literature

- Overall the effectiveness of the INSURE method is not as well studied in infants less than 25 weeks.
  - One RCT included infants as young as 25 weeks: approximately 30 infants
  - One observational study included 163 infants with a median gestational age of 25.4 weeks

Literature on "success rate" INSURE

- In infants from 25- 29^{6}weeks: approximate success rate in the two large RCT's (Dunn et al, 2011 and Sandri et al 2010) of the INSURE method (not requiring MV in the first 5-7 days) is approximately 50-65 %. (includes infants who could not be extubated initially and those who required re-intubation).
- The decision to extubate following surfactant administration in most studies using the INSURE method was based on the assessment of respiratory drive and / OR FiO2 requirements.

Overall recommendation

- **Recommendation statement:**
  - The INSURE method is considered a safe alternative to surfactant and routine mechanical ventilation in preterm infants initially managed on non-invasive respiratory support who meet criteria for surfactant therapy
  - Early selective INSURE when the FiO_2 is > .40-.50, as opposed to later INSURE at an FiO_2 of > 0.6 or prophylactic INSURE is the recommended approach to reduce the need for subsequent mechanical ventilation while minimizing the number of infants who are treated with surfactant who may not require it.
- "Overall" Level of Evidence LOE 1
- "Overall" Quality of Evidence
  - Fair

Lung Health Working Group

BPD Bundle Revision

Corticosteroids for the prevention and treatment of BPD

M. Dunn, B. Lemyre, V. Shah

Clinical Question 1

- P: In preterm infants at risk of BPD
- I: should systemic corticosteroids (dexamethasone, hydrocortisone) or inhaled corticosteroids (fluticasone, budesonide)
- C: vs placebo
- O: be provided to prevent BPD
- T: in the first week of life?

Clinical Question 2

- P: In preterm infants
- I: should systemic corticosteroids (dexamethasone, hydrocortisone) or inhaled corticosteroids (fluticasone, budesonide)
- C: vs placebo
- O: be provided to treat evolving BPD
- T: after the first week of life?

Search Strategy (Search terms and databases)

- Searches were designed and conducted by a librarian experienced in systematic reviews.
- MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946 to June 14, 2018), Embase (1980 to June 14, 2018) and the CENTRAL Trials Registry of the Cochrane Collaboration (May 2018 issue) were searched.
- Randomized controlled trials, cohort studies and systematic reviews were sought. Searches were not restricted by language but were limited to material entering the databases since the last published statement.
- Search terms included bronchopulmonary dysplasia, chronic lung disease, dexamethasone, hydrocortisone, inhaled corticosteroids, postnatal corticosteroids and preterm infants.
- Final number of full texts reviewed: 39

Should early systemic corticosteroids (dexamethasone, hydrocortisone) be provided to babies at risk of BPD in the first week of life?

Evidence Supporting Clinical Question

Good (most/all on list*)	1 meta-analysis 1 large RCT (hydrocortisone				
Fair (some on list)					
Poor (few on list)					
***See last page for list of "Quality Items"**	**1** **Randomized Controlled Trials (or meta-analyses of RCTs)**	**2** **Studies using concurrent controls non-randomized (or meta-analyses of such studies)**	**3** **Studies using retrospective controls**	**4** **Studies without a control group (e.g. case series)**	**5** **Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models)**
Level of evidence					

Evidence opposing clinical question

Good	1 meta-analysis of 32 trials (dexamethasone)				
Fair					
Poor					
***See last page for list of "Quality Items"**	**1 RCT (or meta-analyses)**	**2 Concurrent controls NR (or meta- analyses)**	**3 Retrospective controls**	**4 No control group (eg. case series)**	**5 Indirect studies**
Level of evidence					

Study	Methods	Sample size and number of centers	Eligibility criteria	Intervention	Results
Baud et al	Randomized controlled trial	523 21 centers Planned sample of 786; DSMB stopped recruitment due to technical and financial issues	24+0-27+6 weeks GA, <24h of age; small for GA (<3rd centile) were excluded	hydrocortisone hemisuccinate 1 mg/kg per day x 7 days, then 0.5 mg/kg per day x 3 days (total: 8.5mg/kg)	Survival without BPD & 60% vs 51% (RR: 1.48, 95%CI 1.02, 2.16) No difference in rates of GI perforation Sub-group analysis: More sepsis in 24-25 weeks in treatment group Follow-up at 2 years: No difference in neurodevelopmental impairment or cerebral palsy$ Sub-group analysis: Better global neurodevelopment in 24-25 weeks

Study	Methods	Sample size and number of centers	Eligibility criteria	Intervention	Results
Peltoniemi et al	Randomized controlled trial	51 (37 followed up at 5-7 years) single-center	501-1250 g, 23+0 to 30+0 weeks GA, ventilated in first 24h after birth	Hydrocortisone 2.0 mg/kg per day x 2 days, 1.5 mg/kg per day x 2 days, 0.75 mg/kg per day x 6 days (total 11.5 mg/kg)	Study interrupted due to higher rate of gastrointestinal perforations in the hydrocortisone treated infants 5-7 years follow-up: Mean verbal IQ and functional IQ not different. Mean performance IQ lower in the hydrocortisone-treated children (88.3 (14.5) versus 99.1 (14.0), p = 0.034)
Doyle, LW et al.	Systematic review	4395 32 trials Follow-up data for 13 trials	Preterm infants at risk of developing BPD	21 trials of dexamethasone 11 trials of hydrocortisone	Earlier extubation, decreased risk of BPD, patent ductus arteriosus (PDA) and severe retinopathy of prematurity (ROP) offset by short (GI perforation) and long-term (increased risk of cerebral palsy) harms Most of the benefits and harms attributed to dexamethasone. Risk of GI perforation attributed to hydrocortisone Methodological quality of follow-up studies limited due to follow-up prior to school age or lack of power

Study	Methods	Sample size and number of centers	Eligibility criteria	Intervention	Results
Shaffer et al.(10)	Individual patient data meta-analysis (includes trials by Baud and Peltoniemi)	982 patients, 4 trials	Preterm infants (under 30 weeks) or birth weight under 1 kg in first 48h of life	Hydrocortisone prophylactic replacement for adrenal insufficiency over 10-15 days (total dose 8.5 to 13.5 mg/kg)	Hydrocortisone treated infants had: 1. Improved survival without BPD at 36 weeks: OR 1.45 (95% CI 1.11-1.9); p=0.007; NNT 11 2. Less death prior to discharge: OR 0.70 (95% CI 0.51-0.97); p=0.0327 3. Less treatment for PDA: OR 0.72 (95% CI 0.56-0.93); p=0.012 4. More late-onset sepsis: OR 1.34 (95% CI 1.02-1.75); p=0.0357 Sub-group analysis: Spontaneous intestinal perforation increased with indomethacin and hydrocortisone but not with hydrocortisone alone Effects on survival to 36 weeks without BPD, death before discharge more pronounced in infants exposed to chorioamnionitis or those born at ≥26 weeks

Reviewer's final comments and assessment based on available literature

- Dexamethasone: dexamethasone initiated < 8 days of age to prevent BPD is not recommended, as adverse effects outweigh the benefits

- Hydrocortisone: hydrocortisone replacement at physiological doses, initiated in the first 24-48h provides benefits in survival without BPD, PDA closure and survival to discharge. The risk of spontaneous intestinal perforation and increased risk of late-onset sepsis do not negate the benefits.

Overall recommendation

- Dexamethasone in the first week of life to prevent BPD should not be given. (Level 1 evidence, good quality)
- Clinicians may consider prescribing a course of low-dose hydrocortisone (physiologic replacement dose) beginning in the first 24-48h after birth, for 10 days, to selected infants at the highest risk of BPD (e.g. < 28 weeks GA, exposure to chorioamnionitis). There may be an increased risk of late-onset sepsis associated with this practice. Hydrocortisone should not be combined with indomethacin prophylaxis. (Level 1 evidence, good quality)

Should early inhaled corticosteroids (fluticasone, budesonide) be provided to babies at risk of BPD in the first week of life?

Evidence neutral to clinical question

Good	2 RCTs 1 systematic review				
Fair					
Poor					
***See last page for list of "Quality Items"**	**1 RCT (or meta-analyses)**	**2 Concurrent controls NR (or meta- analyses)**	**3 Retrospective controls**	**4 No control group (e.g. case series)**	**5 Indirect studies**
Level of evidence					

Evidence opposing clinical question

Good	1 meta-analysis of 32 trials (dexamethasone)				
Fair					
Poor					
***See last page for list of "Quality Items"**	**1 RCT (or meta-analyses)**	**2 Concurrent controls NR (or meta- analyses)**	**3 Retrospective controls**	**4 No control group (eg. case series)**	**5 Indirect studies**
Level of evidence					

Study	Methods	Sample size and number of centers	Eligibility criteria	Intervention	Results and effect size
Bassler et al	Randomized controlled trial	863 (40 centers)	23+0-27+6 weeks GA, <12 hours of life on positive pressure respiratory support	Budesonide by metered-dose inhaler 800 micrograms per day x 14 days; 400 micrograms per day until 32 weeks GA or no longer needing oxygen or respiratory support	Death or BPD[&] reduced in infants who received budesonide: 40% vs 46% (RR: 0.71, 95% CI 0.53, 0.97) Survival without BPD higher in infants who received budesonide: 27.8% vs 38% (p=0.004) Death 16.9% vs 13.8% (p=0.17) Neurodevelopmental disability at 18-22 months corrected: 48.1% vs 51.4% (p=0.40) Death by 18-22 months 19.9% vs 14.5% (p=0.04), favoring the control group
Nakamura et al	Randomized controlled trial	211 (12 centers)	<1000 g, requiring intubation and ventilation in first 24 h after birth	Fluticasone propionate 100 micrograms per day x 6 weeks or until extubation	Death or oxygen dependence at discharge 14% vs 22% (p=0.15)

Study	Methods	Sample size and number of centers	Eligibility criteria	Intervention	Results and effect size
Shah et al (includes studies by Bassler and Nakamura)	Cochrane systematic review	1644 (10 trials)	Preterm infants with birth weight <1501g, on respiratory support and randomized within first 1-2 weeks of life (only 2 trials allowed enrollment from 7-14 days of age)	Budesonide, beclomethasone dipropionate, fluticasone propionate or flunisonide by inhalation for at least 2 weeks	Infants treated with inhaled corticosteroids had: • No difference in BPD overall at 36 weeks: RR: 0.97 (95% CI 0.62 to 1.52) • Less BPD at 36 weeks among survivors: RR 0.76 (95% CI 0.63 to 0.93); NNT 14 (95% CI 8 to 50) • Less death or CLD at 36 weeks: RR 0.86 (95% CI 0.75 to 0.99); (p= 0.04); NNTB 17(95% CI 9 to infinity)

Reviewer's final comments and assessment based on available literature

- Although a reduction in BPD in survivors was observed, more infants had died at the 2-year follow-up point. The reduction in BPD may have been gained at the expense of increased mortality.

Overall recommendation

- The routine use of inhaled corticosteroids to prevent BPD is not recommended. (Level 1 evidence)

Should systemic corticosteroids (dexamethasone, hydrocortisone) be provided to babies with evolving BPD after the first week of life?

Evidence Supporting Clinical Question

Good (most/all on list*)	1 systematic review				
Fair (some on list)					
Poor (few on list)					
***See last page for list of "Quality Items"**	**1 Randomized Controlled Trials (or meta-analyses of RCTs)**	**2 Studies using concurrent controls non-randomized (or meta-analyses of such studies)**	**3 Studies using retrospective controls**	**4 Studies without a control group (e.g. case series)**	**5 Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models)**
Level of evidence					

Evidence Neutral to Clinical Question

Good	2 RCTs				
Fair					
Poor					
***See last page for list of "Quality Items"**	**1 RCT (or meta-analyses)**	**2 Concurrent controls NR (or meta-analyses)**	**3 Retrospective controls**	**4 No control group (e.g. case series)**	**5 Indirect studies**
Level of evidence					

Study	Methods	Sample size and number of centers	Eligibility criteria	Intervention	Results and effect size
Parikh et al	Randomized controlled trial	64, single center	≤1000 g at birth, ventilator dependent at 10-21 days with respiratory index score ≥ 2 or score ≥ 3 with improvement in last 24h	Hydrocortisone succinate 3mg/kg/day x 4 days; 2mg/kg/d x 2 days, 1mg/kg/day x 1 day (cumulative dose: 17mg/kg over 7 days)	Brain volume at 38 weeks: no difference No difference in BPD or duration of mechanical ventilation
Onland et al (abstract)	Randomized controlled trial	372, multi-center	< 30 weeks, ventilated at 7-14 days, respiratory index score ≥ 2.5	Hydrocortisone weaning over 22 days; cumulative dose 72 mg/kg Open label steroids permitted: 28% in treatment group; 56% in placebo group	Death or BPD at 36 weeks 70% vs 74%: RR 0.95(95% CI 0.84-1.08) Mortality at 36 weeks: 16% vs 24%: RR 0.65 (95% CI 0.43-0.99)

Study	Methods	Sample size and number of centers	Eligibility criteria	Intervention	Results and effect size
Doyle LW et al (does not include the trial by Onland et al)	Cochrane systematic review	1424 patients; 21 trials	Preterm infants with evolving or established BPD defined as oxygen-dependent, ventilator-dependent, or both, with or without radiographic changes of BPD.	Dexamethasone or hydrocortisone, IV or per os for 7 to 42 days. Total dose varied across trials	Infants treated with late corticosteroids had: • Facilitated extubation on study day 3, 7 and 28 • Less BPD at 36 weeks: RR: 0.77; 95%CI 0.67, 0.88 • Less need for rescue corticosteroids • Less discharge on home oxygen: RR: 0.71; 95% CI 0.54, 0.94 • Increased risk of severe retinopathy of prematurity (no increase in blindness) • No difference in death at 36w: RR 0.82 (95% CI 0.50-1.35) • No difference in cerebral palsy

Reviewer's final comments and assessment based on available literature

- Hydrocortisone to treat evolving BPD (preterm infants still ventilated at 7-21 days with significant lung disease as per their respiratory index score) did not decrease BPD or death. Final results of a large RCT and results of an ongoing large RCT are awaited and may change the consensus on science.

- Dexamethasone in preterm infants who are greater than 1 week of life and ventilator / oxygen dependent reduced BPD, facilitated extubation but increased the risk of severe ROP. Major neurosensory disability and the combined rate of death or major neurosensory disability were not significantly different between steroid and control groups.

Overall recommendation

- The routine use of dexamethasone for all infants who require assisted ventilation after seven days of age to treat evolving BPD is not recommended. (Level 1 evidence, good quality)
- The benefits of late (after day 7 of life) dexamethasone therapy appear to outweigh the adverse effects for infants who are at high risk of BPD. In these circumstances, low-dose dexamethasone (initial dose 0.15 mg/kg/day to 0.2 mg/ kg/day) should be used in most circumstances in tapering doses over a short course (seven to 10 days). (Level 1 evidence, good quality)
- Hydrocortisone to treat infants at high risk of BPD, after the first week of life, or infants with prolonged ventilator dependence is not recommended. (Level 1 evidence, moderate quality)

Should inhaled corticosteroids (budesonide, fluticasone) be provided to babies with evolving BPD after the first week of life?

Evidence Neutral to Clinical Question

Good	1 systematic review				
Fair					
Poor					
***See last page for list of "Quality Items"**	**1 RCT (or meta-analyses)**	**2 Concurrent controls NR (or meta- analyses)**	**3 Retrospective controls**	**4 No control group (e.g. case series)**	**5 Indirect studies**
Level of evidence					

Reviewer's final comments and assessment based on available literature

- Inhalation corticosteroids did not reduce the separate or combined outcomes of death or BPD. The meta-analyses showed a reduced risk in favor of inhalation steroids regarding failure to extubate at seven days (only 79 infants) and at the latest reported time point after treatment onset. Inhalation steroids did not impact total duration of mechanical ventilation or oxygen dependency. There was a trend toward a reduction in the use of systemic corticosteroids in infants receiving inhalation corticosteroids.
- There was a paucity of data on short- and long-term adverse effects. Results should be interpreted with caution: small total number of randomised

Overall recommendation

- Use of inhaled corticosteroids to treat BPD is not recommended. (Level 1 evidence, good quality)

Lung Health Working Group

"BPD Bundle": Extubation Readiness Predictors

Dr. S. Augustine MBBS, MD, RCPSC (SEAP)
Donna Pilutti RRT, BSc.
Windsor Regional Hospital, Windsor, ON

Dec 4, 2019

Clinical Question

- Population: (In) Preterm intubated infants (at risk for BPD)
- Intervention: (does an) index test
- Comparison: (Vs) clinical judgement
- Outcome: (accurately predict) successful extubation?

Search Strategy (Search terms and databases)

- Librarian assisted scoping search
- EBSCOHost WRH library search platform CINAHL Complete; MEDLINE Complete; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; Cochrane Methodology Register; Cochrane Clinical Answers; Clinical trials.gov; Google Scholar search for 2016 to 2019
- Search limited to after the last published systematic review
- Search term: ‘preterm’ OR ‘premature birth’ OR ‘very low birth weight’ OR ‘extremely low birth weight’ AND ‘extubation’ AND ‘predictors’ OR ‘predictive factors’ OR ‘predictive parameter’
- Grey literature search

List of exclusion criteria

- Term neonates
- Post-extubation test/parameters
- No full text available

Results of Search Strategy (2016-19)

- Total number of articles identified: 808
- Articles after removal of duplicates: 683
- Articles remaining after screening of titles/abstracts: 43
- Articles included after full text review: 16
- Additional articles identified (e.g. from references): 0
- Final number of articles in this review: 16

Classify Level of Evidence for each article

Levels of Evidence for Therapeutic Interventions
LOE 1: Randomised Controlled Trials (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomisation (eg. “pseudo”-randomised) (or meta-analyses of such studies)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (eg. case series)
LOE 5: Studies not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.)

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Methodological quality for each article

Good studies would be expected to have **most/all of the quality items** suggested to assess the type of study (see below).
Fair studies would be expected to have **some of the quality items** suggested to assess the type of study (see below).
Poor studies would be expected to have **few of the quality items** suggested to assess the type of study (see below), but to be of sufficient vale to include for further review.
Specific quality items are listed below for each type of intervention study (http://www.cebm.net/index.aspx?o=1157). For further information, including quality for diagnosis and prognosis questions, see separate document: Defining Quality of Evidence.doc).

Meta-analysis (of LOE 1 or LOE 2 studies) [Scott 2006]

- Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were identified)
- Was study design defined?
- Were selection criteria stated for studies to be included (based on trial design and methodological quality)?
- Were inclusive searches undertaken (using appropriately crafted search strategies)?
- Were characteristics and methodological quality of each trial identified?
- Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?

Randomised Controlled Trials (LOE 1) (http://www.cebm.net/index.aspx?o=1157)

- Was the assignment of patients to treatment randomised?
- Was the randomisation list concealed?
- Were all patients who entered the trial accounted for at its conclusion?
- Were the patients analysed in the groups to which they were randomised?
- Were patients and clinicians "blinded" to which treatment was being received?
- Aside from the experimental treatment, were the groups treated equally?
- Were the groups similar at the start of the trial?

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Methodological quality for each article (cont'd)

- **Studies using controls without randomisation (concurrent LOE 2, or retrospective LOE 3) (http://www.cebm.net/index.aspx?o=1157)**
- Were comparison groups clearly defined?
- Were outcomes measured in the same (preferably blinded) objective way in both groups?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete?
- **Studies without controls (LOE 4)**
- Were outcomes measured in an objective way?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete?
- **Studies not directly related to the specific patient/population (LOE 5)**
- Studies not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.) should have their methodological quality allocated to the type of study (ie. RCTs = good, studies without randomised controls = fair, and studies without controls = poor). Animal studies should also be designated using *italics*.

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Summary of evidence based on LOE and methodological quality

Evidence Supporting Clinical Question

Good	2 RCT	2 Prospective	3 Retrospective		
Fair		2 Prospective			
Poor		1 Retrospective			
	1 RCT (or Meta-analyses of RCTs	2 Studies using concurrent controls non randomized (or meta-analyses of such studies)	3 Studies using retrospective controls	4 Studies without a control group	5 Studies not directly related to the specific patient/population
Level of Evidence					

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical /Physiological/Composite)	Test determined decision to extubate?	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/Neutral/Oppose	Level of Evidence/ Quality
Chawla S et al. 2017 N=926 USA	24 0/7-27 6/7wks	2^0 analysis of RCT (SUPPORT study) Multi center	<u>Baseline & Peri-extubation characteristics</u> BW, GA, Antenatal steroids, 5' APGAR, SGA, pH, peak FiO2 (24h, extubation), PCO2@extubation, Randomization (CPAP vs Surfactant) Successful vs. Failed	No	NR <u>Criteria</u> <u>CPAP</u> PCO2<65 pH >7.2 FiO2 ≤ 0.50 MAP <10 VR ≤ 20bpm <u>Surfactant</u> PCO2< 50 pH >7.3 FiO2 ≤ 0.35 MAP < 8 VR ≤ 20bpm	NR	5 days	<u>Success</u> ↑5'Apgar ↑ pH <u>Failure</u> SGA ↑FiO2 (24h & PTE) ↑PCO2 (PTE) PTE: Prior to Extubation	Support	LOE 1 Good
Dassios T et al. 2019 N= 56 UK	<32 weeks	Prospective observational 2 centers	Vt expired (tidal volume) prior to extubation predicts success	No	Not reported <u>Criteria:</u> FiO2 <0.4 pH >7.25 PaCO2 <65mmHg Breathing rate> ventilator rate	HFNC/ NCPAP	72 hours <u>Failure</u> pH <7.25 PaCO2 >8.5 kPa Sig apnea Freq apnea FiO2 >0.6	<u>Success</u> Vt >4.5 ml (82/58) AUC 0.786 GA NS	Supports use of higher V_T and unadjusted-for-weight V_T	LOE 2 Good

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Dassios T et al. 2017 N=46 UK	<34wks	Prospective study. Single center	Time constant of relaxation during SBT	No	SBT CPAP=PEEP on MV 5-10min Criteria RR above vent rate; PaCO2<63, pH>7.25, FiO2< 0.40.	HFNC or CPAP, determined by physician.	72 hours	Failure T2 ↑ ΔT 1.02 s/cm (94/83) T1, T2: time constants of respiratory muscle relaxation during 1st& last min of SBT ΔT= T2-T1	↑ Time constants predict extubation failure Supports	LOE 2 Good
Gupta D et al. 2019 N=312 USA	Preterm ≤ 1250 g	Retrospective observational study	GA wks PMA at extubation wks. Wt Pre-extubation pH, FiO2, PCO2 Pre-extubation RSS (MAPxFiO2) Pre-extubation Ventilation rate, MAP, PIP, VI VI (Ventilation index) = RRxPaCO2)x (PIP-PEEP)/1000	No	NR Criteria: CMV RR of 16–20, MAP<8cm FiO2 <0.4 pH>7.25 PCO2 <60	NCPAP/NIPPV or nasal cannula	5days Sub group ≥72 hours	Success: GA OR 1.5 PMA @extubation OR 1.04 pH @extubation OR 1.68 Peak RSS <6h OR 0.88 Pre-extubation FiO2 OR 0.93 Model Success: Sens/Spec 60%: 87%/53% 70%: 76%/66% 80%: 54%/81%	Extubation readiness calculator predict extubation success Supports	LOE 3 Good

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Mandhari HA et al. 2019 N=84 Canada	All intubated infants (Preterm & term) Subgroup Preterm ≤32 6/7 wks	Retrospective "Before-after"	<u>Extubation Readiness Test (ERT) protocol</u> <u>2-Stage SBT</u> 3 minutes ETT CPAP THEN 7 minutes CPAP + PS 5- 8 cmH2O (to achieve spont Vt ~ 4ml/kg)	Group 1 (Before): No. At discretion of team Group 2 (After): 2 stage SBT	10 min SBT <u>Criteria</u> CMV RR 45, PEEP 7, FiO2 0.40, PIP 25, VG 3.5-6ml/kg pH> 7.25, PaCo2 35-55 Clinically stable	Infants <1250 g NCPAP and, if required, NIPPV	72 hours	ERT protocol ↓extubation failure from 21.7% to 2.6.	Supports use of ERT	LOE 3 Good
Kanbar LJ et al, 2018 N=189 Canada *Related with 2 Articles by Onu C for same population	< 1250 g	Prospective, observational study	Cardiorespiratory variability. Data obtained from 2nd minute of SBT	No	SBT done for 5 minutes	Not reported	72 hours	Cardiorespiratory vairiablity had AUC= 0.74 (78/71)	Supports	LOE 2, fair

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Manley BJ et al. 2016 N=174 Australia	<32 weeks	2^0 analysis of RCT of post extubation respiratory support (HFNC, CPAP). Multicentre*	<u>Dichotomous:</u> GA, BW, pH, mean FiO2, mean PCO2, APGAR score, pre extubation pH and PCO2, age at extubation. Randomized to HFNC/CPAP, male, antenatal steroids, labor prior to delivery, ROM >24h, clinical ROM, inborn, multiples, intubated in DR Surfactant Rx <u>Continuous/ categorical:</u> GA, BW, BW z-score, APGAR 5 min, Pre-extubation FiO2, pH, PCO2, Age at extubation	No	Not reported	HFNC OR NCPAP, NIPPV with max PIP 25, max RR40, FiO2<0.30	7 days	<u>Success</u> GA OR 2.1 Pre-extubation PCO2: OR 0.93 ROC: AUC=0.81 Pre-extubation FiO2, Age at extubation, BW, BW z score **did not** predict success	Supports use of GA and Pre-extubation CO2	LOE 1, Good

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/ Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Mhanna MJ et al. 2017 N=147 USA	<1500 g	Retrospective cohort study 1 unit	Respiratory Severity Score (RSS)= MAPxFiO2 Severe RF Criteria (≥1) PCO2 >65 pH <7.2 FiO2 >0.5 MAP >10cm	No	Not reported <u>Criteria:</u> PIP< 20 RR MV < 20, PEEP < 5, FiO2< 0.30	NIMV, NCPAP, Low flow NC (< 2L) Physician driven choice	48 hrs	<u>Failure</u> ↑RSS 1.26 Sensitivity= 0.86, Specificity= 0.45 RSS 2.5 Sensitivity= 0.29, Specificity= 0.88 Adjusted OR 1.63, p=0.01 Severe RF Criteria (≥1) Sensitivity 0.25 Specificity 0.88	Respiratory Severity Score predicts extubation failure Supports	LOE 3, Good

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Nakato, A.M et al. 2018 N=45 Brazil	24-36+6 wks	Observational study Single center	Clinical HR, Body Temperature, Incubator Temperature, SpO2 (%), RR EtCO2 (mmHg) Physiological ABG,PaO2/FiO2 Ventilator PEEP (cmH2O),PIP (cmH2O),P plateau (cmH2O),VT (ml/kg), Tinp (s),FiO2, Ve (l/m),Cst (ml/cmH2O) Cdyn (ml/cmH2O),	No	Not reported	CPAP and NIPPV, Bi-level. CPAP mostly used.	72 hours	Failure ↓PEEP, ↓P plateau pressure ↑Heart Rate ↑PaCO2 ↓pH ↑EtCO2	Supports normal Pressure values, ABG's, and capnometry	LoE 2, poor
Silva MGF et al.2019 N=46 Brazil	Preterm	Prospective case control	Heart rate variability	No	Not reported Criteria for extubation: RR MV 20, pH 7.25, FiO2,0.40, PIP ≤20, PEEP 3-5, Ti 0.3-0.5s	Not reported	48 hours	Failure <1000g: Difference in HRV in nonlinear domain (67/87) (HRV less in infants that failed extubation) Whole group: No difference in HRV	Supports HRV use in <1000gram sub group.	LOE 2, Fair

Summary of evidence based on LOE and methodological quality

Evidence Neutral to Clinical Question

Good	1 Systematic review and meta analysis				
Fair			2 Retrospective		
Poor					1 Prospective
	1 RCT (or Meta-analyses of RCTs	2 Studies using concurrent controls non randomized (or meta-analyses of such studies)	3 Studies using retrospective controls	4 Studies without a control group	5 Studies not directly related to the specific patient/population
Level of Evidence					

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/Physiological/Composite)	Test determined decision to extubate?	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Chico et al, Perinatology 2018 N=51 India	Term and preterm	Prospective observational study Single center	GA,BW, PDA, IVH, sepsis, steroids, sedation, blood products, Max PIP, Max FiO2, MAX Alveolar-arterial oxygen gradient, OI, Duration of ventilation, Vt, Compliance, Ve	No	Not reported <u>Criteria</u> PIP <14 RR < 25 pH >7.25, FiO2<0.40, SPo2 ≥90% PaCO2<55 mmHg	CPAP min 5 (<1500 g) Oxyhood for all others with nebulized adrenaline	48 hours	Higher minute ventilation in successful group	Neutral	LOE 5 Poor

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical / Physiological/Composite)	Test determined decision to extubate?	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Goel Net al. 2018 N=66 United Kingdom	All ventilated infants (26.1-35.5wks)	Retrospective observational cohort study	Heart rate characteristics index (HRCi)	No	Not reported	Not reported	72 hours	<u>Failure</u> ↑HRCi baseline epoch & PEE-1 scores (PEE: Postextubation epoch)	Neutral on use of HRCi as standalone variable.	LOE 3, Fair

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW, GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/Neutral/Oppose	Level of Evidence
Shalish W, et al. 2019 Median 49 Canada	<37wks (784g-1934 g; 26.1-32.8wk)	Systematic review and meta-analysis <u>35 studies</u> 12 RCT 22 prospective 1 retrospective 31 single center	RR,% baseline RR after assessing external deadspace, Tidal volume (ml>kg), % baseline tidal volume after adding external deadspace, spontaneous minute ventilation, % time spent with minute ventilation below (125 ml/kg), minute ventilation ratio MVs/MVm, RSBi (RR/Vt, breaths / minute/mL/kg), breathing pattern, Ti, Te, ratio of Ti over total respiratory cycle time, Ti/T to, mean inspiratory flow (Vt/Ti (Ml/kg/s)), lung mechanics- compliance, resistance, WOB (g x cm/kg), Respiratory muscle function, Mean IP, Mean IP adjusted to weight, Max IP, Max IP adjusted for weight, Max EP, Ratio of mean inspiratory pressure/MIP, respiratory drive, mean diaphragmatic pressure, maximum diaphragmatic pressure adjusted for weight, ratio of mean/max diaphragmatic pressure, trans diaphragmatic pressure-time product, tension time index of the diaphragm, tension time index of the diaphragm, tension time index of the respiratory muscles, Vitals-FiO2, HR beats per minute, oxygen saturation%, transcutaneous O2 pressure mmHg, transcutaneous Co2 mmHg	Yes (n=20)	SBT: n=35 < 3min: n= 7 3-10 min: n=14 30min- 2h: n= 8 4-24 hours:n=4 Not specified: n=2 <u>PEEP cm H2O</u> 0: n=6 2-4: n=9 5-6: n=5 Bi: n=2 NS: n=13	Variable.	Anytime(n=1 24 hrs: n=6 48 hrs: n=15 72 hrs: n=11 120 hrs: n= 1 Unknown: n=1	Vt 75/28 MVs (minute ventilation) (84/71) VI (variability index in breathing pattern) (100/8) SBT (95/62) SBT+VI 99/73 Ttdi (diaphrgrmatic tension time index) (86/95) TTmus (tension time index of respiratory muscles(94/75)	Neutral	LOE 1 Good

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Wang S-H et al. 2017 N=68 Taiwan	ELBW	Retrospective observational study	<u>Lung function parameters:</u> MAP, RR, FiO2, PEEP, pH, pCo2, PO2, HC03, SpO2, PIP prior to extubation. PMA at time of extubation	No	Not reported <u>Criteria:</u> MV RR 20, FiO2<0.40, PIP	NCPAP. Escalation to NIPPV	7 days	<u>Failure</u> pH<7.3 No difference HCO3 <18mM/L No diff PMA	Neutral on use of pre extubation arterial pH value and Bicarb monitoring.	LOE 3, Fair,

Summary of evidence based on LOE and methodological quality

Evidence opposing Clinical Question

Good					
Fair		1 Prospective			
Poor		2 Prospective			
	1 RCT (or Meta-analyses of RCTs	2 Studies using concurrent controls non randomized (or meta-analyses of such studies)	3 Studies using retrospective controls	4 Studies without a control group	5 Studies not directly related to the specific patient/population
Level of Evidence					

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical/Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusios Support/ Neutral/ Oppose	Level of Evidence
Iyer NP et al. 2017 N=25 USA	All intubated infants (587g-1768.8g 23.4-30.8)	Observational prospective study	EAdi min, EAdi max, EAdi delta, measured 30 mins prior to extubation and continued for 2 hours after extubation mean data values obtained q30 mins. EAdi was measured with a validated method.	No	NR	Modality at discretion of team. NAVA, SiPAP, NIV PC-IMV, NCPAP, NC PEEP 5.6-7.4 cmH2O	72 hours	<u>Failure</u> ↓ EAdi max and delta (pre to post ex.) Expected higher delta and max EAdi but, in failure group diaphragm activity was lower	Opposes EAdi (NS) pH post, BW, GA (Sig)	LOE 2 poor
Janjindamai W, et al. 2017 N=51 Thailand	<2500g (1020g-1775g) (26.6-34.1)	Observational prospective study Single center	<u>SBT</u> VTe Ve Freq Cstat	No	3 mins CPAP at same PEEP as MV	NIPPV, Oxyhood, RA, NC, CPAP (4-6 cmH2O)	72 hours	<u>Success</u> SBT (98/0) Ratio Ve (SBT/MV)≥0.8 (56/67) Ratio Ve (SBT/MV)≥0.5 (91/33), Ratio freq (SBT/MV)<1.5 (96/17)	Oppose	LOE 2 fair

Summary of Findings from each study

Author (year); Sample size; Country	Population (BW,GA)	Study Design, Single/ Multicenter	Extubation Prediction Index Test (Demographic/Clinical /Physiological/Composite)	Test determined decision to extubate	Extubation Readiness Assessment*: Duration/ Level of PEEP	Post - extubation support	Time of Assessment for Outcome	Outcomes: Successful Extubation Prediction Sensitivity/ Specificity (xx/xx)	Authors' Conclusions Support/ Neutral/ Oppose	Level of Evidence
Singh N et al 2018 N=21 USA	<35 wks	Observational study	Peak Pre extubation EAdi measured for 24 hours in 1 minute intervals prior to extubation (measurement of neural respiratory drive and inspiratory load) .	No	NR Criteria: FiO2<0.40, low MAP 8-10, pH > 7.25, pCO2 45-55mmHg, decided by clinical care team	NIPPV, Bubble CPAP	72 hours	No difference in EAdi between two group	Oppose use of peak EAdi to predict extubation outcome.	LOE 2, Poor,

Reviewer's final comments and assessment based on available literature

- Array of index tests (demographic, clinical, physiological, composite) used to predict extubation readiness in preterm
- Spontaneous breathing trial was the most frequently used
- Mostly explored in a heterogeneous study population with diverse study design, inconsistent peri-extubation practices and timing of outcome assessment, which precludes inter-study comparisons
- Need to standardize protocols for extubation and outcome assessments

Overall recommendation

- Recommendation statement:
  Available data is unchanged and inconclusive requiring further research
- “Overall” Level of Evidence (LOE 1 → LOE 5)
  LOE 1 (n=3)
  LOE 2 (n=8)
  LOE 3 (n=5)
- “Overall” Quality of Evidence
  A: Good (n=8)
  B: Fair (n=5)
  C: Poor (n=4)

Lung Health Working Group

"BPD Bundle" Revision

MIST/LISA Literature Review

BC Women's Hospital

Conflicts of Interest

No conflicts of interest and no disclosures were needed by the reviewers

Clinical Question

- In neonates requiring surfactant replacement therapy, does Minimally Invasive Surfactant Technique or Less Invasive Surfactant Administration reduce the incidence of Bronchopulmonary Dysplasia?

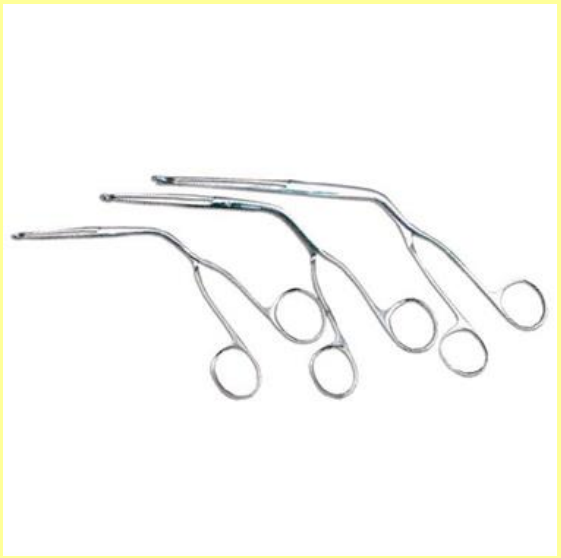
  - **P**opulation: In neonates meeting the clinical indications for Exogenous Surfactant Replacements Therapy. (Synonyms: RDS, Respiratory Distress Syndrome, Surfactant, Neonates)
  - **I**ntervention: Minimally Invasive Surfactant or Less Invasive Surfactant Administration (Synonyms: MIST, LISA)
  - **C**omparison: Intubate – Surfactant – Extubate Method or Surfactant Replacement Therapy through intubation (Synonyms: INSURE, conventional therapy)
  - **O**utcome: Incidences of Bronchopulmonary Dysplasia (Synonyms: BPD)

What is LISA/MIST?

The use of a thin catheter to instill surfactant while the patient is breathing spontaneously

Cologne Method

- The Cologne method generally has a 4 to 5F feeding catheter and Magill forceps to introduce the catheter.



Hobart Method

- The Hobart method does not require Magill forceps, but instead uses a stiffer angiocatheter

Search Strategy (Search terms and databases)

- We conducted an online search through web databases including Cochrane Library, MEDLINE, Scopus, Web of Science, and Google Scholar. Key terms were imputed regarding our research topic: “MIST”, “LISA”, “Minimally Invasive Surfactant Technique”, “Less Invasive Surfactant Administration”, “Bronchopulmonary Dysplasia”.

List of exclusion criteria

- Articles that were duplicates
- Articles that did not state BPD as a primary or secondary outcome
- Articles that did not state the specific method of surfactant administration
- Articles that were not primary research for less invasive surfactant administration (i.e LISA or MIST)

Results of Search Strategy

- Total number of articles identified: 59
- Articles after removal of duplicates: 51
- Articles remaining after screening of titles/abstracts: 47
- Articles included after full text review: 29
- Additional articles identified (e.g. from references): 3

- Final number of articles in this review: 32

Summary of Evidence based on Methodological Quality and LOE

Evidence Supporting Clinical Question

Good (most/all on list*)	1. Aldana-Aguirre et al(2017) 2. Isayama et al (2016) 3. Kanmaz et al (2012) 4. Rigo et al (2016) 5. Wu et al (2017)	1. Gopel et al (2015) 2. Hartel et al (2018) 3. Kirbs et al (2010) 4. Langhammer et al (2018)	1. Aguar et al (2014) 2. Klebermass-Schrehof et al (2013)		
Fair (some on list)			1. Dargaville et al (2018) 2. Krajewski et al (2014)		
Poor (few on list)			1. Kribs et al (2007)		1. Dargaville (2012) 2. Foglia et al (2017) 3. Gyu-Hong Shim (2017) 4. Sweet et al (2019)
***See last page for list of "Quality Items"**	**1** **Randomized Controlled Trials (or meta-analyses of RCTs)**	**2** **Studies using concurrent controls non- randomized (or meta- analyses of such studies)**	**3** **Studies using retrospective controls**	**4** **Studies without a control group (e.g. case series)**	**5** **Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models)**
Level of evidence					

Summary of Evidence based on Methodological Quality and LOE

Evidence Neutral to Clinical Question

Good	1. Ali et al (2016) 2. Bao et al (2015) 3. Gopel et al (2013) 4. Heidarzadeh et al (2013) 5. Kribs et al (2015) 6. Lau et al (2017) 7. Mahammadizadeh et al (2015) 8. Mosayebi et al (2017) 9. Olivier et al (2017)		1. Berneau et al (2018) 2. Choupani et al (2018)		
Fair			1. Dargavill et al (2011) 2. Ramos-Navarro et al (2015)		
Poor				1. Gengaimuthu (2018)	1. More et al (2014)
***See last page for list of "Quality Items"**	**1** **RCT (or meta-analyses)**	**2** **Concurrent controls NR (or meta- analyses)**	**3** **Retrospective controls**	**4** **No control group(e.g. case series)**	**5** **Indirect studies**
Level of evidence					

Summary of Evidence based on Methodological Quality and LOE

Evidence Opposing Clinical Question

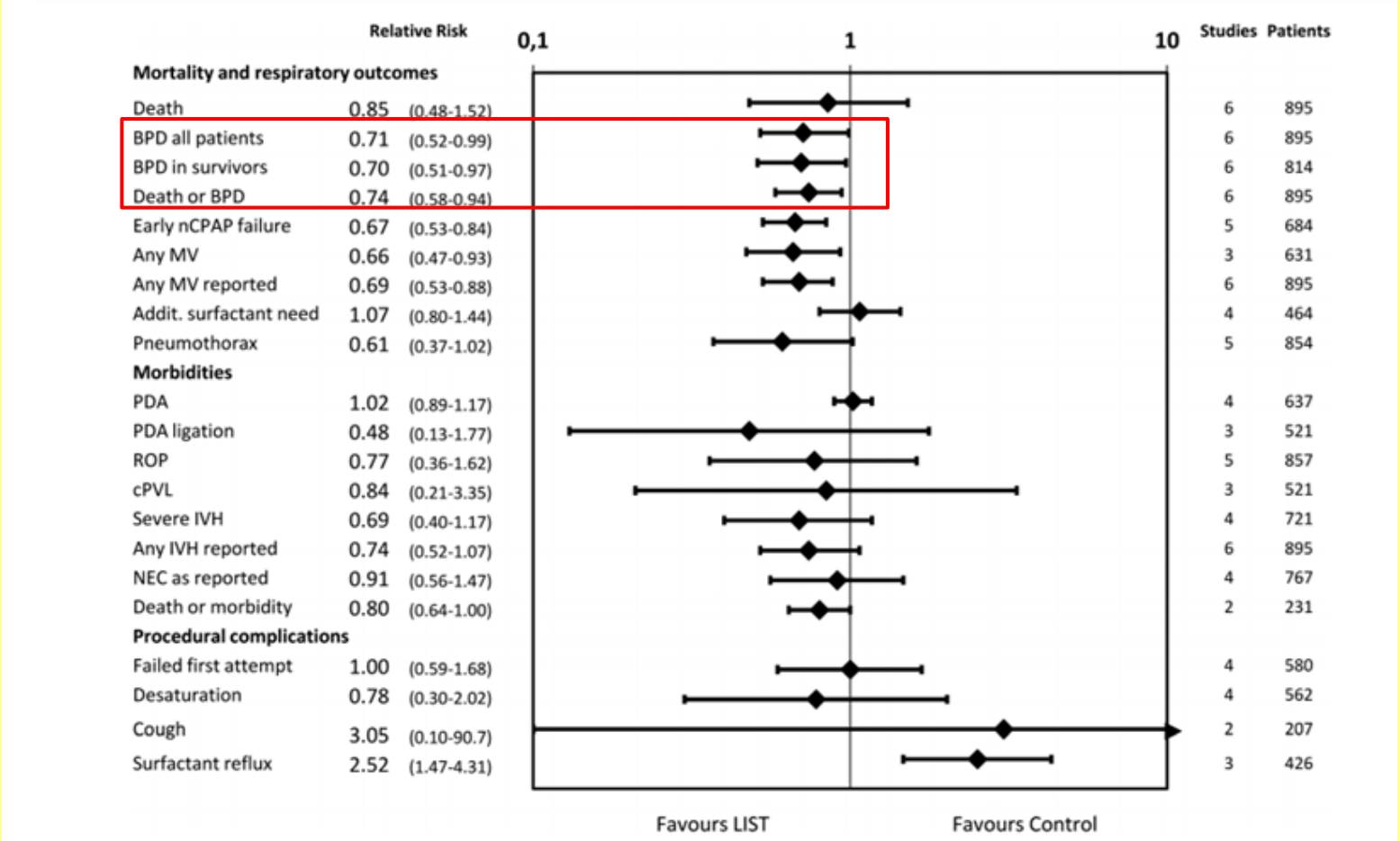
Good					
Fair					
Poor					
***See last page for list of "Quality Items"**	**1 RCT (or meta-analyses)**	**2 Concurrent controls NR (or meta-analyses)**	**3 Retrospective controls**	**4 No control group (eg. case series)**	**5 Indirect studies**
Level of evidence					

Article in Support of LISA/MIST

Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis

Rigo, V., Lefebvre, C., & Broux, I. (2016)

- 6 RCTs comparing LISA to various other methods
- BPD reduced all patients, RR = 0.71 (0.52 to 0.99),with an NNT of 21.
- BPD in survivors, RR = 0.70 (0.51-0.97), NNT 19.
- BPD or death, RR = 0.74 (0.58 - 0.94), NNT 15.



Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis

Rigo, V., Lefebvre, C., & Broux, I. (2016)

- Subgroup analysis comparing specifically other types of managements
- Reduction in death or BPD for LIST versus InSurE, NNT of 11
- Reduction in need of mechanical ventilation, NNT of 5

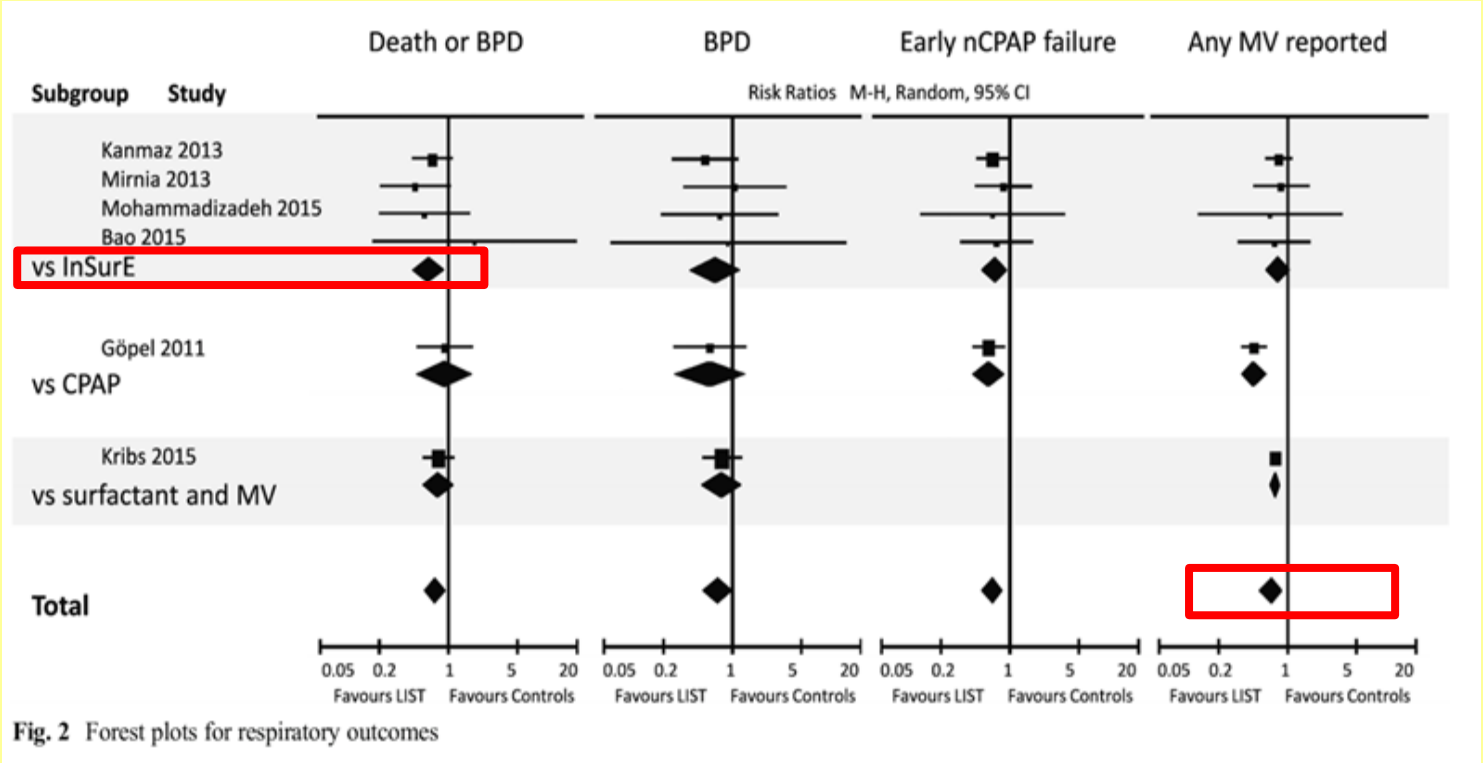


Fig. 2 Forest plots for respiratory outcomes

Impact of Minimally Invasive Surfactant Therapy in Preterm Infants at 29–32 Weeks Gestation

Dargaville, P. A., Ali, S. K., Jackson, H. D., Williams, C., & Paoli, A. G. D. (2018)

- Specific analysis of infants at 29-32 weeks gestation
  - "The use of CPAP at the outset, without prior intubation and surfactant therapy, is common within this gestation range"
  - Generally, intubation solely for surfactant administration is necessary

- MIST versus conventional management from other centres in the Australian and New Zealand Neonatal Network (ANZNN)
  - MIST did have a lower BPD rate (1.7% vs 5.8%, p < 0.05)
  - BPD or death (2.1% vs 6.7%, p < 0.05)

Table 2. Resource consumption and outcomes

	RHH epoch 1	RHH epoch 2	Other ANZNN centres
Timespan	Jan 2004–Feb 2009	Mar 2009–Dec 2015	Jan 2007–Dec 2013
n	162	291	12,080
Surfactant therapy	31 (19)[b]	67 (23)[b]	4,230 (35)
Surfactant therapy via endotracheal tube	31 (19)[b]	32 (11)[a,b]	4,207 (35)
Duration of CPAP, days	2.0 (0.71–4.0)	2.5 (1.1–4.4)	2.2 (0.79–5.5)
Any MV	40 (25)[b]	50 (17)[b]	4,776 (40)
Duration of MV, days	0 (0–0)[b]	0 (0–0)[a,b]	0 (0–0.71)
Average duration of MV, days per infant[c]	0.64	0.43	0.71
Duration of MV + CPAP, days	2.5 (0.88–5.3)	2.8 (1.2–4.8)	2.6 (0.88–6.1)
Length of hospital stay, days	44 (35–57)	44 (36–54)	43 (33–54)
Pneumothorax	13 (8.0)[b]	7 (2.4)[a]	284 (2.4)
BPD	3 (1.9)[b]	5 (1.7)[b]	699 (5.8)
Died	0 (0)	1 (0.3)	117 (1.0)
Died or BPD	3 (1.9)[b]	6 (2.1)[b]	810 (6.7)
IVH grade III/IV	2 (1.2)	1 (0.3)	110 (0.91)

Data are presented as the median (IQR) or *n* (%).
[a] Differs from epoch 1, $p < 0.05$. [b] Differs from ANZNN, $p < 0.05$. [c] Calculated as total days of MV in all infants (excluding outliers ventilated for ≥14 days), divided by the total number of infants.

Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants

Göpel, W., Kribs, A., Härtel, C., Avenarius, S., Teig, N., Groneck, P., … . (2015)

- Large multicentre trial enrolling 1103 infants across 37 centres
- BPD rates 12% vs 18% (P < 0.01)
- BPD or death rates 14% vs 21% (p < 0.01).
- No greater incidences of complications, i.e pneumothorax, PVL, IVH, NEC, or ROP

Table 3 Outcome data

	Matched controls (n = 1103)	LISA-treated infants (n = 1103)	Nominal p*	Adjusted p
Pneumothorax (%, n/n)	7 70/1077	6 61/1101	0.34	1
Bronchopulmonary dysplasia (%, n/n)	18 200/1098	12 134/1101	7.9×10^{-5}	0.001
Bronchopulmonary dysplasia or death (%, n/n)	21 232/1103	14 157/1103	2.8×10^{-5}	<0.001
IVH grade III or IV (%, n/n)	6 64/1097	5 55/1092	0.41	1
Periventricular leukomalacia (%, n/n)	4 38/1077	3 27/1084	0.15	1
Surgery for necrotising enterocolitis or focal intestinal perforation (%, n/n)	5 50/1090	6 60/1098	0.34	1
Laser or cryotherapy for retinopathy of prematurity (%, n/n)	4 38/1098	2 22/1101	0.035	0.56
Severe complications† (%, n/n)	16 171/1103	12 137/1103	0.037	0.59
Death (%, n/n)	4 43/1103	3 31/1103	0.15	1

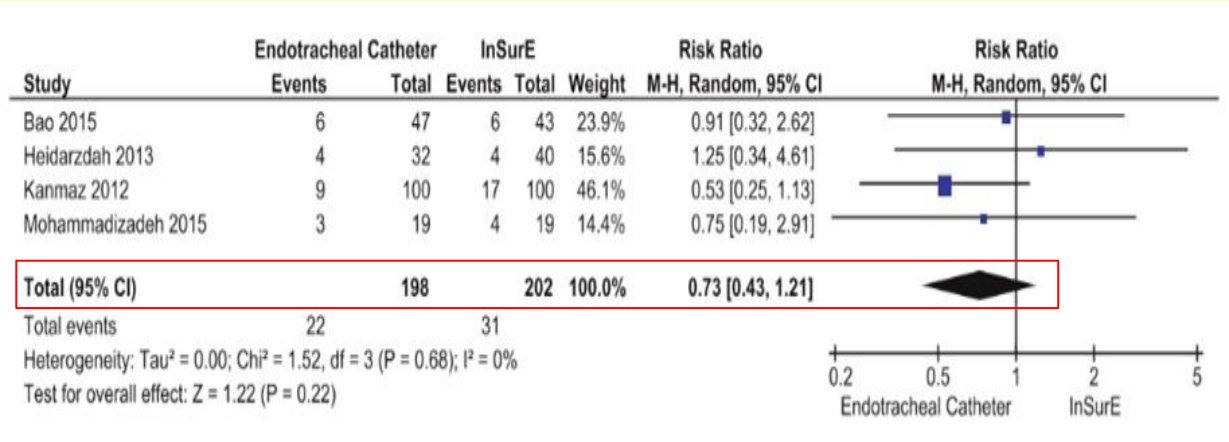
Nominal p-values are given as exact values (e.g.: $3.9 \times 10^{-4} = 0.00039$). Adjusted p-values were corrected for 16 comparisons.
*Chi-square test.
†Severe complications were defined as IVH grade III or IV, periventricular leukomalacia, surgical treatment of necrotising enterocolitis or focal intestinal perforation, laser or cryotherapy of retinopathy of prematurity, death and a combination of any of these complications.

Articles Neutral to LISA/MIST

New modalities to deliver surfactant in premature infants: a systematic review and meta-analysis

Ali, E., Wahed, M. A., Alsalami, Z., Abouseif, H., Gottschalk, T., Rabbani, R., … Abou-Setta, A. M. (2016).

- Overall BPD rates did not differ between MIST/LISA group vs InSurE
- Limited number of studies included, with weight favoring 1 trial



Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants A Randomized Clinical Trial

Kribs, A., Roll, C., Göpel, W., Wieg, C., Groneck, P., Laux, R., … Roth, B. (2015)

- Survival without BPD did not show significant increase (67.3% vs 58.7%, p = 0.20)
  - Noted that BPD rates in general were lower for control vs historical averages
- Other outcomes had benefit
  - Survival without major complications (50.5% vs 35,6%, p = 0.02)
  - Pneumothorax incidences were lower (4.8% vs 12.6%, p = 0.04)

Table 2. Primary Outcome and Predefined Secondary Outcomes

Characteristic	Group, No. (%)		Absolute Risk Reduction (95% CI)	*P* Value[a]
	Intervention (n = 107)	Control (n = 104)		
Survival without BPD[b]	72 (67.3)	61 (58.7)	8.6 (−5.0 to 21.9)	.20
Death	10 (9.3)	12 (11.5)	2.2 (−11.5 to 15.6)	.59
Surviving infants with BPD	25 (23.4)	31 (29.8)	7.9 (−6.6 to 22.1)	.19
Survival without major complications[c]	54 (50.5)	37 (35.6)	14.9 (1.4 to 28.2)	.02*
Mechanical ventilation[d]				
All infants	80 (74.8)	103 (99.0)[e]	24.3 (16.2 to 33.8)	<.001
Gestation, wk				
23	14/15 (93.3)	9/9 (100.0)	6.7 (−26.6 to 33.5)	>.99
24	24/26 (92.3)	30/31 (96.8)	4.5 (−9.9 to 22.3)	.59
25	24/31 (77.4)	41/41 (100.0)	22.6 (9.4 to 41.1)	.002
26	18/35 (51.4)	23/23 (100.0)	48.6 (30.3 to 66.0)	<.001
Pulmonary outcome[d]				
Duration of mechanical ventilation, median (IQR), d				
All infants	5 (0 to 17)	7 (2.5 to 19.5)		.031, .029[f]
Intubated infants	8 (4 to 20)	7 (3 to 20)		.27, .30[f]
Any respiratory support (MV or CPAP), median (IQR), d	47 (30 to 60)	48.5 (35 to 64)		.60, .22[f]
Supplemental oxygen (all infants), median (IQR), d	22 (5 to 53)	35 (9 to 56)		.36
Pulmonary hemorrhage	4 (4.8)	6 (5.8)		.53
Pneumothorax	5/105 (4.8)	13/103 (12.6)		.04
Clinical BPD	14/97 (14.4)	23/92 (25.0)		

A Randomized Trial Comparing Surfactant Administration Using InSurE Technique and the Minimally Invasive Surfactant Therapy in Preterm Infants (28 to 34 Weeks of Gestation) with Respiratory Distress Syndrome

Mosayebi, Z., Kadivar, M., Taheri-Derakhsh, N., Nariman, S., Marashi, S. M., & Farsi, Z. (2017)

- BPD did not significantly different in both groups

- Mean FiO2 decreased significantly in MIST compared to InSuRE (42.5% vs 48.4%, p = 0.009)

Secondary Outcomes			
Pulmonary hemorrhage, n (%)	1 (3.8%)	0 (0%)	0.49
Intra ventricular hemorrhage (> grade 2), n (%)	1 (3.8%)	0 (0%)	0.49
Patient ductus arteriosus, n (%)	3 (11.5%)	3 (11.1%)	1.000
Broncho pulmonary dysplasia, n (%)	1 (3.8%)	0 (0%)	0.49
Retinopathy of prematurity (> stage 2), n (%)	0 (0%)	0 (0%)	1.000
Necrotizing enterocolitis, n (%)	1 (3.8%)	0 (0%)	0.49
Length of stay in NICU (D)	9 (10.4)	7.3 (7.2)	0.81
Death, n (%)	0 (0%)	1(3.7%)	0.98

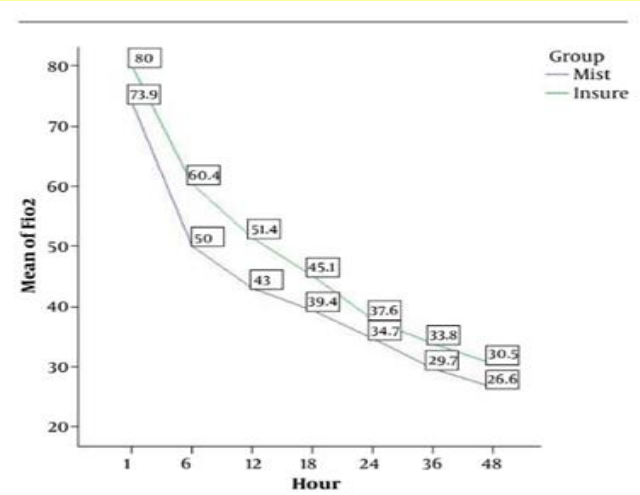


Figure 2. Mean FiO_2 Requirement in Each Group Within 48 Hours of Surfactant Administration

Reviewer's final comments and assessment based on available literature

- LISA/MIST may reduced the incidence of BPD due to the exposure of positive pressure ventilation
- LISA/MIST has been postulated to increase surfactant deposition due to spontaneous breathing by infants
- Although slightly more technical in nature, LISA/MIST does not have any long term complications
- Available with the current material used in practice

Overall recommendation

- Recommendation statement: LISA/MIST can be a viable alternative for surfactant administration for those infants with RDS to limit the exposure of mechanical ventilation.

- “Overall” Level of Evidence: 2

- “Overall” Quality of Evidence: Good

Lung Health Working Group

"BPD Bundle" Revision

Tidal Volume recommendations

Ayman Abou Mehrem & Dan McGovern

Volume-targeted versus pressure-limited ventilation in neonates (Review)

Klingenberg C, Wheeler KI, McCallion N, Morley CJ, Davis PG

Table 1 Documented benefits of volume-targeted ventilation. Data from Cochrane meta-analysis 2017 (Ref 2)

	Relative risk or mean difference	95% CI	NNTB (95% CI)
Death or BPD at 36 weeks PMA	0.75	0.53 to 1.07	NA
BPD at 36 weeks PMA	0.73	0.59 to 0.89	8 (5 to 20)
Grade 3–4 IVH	0.53	0.37 to 0.77	11 (7 to 25)
PVL ± severe IVH	0.47	0.27 to 0.80	11 (7 to 33)
Pneumothorax	0.52	0.31 to 0.87	20 (11 to 100)
Hypocapnia	0.49	0.33 to 0.72	3 (2 to 5)
Days of mechanical ventilation	−1.35	−1.83 to −0.86	

Clinical Question

- Does tidal volume requirement differ by GA and/or chronological age in preterm infants?

Search Strategy (Search terms and databases)

- Databases: Medline AND Cochrane Database
- Terms: tidal volume AND (preterm OR premature)

List of exclusion criteria

- Studies in languages other than English.
- Animal studies

Results of Search Strategy

- Total number of articles identified: Medline 592; Cochrane 35
- Articles after removal of duplicates:
- Articles remaining after screening of titles/abstracts:
- Articles included after full text review:
- Additional articles identified (e.g. from references):

- Final number of articles in this review: 12

Summary of Findings: Tidal Volume in DR

- Study 1 (Mian 2015):
  - Title: Spontaneously Breathing Preterm Infants Change in Tidal Volume to Improve Lung Aeration Immediately after Birth
  - Observational
  - Population: N = 30, GA mean (SD) = 30 (1), spontaneously breathing
  - First 100 breath in DR.
  - Vt: first 30 breaths 5-6 ml/kg, next 20 breaths 7-8ml/kg, then 4-6 ml/kg.

  - Conclusion: This study does not address the target Vt for various GA, but it shows that the spontaneously breathing preterm infants have mean Vt of 4-6 ml/kg.

Summary of Findings: Tidal Volume in DR

- Study 2 (Mian 2019):
  - Title: Impact of delivered tidal volume on the occurrence of intraventricular haemorrhage in preterm infants during positive pressure ventilation in the delivery room
  - Observational
  - Population: N=165 infants; GA < 29 wks (mean 26 wks), received PPV for 120 s at least in DR
  - V_t < 6 (N = 41) vs. > 6 ml/kg (N = 124)
  - V_t median (IQR):
    - V_t < 6 ml/kg group = 5.3 (4.6-5.7) mL/kg
    - V_t > 6 ml/kg group = 8.7 (7.3-10.6) mL/kg
  - Severe IVH was higher in the group with V_t > 6 ml/kg (27 vs. 6%)
  - Conclusion: avoiding Vt larger than 6 ml/kg during DR management is warranted.
  - Limitations:
    - The group with Vt > 6 ml/kg actually received much higher Vt, 75% of babies receiving ≥ 7.3 ml/kg.
    - It would have been helpful to know the Vt of those who developed Severe/Any IVH vs who did not.
    - No mention of EtCO2.

Summary of Findings: Vt during first 48 h in the NICU

- Study 3 (Dawson 2005):
  - Title: Volume-targeted ventilation and arterial carbon dioxide in neonates.
  - Retrospective study of prospectively collected data
  - Population: 38 infants; GA < 33 weeks, mean (SD) 26.9 (2.1) weeks; ventilated in the first 48 h.
  - All infants were ventilated with VG mode targeting 4 ml/kg (range = 2.9-5.1).
  - Severe hypocarbia (< 25 mmHg) or hypercarbia (>65 mmHg) occurred only in 8% of first gas.
  - Conclusion: targeting 4 ml/kg is reasonable.
  - Limitations:
    - Definition of hypocarbia is generous
    - They did not correlate PCO2 and baby's wt or GA

Summary of Findings: Inflammatory markers and VG

- Study 4 (Lista 2006):
  - Title: Lung inflammation in preterm infants with respiratory distress syndrome: effects of ventilation with different tidal volumes.
  - Randomized unblinded.
  - Population: 30 infants 25 – 32 weeks (mean 27 weeks), enrollment at 1 hour of life.
  - SIPPV +VG (3 ml/kg) vs SIPPV +VG (5ml/kg)
  - VG 3ml/kg: longer MV, higher TNF-α and IL-8
- Conclusion: avoid low tidal volume (3 ml/kg)
- Limitation:
  - Small sample size.
  - No correlation with BPD.

Summary of Findings: WOB and VG in the first 8 days

- Study 5 (Patel 2009):
  - Title: Work of breathing and different levels of volume-targeted ventilation
  - Randomized cross-over study
  - Population: 20 infants, 25-36 weeks, 1-8 days of age
  - AC or SIMV at baseline, added VG of 4, 5, 6 ml/kg in a randomized order.
  - VG 6 ml/kg associated with lower WOB measured by transdiaphragmatic pressure-time product and less RR.
- Conclusion:
  - Higher VG resulted in lower WOB during the first week of life.
- Limitations:
  - Small sample size
  - Heterogeneous group of babies.

Summary of Findings: IDS and VG in first 2 days

- Study 6 (Nassabeh-Montazami 2009):
  - Title: The impact of instrumental dead-space in volume-targeted ventilation of the extremely low birth weight (ELBW) infant.
  - Retrospective study
  - Population: 38 babies; BW< 800g, GA mean 25.45±1.4 (range 24–29) wks; ventilated with VG 4-6 ml/kg in the first 48 hrs of life with normocarbia (PCO_2 35-55).
  - Measured instrumental dead space: internal volume of a 2.5 mm ET cut to a 10 cm length and attached to a connector + in-line suction catheter + flow sensor = 2.7 ml
  - Estimated anatomical dead space = 0.5 ml/kg
  - The mean VT/kg to maintain normocarbia: birth weight ≤ 500g = 5.92±0.30 mL, birth weight ≥ 700g = 4.69±0.45 mL
- Conclusion:
  - Adequate VG should be adjusted for birth weight.
- Limitations:
  - Retrospective
  - Limited to the equipment used in their institution.

Summary of Findings: VG in the first 3 weeks

- Study 7 (Keszler 2009):
  - Title: Evolution of tidal volume requirement during the first 3 weeks of life in infants <800 g ventilated with Volume Guarantee
  - Retrospective study
  - Population: 26 infants; BW< 800g, ventilated with VG 4-6 ml/kg for the first 3 weeks of life with normocarbia (first week 35-55; later 45-65 mmHg)
  - Reviewed measured tidal volume at DOL 1-2, 5-7, 14-17, and 18-21.
  - Measured Vt rose from 5.15 (0.62) ml/kg on days 1–2 to 6.07 (1.4) ml/kg on days 18–21.
- Conclusion:
  - Vt requirement rises with advanced postnatal age despite permissive hypercarbia.
  - Heterogeneity in Vt and PCO2 increased with increased age.
- Limitation:
  - Retrospective
  - Leak may have developed over time (unlikely to be a contributor)

Summary of Findings from each study

- Study 8 (Armstrong 2011):
  - Title: Distribution of tidal ventilation during volume-targeted ventilation is variable and influenced by age in the preterm lung
  - Observational
  - Population: GA< 32 weeks; Age 24 hours – 10 weeks
  - SIPPV + VG
  - Infants older than 7 days required higher VG.
- Excluded: not really relevant

Summary of Findings: GA to DS/VT in DOL 1

- Study 9 (Neumann 2015):
  - Title: Influence of gestational age on dead space and alveolar ventilation in preterm infants ventilated with volume guarantee
  - Observational
  - Population: 43 infants; 23-32 weeks (mean (SD) 27.5(2.6)), on DOL 1
  - Ventilated with VG 4-5 ml/kg
  - V_D/V_T ratio is inversely associated with GA
  - When the appliance dead space was subtracted, the association disappeared.
- Conclusion:
  - The ratio of V_D to V_T is higher in younger GA.

Summary of Findings: Pulmonary dead space

- Study 10 (Dassios 2017):
  - Title: Determinants of pulmonary dead space in ventilated newborn infants
  - Secondary analysis of observational study
  - Population: 61 infants (15 term, 46 preterm < 34 wks tested at median DOL 8)
  - Measure pulmonary dead space (V_D), defined as anatomical dead space + alveolar dead space, and identify its predictors
  - V_D/Kg correlated to GA, BW, PMA, ventilation days, and T_{PTEF}/T_E
  - V_D/Kg is higher in preterm infants who develop BPD; however, timing of test is different: Preterm no-BPD DOL median 2 (1–4), and Preterm-BPD DOL median 24 (8–61)
- Conclusion:
  - Numerous factors such as gestation, anthropometry and duration of ventilation influence pulmonary dead space and thus an optimum tidal volume will differ according to the underlying demographics and respiratory status

Summary of Findings from each study

- Study 11 (Dassios 2018):
  - Title: Physiological and anatomical dead space in mechanically ventilated newborn infants
  - Secondary analysis of observational study
  - Population: 56 infants (11 term tested at median DOL 2, 45 preterm < 34 wks tested at median DOL 11)
  - Measure anatomical and alveolar dead space.
  - $V_{D\text{-}Ana}$/kg was related to postmenstrual age, birth weight, and weight at measurement
  - $V_{D\text{-}Alv}$/kg was related to postmenstrual age, birth weight, and weight at measurement, and related to days of ventilation.

Summary of Findings: VG and WOB

- Study 12 (Hunt 2019):
  - Volume targeting levels and work of breathing in infants with evolving or established bronchopulmonary dysplasia
  - Randomised crossover study
  - Population: 18 infants; GA median (range) 26 (24-30) weeks; ventilated beyond 1 week of age
  - Studied at DOL median (range) = 18 (7-60)
  - Baseline, then VG of 4, 5, 6, 7 ml/kg
  - WOB measured by transdiaphragmatic pressure-time product was lowest at VG 7ml/kg
- Conclusion:
  - VG of 7 ml/kg may be tried in babies with evolving or established BPD.
- Limitation:
  - Small sample
  - Did not specify if there is a difference depending on DOL
  - Did not correlate with BPD

Reviewer's final comments and assessment based on available literature

- The ratio of V_D/V_T should be taken into account when ventilating ELBW infants.
- Infants with BW < 800g should be ventilated with VG of 4.5 – 5.5 ml/kg with the higher VG for smaller infants.
- Infants with evolving BPD requires higher VG. Consider 6-7 ml/kg after 2-3 weeks of life.
- This strategy was not compared to HFOV.

Summary of evidence based on LOE and methodological quality

Clinical Question: Does tidal volume requirement differ by GA and/or chronological age in preterm infants?

Summary of evidence

Evidence Supporting Clinical Question

Good					
Fair					
Poor				6, 7, 9, 10, 11	
	1	2	3	4	5
Level of evidence					

Summary of evidence based on LOE and methodological quality

Clinical Question: Does tidal volume requirement differ by GA and/or chronological age in preterm infants?

Summary of evidence

This evidence added to the body of knowledge used to make VT recommendations without addressing the clinical question specifically.

Good					
Fair					
Poor	4			1, 2, 3, 5, 12	
	1	2	3	4	5
Level of evidence					

Overall recommendation

- Recommendation statement:
  - **Numerous factors such as gestation, anthropometry and duration of ventilation influence pulmonary dead space and thus an optimum tidal volume will differ according to the underlying demographics and respiratory status[10].**
  - **BW < 800g: VT = 4.5 – 5.5 ml/kg with the higher VT for smaller infants (fixed flow sensor dead space).**
  - **Larger preterms: VT = 4 - 5 ml/kg**
  - **Preterms with evolving BPD (2+ weeks old): 5.5 - 6.0 ml/kg (increased anatomical and alveolar dead space). In infants with evolving BPD, selection of mode of ventilation should follow careful assessment of clinical status and radiological findings such as presence of atelectasis or pulmonary interstitial emphysema. High frequency oscillatory or jet ventilation are frequently used in those infants. Conventional ventilation might be used as well; however, some observational studies showed older preterm infants have increased alveolar dead space and may require VT > 6 ml/kg with reduced work of breathing with VG of 7 ml/kg. BPD rates were not reported with this strategy.**
- "Overall" Level of Evidence (LOE 1 → LOE 5)
  - **4**
- "Overall" Quality of Evidence
  - A: Good
  - B: Fair
  - C: Poor **Mostly small observational studies with no controls.**

References

1. Mian Q, Cheung P-Y, O'Reilly M, Pichler G, van Os S, Kushniruk K, Aziz K, Schmölzer GM. **Spontaneously Breathing Preterm Infants Change in Tidal Volume to Improve Lung Aeration Immediately after Birth.** *J Pediatr* 2015;167:274-8.
2. Mian Q, Cheung P, O'Reilly M, et al. **Impact of delivered tidal volume on the occurrence of intraventricular haemorrhage in preterm infants during positive pressure ventilation in the delivery room.** *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2019;104:F57-F62
3. Dawson, C. and Davies, M. W. (2005), **Volume-targeted ventilation and arterial carbon dioxide in neonates.** *Journal of Paediatrics and Child Health*, 41: 518-521. doi:10.1111/j.1440-1754.2005.00695.x
4. Lista G, Castoldi F, Fontana P, et al. **Lung inflammation in preterm infants with respiratory distress syndrome: effects of ventilation with different tidal volumes.** *Pediatr Pulmonol* 2006;41:357–63.
5. Patel DS, Sharma A, Prendergast M, Rafferty M, Greenough A. **Work of Breathing and Different Levels of Volume-Targeted Ventilation**. *Pediatrics* 2009;123:e679–e684
6. Nassabeh-Montazami S, Abubakar KM, Keszler M. **The impact of instrumental dead-space in volume-targeted ventilation of the extremely low birth weight (ELBW) infant**. *Pediatr Pulmonol* 2009;44:128–33.

References

7. Keszler M, Nassabeh-Montazami S, Abubakar K. **Evolution of tidal volume requirement during the first 3 weeks of life in infants <800 g ventilated with Volume Guarantee**. *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2009;94:F279-F282.
8. Armstrong, R.K., Carlisle, H.R., Davis, P.G. et al. **Distribution of tidal ventilation during volume-targeted ventilation is variable and influenced by age in the preterm lung**. *Intensive Care Med* (2011) 37: 839. https://doi.org/10.1007/s00134-011-2157-9
9. Neumann RP, Pillow JJ, Thamrin C, Larcombe AN, Hall GL, Schulzke SM. **Influence of gestational age on dead space and alveolar ventilation in preterm infants ventilated with volume guarantee**. *Neonatology*. 2015;107:43–49.
10. Dassios T, Kaltsogianni O, Greenough A. **Determinants of pulmonary dead space in ventilated newborn infants**. *Early Hum Dev*. 2017;108:29–32.
11. Dassios, T, Dixon, P, Hickey, A, Fouzas, S, Greenough, A. **Physiological and anatomical dead space in mechanically ventilated newborn infants**. *Pediatric Pulmonology*. 2018; 53: 57– 63. https://doi.org/10.1002/ppul.23918
12. Hunt K, Dassios T, Ali K, et al. **Volume targeting levels and work of breathing in infants with evolving or established bronchopulmonary dysplasia**. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F46– F49.

Classify Level of Evidence for each article

Levels of Evidence for Therapeutic Interventions
LOE 1: Randomised Controlled Trials (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomisation (eg. “pseudo”-randomised) (or meta-analyses of such studies)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (eg. case series)
LOE 5: Studies not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.)

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Methodological quality for each article

Good studies would be expected to have **most/all of the quality items** suggested to assess the type of study (see below).
Fair studies would be expected to have **some of the quality items** suggested to assess the type of study (see below).
Poor studies would be expected to have **few of the quality items** suggested to assess the type of study (see below), but to be of sufficient vale to include for further review.
Specific quality items are listed below for each type of intervention study (http://www.cebm.net/index.aspx?o=1157). For further information, including quality for diagnosis and prognosis questions, see separate document: Defining Quality of Evidence.doc).

Meta-analysis (of LOE 1 or LOE 2 studies) [Scott 2006]

- Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were identified)
- Was study design defined?
- Were selection criteria stated for studies to be included (based on trial design and methodological quality)?
- Were inclusive searches undertaken (using appropriately crafted search strategies)?
- Were characteristics and methodological quality of each trial identified?
- Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?

Randomised Controlled Trials (LOE 1) (http://www.cebm.net/index.aspx?o=1157)

- Was the assignment of patients to treatment randomised?
- Was the randomisation list concealed?
- Were all patients who entered the trial accounted for at its conclusion?
- Were the patients analysed in the groups to which they were randomised?
- Were patients and clinicians "blinded" to which treatment was being received?
- Aside from the experimental treatment, were the groups treated equally?
- Were the groups similar at the start of the trial?

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Methodological quality for each article (cont'd)

- **Studies using controls without randomisation (concurrent LOE 2, or retrospective LOE 3) (http://www.cebm.net/index.aspx?o=1157)**
- Were comparison groups clearly defined?
- Were outcomes measured in the same (preferably blinded) objective way in both groups?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete?
- **Studies without controls (LOE 4)**
- Were outcomes measured in an objective way?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete?
- **Studies not directly related to the specific patient/population (LOE 5)**
- Studies not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.) should have their methodological quality allocated to the type of study (ie. RCTs = good, studies without randomised controls = fair, and studies without controls = poor). Animal studies should also be designated using *italics*.

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Lung Health Working Group

"BPD Bundle" Revision

Macrolides Literature Review

Amit Mukerji, McMaster University
Jaya Bodani, University of Saskatchewan

Clinical Question

- P – Preterm infants
- I – Macrolides (AZM, ERM, CRM – prophylactic *OR* targeted use)
- C – Placebo
- O – Prevention of BPD at 36 weeks PMA

Search Strategy (Search terms and databases)

- ((macrolide[Title] OR macrolides[Title] OR azithromycin[Title] OR clarithromycin[Title] OR erythromycin[Title]) AND (bronchopulmonary dysplasia[Title/Abstract] OR chronic lung disease[Title/Abstract] OR BPD[Title/Abstract] OR CLD[Title/Abstract] OR ureaplasma[Title/Abstract])) AND (("bronchopulmonary dysplasia"[MeSH Terms] OR ("bronchopulmonary"[All Fields] AND "dysplasia"[All Fields]) OR "bronchopulmonary dysplasia"[All Fields]) OR (chronic[All Fields] AND ("lung diseases"[MeSH Terms] OR ("lung"[All Fields] AND "diseases"[All Fields]) OR "lung diseases"[All Fields] OR ("lung"[All Fields] AND "disease"[All Fields]) OR "lung disease"[All Fields])) OR BPD[All Fields] OR ("cld"[All Fields]) OR "ureaplasma"[MeSH Major Topic])

- Searched on MEDLINE (through Pubmed) – Jan 31, 2019

List of exclusion criteria

- N/A

Results of Search Strategy

- Total number of articles identified: 83
- Articles after removal of duplicates: 83
- Articles remaining after screening of titles/abstracts: 25
- Articles included after full text review: 19
- Additional articles identified (e.g. from references): 1

- Final number of articles in this review: 20

Classify Level of Evidence for each article

Levels of Evidence for Therapeutic Interventions
LOE 1: Randomised Controlled Trials (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomisation (eg. “pseudo”-randomised) (or meta-analyses of such studies)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (eg. case series)
LOE 5: Studies not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.)

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Methodological quality for each article

Good studies would be expected to have **most/all of the quality items** suggested to assess the type of study (see below).
Fair studies would be expected to have **some of the quality items** suggested to assess the type of study (see below).
Poor studies would be expected to have **few of the quality items** suggested to assess the type of study (see below), but to be of sufficient vale to include for further review.
Specific quality items are listed below for each type of intervention study (http://www.cebm.net/index.aspx?o=1157). For further information, including quality for diagnosis and prognosis questions, see separate document: Defining Quality of Evidence.doc).

Meta-analysis (of LOE 1 or LOE 2 studies) [Scott 2006]

- Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were identified)
- Was study design defined?
- Were selection criteria stated for studies to be included (based on trial design and methodological quality)?
- Were inclusive searches undertaken (using appropriately crafted search strategies)?
- Were characteristics and methodological quality of each trial identified?
- Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?

Randomised Controlled Trials (LOE 1) (http://www.cebm.net/index.aspx?o=1157)

- Was the assignment of patients to treatment randomised?
- Was the randomisation list concealed?
- Were all patients who entered the trial accounted for at its conclusion?
- Were the patients analysed in the groups to which they were randomised?
- Were patients and clinicians "blinded" to which treatment was being received?
- Aside from the experimental treatment, were the groups treated equally?
- Were the groups similar at the start of the trial?

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Methodological quality for each article (cont'd)

- **Studies using controls without randomisation (concurrent LOE 2, or retrospective LOE 3) (http://www.cebm.net/index.aspx?o=1157)**
- Were comparison groups clearly defined?
- Were outcomes measured in the same (preferably blinded) objective way in both groups?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete?
- **Studies without controls (LOE 4)**
- Were outcomes measured in an objective way?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete?
- **Studies not directly related to the specific patient/population (LOE 5)**
- Studies not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.) should have their methodological quality allocated to the type of study (ie. RCTs = good, studies without randomised controls = fair, and studies without controls = poor). Animal studies should also be designated using *italics*.

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Summary of evidence based on LOE and methodological quality

Each study will go into one of these boxes

Summary of evidence

Evidence Supporting Clinical Question

Good					
Fair					
Poor					
	1	2	3	4	5
Level of evidence					

Summary of Findings from RCTs

- Study 1: (Ballard, 2007)
  - Pilot RCT among babies <1,000 [Total N = 43; although some excluded]
  - Excluded patients who were positive for Ureaplasma
  - AZM or placebo within 12 hours of EMV (and 72 hours of birth)
  - AZM x 7 ds at 10 mg/kg/d then lower dose until no longer needed EMV or sup O2 (to max 6 weeks)
  - No diff in BPD (64.3% vs. 83.3%; P=0.26)
  - Lower postnatal steroid use (31% vs. 62%) and decreased median duration of EMV (13 vs 35 days)

- Study 2: (Ballard, 2011)
  - RCT among infants <1,250 g [included ureaplasma positive cases)
  - Randomized to AZM (n=111) or placebo (n=109) within 12 hours of EMV (and within 72 hours of birth)
  - Same dosing as above
  - BPD 76% AZM and 84% in placebo (P=0.2)
  - BPD in ureaplasma positive subgroup was 73% (19/26) vs 94% (33/35) (P=0.03)
  - Adjusted OR for BPD/Death in ureplasma positive subgroup: 0.026 (0.001 – 0.618)

Summary of Findings from RCTs

- Study 3: (Jonsson, 1998)
  - Ventilated preterm infants <30 weeks GA (n=155) cultured for ureaplasma in tracheal and nasopharyngeal aspirates
  - Colonized infants were randomly assigned to treatment with (oral or IV) erythromycin
  - Treatment started on DOL 7
  - No significant differences were found between the colonized treated infants (n = 14) and those not treated (n = 14) in time with supplemental oxygen

- Study 4: (Lyon, 1998)
  - Infants <30 weeks GA and on EMV from birth randomized to ERM (7 day course) vs no treatment [total N = 75]
  - Those treated with erythromycin showed no significant differences from the non-treated group in the differential cell counts or concentrations of the cytokines, nor CLD rates

Summary of Findings from RCTs

- Study 5: (Ozdemir, 2011)
  - Nasopharyngeal swabs for U urealyticum culture were taken from infants with a birth weight between 750 and 1250 g in the first 3 postnatal days. (33% positivity rate)
  - Infants with a positive culture for U urealyticum [N = 74] were randomly assigned to 1 of 2 groups to receive either intravenous clarithromycin or placebo
  - Clarithromycin treatment resulted in eradication of U urealyticum in 68.5% of the patients
  - The incidence of BPD was significantly lower in the clarithromycin group than in the placebo group (2.9% vs 36.4%; $P < .001$)

Summary of Findings from RCTs

- Study 6: (Gharehbaghi, 2012)
  - RCT among infants <1500g [N = 108]
  - Tracheal aspirates not routinely checked
  - Oral AZM x 1 week at 10mg/kg/d then another week at 5 mg/kg/d
  - Treatment started on DOL 7
  - 9/52 control group and 3/56 in treatment group had BPD (P=0.04)

Table 1. Characteristics of the trials included in the analysis

Source	Inclusion criteria	*Ureaplasma* colonization rate and detection technique	Macrolides used	Dosage and duration	Macrolide initiation	Primary outcome
Jonsson et al. [21], Sweden	<30 weeks, ventilated and *Ureaplasma* positive	19%; tracheal and nasopharyngeal aspirate cultures	erythromycin	40 mg/kg/day × 10 days	as soon as cultures were available (mean: 7 days)	BPD, clearance of colonization with *Ureaplasma*
Lyon et al. [20], Edinburgh	<30 weeks and ventilated	15%; tracheal aspirate cultures and PCR	erythromycin	45 mg/kg/day × 7 days	at birth	BPD, cytokine levels in tracheal aspirates
Ballard et al., USA [22]	BW <1,000 g and ventilated	19%; tracheal aspirate cultures	azithromycin	10 mg/kg/day × 7 days[1]	0–72 h of age	BPD
Ballard et al. [23], USA	BW <1,250 g and ventilated	35%; tracheal aspirate PCR	azithromycin	10 mg/kg/day × 7 days[1]	0–72 h of age	BPD
Ozdemir et al. [25], Turkey	BW 750–1,250 g and *Ureaplasma* culture positive	33%; nasopharyngeal swab cultures	clarithromycin	20 mg/kg/day × 10 days	0–72 h of age	BPD
Gharehbaghi et al. [24], Iran	<32 weeks and <1,500 g	sampling not done	azithromycin	10 mg/kg/day × 7 days followed by 5 mg/kg/day × 7 days	day 7 of life	BPD

IMV = Intermittent mandatory ventilation; BW = body weight. [1] Followed by 5 mg/kg/day until the infant no longer required IMV or supplemental O_2, to a maximum of 6 weeks.

Nair et al. Neonatology. 2014

Study or subgroup	Azithromycin events	Azithromycin total	Control events	Control total	Weight, %	RR M-H, fixed (95% CI)
Ballard [22]	9	14	10	12	11.5	0.77 (0.48, 1.23)
Ballard [23]	69	91	71	85	78.5	0.91 (0.78, 1.05)
Gharehbaghi [24]	3	56	9	52	10.0	0.31 (0.09, 1.08)
Total (95% CI)		**161**		**149**	**100.0**	**0.83 (0.71, 0.97)**
Total events	81		90			

Heterogeneity: $\chi^2 = 3.80$, d.f. = 2 ($p = 0.15$), $I^2 = 47\%$
Test for overall effect: $Z = 2.35$ ($p = 0.02$)

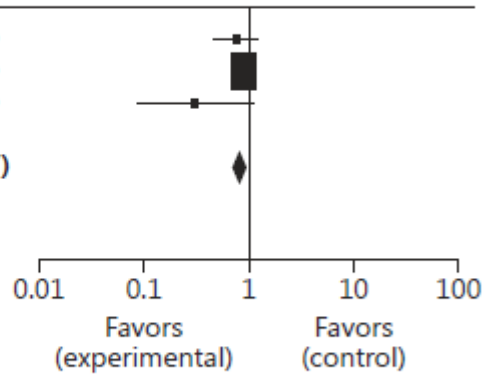


Fig. 3. Forest plot for effect of prophylactic azithromycin on the incidence of BPD.

Study or subgroup	Macrolide events	Macrolide total	Control events	Control total	Weight, %	RR M-H, fixed (95% CI)
Lyon [20]	13	30	11	33	10.1	1.30 (0.69, 2.45)
Ballard [22]	9	14	10	12	10.4	0.77 (0.48, 1.23)
Ballard [23]	69	91	71	85	70.6	0.91 (0.78, 1.05)
Gharehbaghi [24]	3	56	9	52	9.0	0.31 (0.09, 1.08)
Total (95% CI)		**191**		**182**	**100.0**	**0.88 (0.75,1.03)**
Total events	94		101			

Heterogeneity: $\chi^2 = 4.62$, d.f. = 3 ($p = 0.20$), $I^2 = 35\%$
Test for overall effect: $Z = 1.63$ ($p = 0.10$)

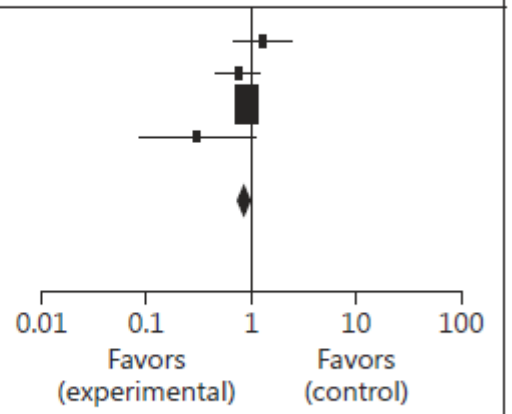


Fig. 6. Forest plot for effect of prophylactic macrolides on the incidence of BPD.

Nair et al. Neonatology. 2014

Study or subgroup	Macrolide events	Macrolide total	Control events	Control total	Weight, %	RR M-H, random (95% CI)
Jonsson [21]	9	14	10	14	40.8	0.90 (0.54, 1.50)
Ballard [23]	19	26	33	34	48.6	0.75 (0.59, 0.96)
Ozdemir [25]	1	35	12	33	10.6	0.08 (0.01, 0.57)
Total (95% CI)		**75**		**81**	**100.0**	**0.64 (0.31,1.31)**
Total events	29		55			

Heterogeneity: $\tau^2 = 0.26$; $\chi^2 = 8.80$, d.f. = 2 ($p = 0.01$), $I^2 = 77\%$
Test for overall effect: $Z = 1.22$ ($p = 0.22$)

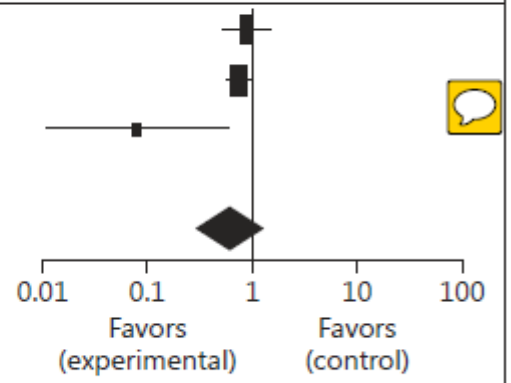


Fig. 9. Forest plot for effect of macrolides on the incidence of BPD among *Ureaplasma*-positive infants.

Nair et al. Neonatology. 2014

Reviewer's final comments and assessment based on available literature

- Routine prophylactic macrolides *may* reduce BPD [small numbers overall]
- Targeted macrolide use (ureaplasma positivity or RFs – vaginal delivery, PROM, chorioamnionitis) may be more impactful
- AZM or CRM are likely better choices than ERM (better anti-inflammatory property)
- Optimal dosing of AZM remains unknown
  - Some PK studies claim 20 mg/k/d x 3 days may have superior eradication

Overall recommendation

- Recommendation statement:
  - **Routine prophylaxis with macrolides for BPD prevention in preterm infants is not recommended. However, select high risk populations/Ureaplasma positive patients may benefit – especially with early treatment with azithromycin/clarithromycin. Currently, optimal dosing remains unknown.**

- "Overall" Level of Evidence (LOE 1 → LOE 5)
  - **LOE 1**

- "Overall" Quality of Evidence
  - **A: Good**
  - B: Fair
  - C: Poor

References – Part 1

- Ballard, H. O., et al. (2007). "Azithromycin in the extremely low birth weight infant for the prevention of bronchopulmonary dysplasia: a pilot study." Respir Res **8**: 41.
- Ballard, H. O., et al. (2011). "Use of azithromycin for the prevention of bronchopulmonary dysplasia in preterm infants: a randomized, double-blind, placebo controlled trial." Pediatr Pulmonol **46**(2): 111-118.
- Ozdemir, R., et al. (2011). "Clarithromycin in preventing bronchopulmonary dysplasia in Ureaplasma urealyticum-positive preterm infants." Pediatrics **128**(6): e1496-1501.
- Jonsson, B., et al. (1998). "Ureaplasma urealyticum, erythromycin and respiratory morbidity in high-risk preterm neonates." Acta Paediatr **87**(10): 1079-1084.
- Lyon, A. J., et al. (1998). "Randomised trial of erythromycin on the development of chronic lung disease in preterm infants." Arch Dis Child Fetal Neonatal Ed **78**(1): F10-14.
- Gharehbaghi M.M. et al. (2012). “Effi cacy of azithromycin for prevention of bronchopulmonary dysplasia (BPD).” Turk J Med Sci **42** (6): 1070-1075.
- Nair, V., et al. (2014). "Azithromycin and other macrolides for prevention of bronchopulmonary dysplasia: a systematic review and meta-analysis." Neonatology **106**(4): 337-347.
- Smith, C., et al. (2015). "Use and safety of azithromycin in neonates: a systematic review." BMJ Open **5**(12): e008194.
- Merchan, L. M., et al. (2015). "Pharmacokinetics, microbial response, and pulmonary outcomes of multidose intravenous azithromycin in preterm infants at risk for Ureaplasma respiratory colonization." Antimicrob Agents Chemother **59**(1): 570-578.
- Viscardi, R. M., et al. (2013). "Azithromycin to prevent bronchopulmonary dysplasia in ureaplasma-infected preterm infants: pharmacokinetics, safety, microbial response, and clinical outcomes with a 20-milligram-per-kilogram single intravenous dose." Antimicrob Agents Chemother **57**(5): 2127-2133.

References – Part 2

- Anbu Chakkarapani, A., et al. (2015). "Macrolides do not affect the incidence of moderate and severe bronchopulmonary dysplasia in symptomatic ureaplasma-positive infants." Acta Paediatr **104**(10): e427-432.
- Baier, R. J., et al. (2003). "Failure of erythromycin to eliminate airway colonization with ureaplasma urealyticum in very low birth weight infants." BMC Pediatr **3**: 10.
- Bowman, E. D., et al. (1998). "Impact of erythromycin on respiratory colonization of Ureaplasma urealyticum and the development of chronic lung disease in extremely low birth weight infants." Pediatr Infect Dis J **17**(7): 615-620.
- Resch, B., et al. (2016). "Neonatal Ureaplasma urealyticum colonization increases pulmonary and cerebral morbidity despite treatment with macrolide antibiotics." Infection **44**(3): 323-327.
- Li, H., et al. (2014). "Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases." Antimicrob Agents Chemother **58**(1): 511-517.
- Mabanta, C. G., et al. (2003). "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(4): Cd003744.
- Aghai, Z. H., et al. (2007). "Azithromycin suppresses activation of nuclear factor-kappa B and synthesis of pro-inflammatory cytokines in tracheal aspirate cells from premature infants." Pediatr Res **62**(4): 483-488.
- Hassan, H. E., et al. (2011). "Pharmacokinetics, safety, and biologic effects of azithromycin in extremely preterm infants at risk for ureaplasma colonization and bronchopulmonary dysplasia." J Clin Pharmacol **51**(9): 1264-1275.
- Hodge, S., et al. (2017). "Nonantibiotic macrolides restore airway macrophage phagocytic function with potential anti-inflammatory effects in chronic lung diseases." Am J Physiol Lung Cell Mol Physiol **312**(5): L678-l687.
- Pansieri, C., et al. (2014). "Ureaplasma, bronchopulmonary dysplasia, and azithromycin in European neonatal intensive care units: a survey." Sci Rep **4**: 4076.

Lung Health Working Group

"BPD Bundle" Revision

Strategies to Prevent Extubation Failure

Brooke Read

Current Recommendation

Immediate post-extubation management	**Use nasal CPAP (nCPAP) or other non-invasive positive pressure ventilation, excluding high flow nasal cannula (HFNC), to provide optimal distending pressure post extubation**	**1c**
	Do not use high flow nasal cannula (HFNC) in the immediate post extubation period	**No evidence, not recommended**

Clinical Question

- In preterm infants, what interventions post extubation reduce extubation failure?

Search Strategy (Search terms and databases)

Search Terms

- Extubation failure or Extubation success, preterm infants
- Limit: humans, newborn, English

Databases: Cochrane, MEDLINE

Exclusion Criteria

- Abstract only results

Results of Search Strategy

- Pubmed: 224 Cochrane: 25 Total: 249
- Total number of articles identified: Articles after removal of duplicates: 239
- Several articles regarding caffeine, corticosteroids, decision made to limit search to respiratory support following extubation
- Comprehensive Systematic Review and Meta-analysis found on topic

  Ferguson KN, Roberts CT, Manley BJ, Davis PG. **Interventions to Improve Rates of Successful Extubation in Preterm Infants: A Systematic Review and Meta-analysis**. JAMA Pediatr. 2017 Feb 1;171(2):165-174

  - Conducted secondary search of articles since this publication

Articles Published since December 2016

1. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev. 2017
   - Jasani B, Nanavati R, Kabra N, Rajdeo S, Bhandari V. Comparison of non-synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as post-extubation respiratory support in preterm infants with respiratory distress syndrome: a randomized controlled trial. J Matern Fetal Neonatal Med. 2016;29(10):1546-51. (**Included in updated Cochrane Review)**
2. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2016

- **Final number of articles in this review: 3**

Cochrane Review

- **Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation** (Lemyre et al, 2017)
- LOE 1, Good Quality
- 10 trials enrolling a total of 1431 infants
- Findings: NIPPV reduces the incidence of extubation failure and the need for re-intubation within 48 hours to one week more effectively than NCPAP; however, it has ***no effect on chronic lung disease nor on mortality***
- Ferguson et al 2017, study had similar findings but only included 9 of 10 studies

Interventions to Improve Rates of Successful Extubation in Preterm Infants: A Systematic Review and Meta-analysis (Ferguson et al, 2017)

- LOE 1, Good Quality, used the methods of the Cochrane Collaboration
- Included randomized clinical trials published in English that enrolled intubated preterm infants where treatment failure or re-intubation was an outcome
- 50 studies were eligible for inclusion
  - CPAP versus head box, CPAP versus NIPPV, Lower CPAP versus high CPAP,CPAP device, CPAP interface, High flow versus CPAP, *Methylxanthines versus placebo, High versus low dose caffeine Corticosteroids, Doxapram, Chest Physiotherapy*
- Conclusions: Preterm infants should be extubated to non-invasive respiratory support

Cochrane Review

- **High flow nasal cannula for respiratory support in preterm infants (Wilkinson et al, 2016)**
- Six studies included evaluated its use following extubation (932 infants)
- High Flow had similar efficacy as CPAP following extubation
- Limitations: Very few infants less than 28 weeks included in studies, many high flow participants could be rescued with CPAP or NIPPV
- Conclusions: Further evidence is required for evaluating the safety and efficacy of HFNC in extremely preterm and mildly preterm subgroups following extubation

A randomized controlled trial of two nasal continuous positive airway pressure levels after extubation in preterm infants. (Buzzella et al, 2014)

- 93 infants 23- 30 weeks gestation, randomized to 4-6cmH_2O or 7-9cmH_2O post extubation
- Re-intubation rates within 7 days were higher CPAP group (30% versus 51%)

Reviewers Comments

Cochrane Review (NIPPV versus NCPAP)

- Subjects randomized to NCPAP were largely not allowed to have NIPPV as a rescue therapy and majority of NCPAP utilized levels < 7cmH20
- Still unknown: Is NCPAP using higher NCPAP levels with rescue NIPPV if needed as effective as extubation to NIPPV at reducing extubation failure?
- Comparative Effectiveness Research: NIPPV versus NCPAP study

Overall recommendation

Recommendation statement:

- NIPPV or CPAP should be used as post extubation support to reduce extubation failure in preterm infants (LOE 1)
- If using CPAP as primary post extubation support; use higher CPAP levels (? > 6cmH20) with escalation to NIPPV (via a ventilator) as rescue therapy to minimize risk of extubation failure
- Do not use high flow nasal cannula (HFNC) in the immediate post extubation period

References

1. Ferguson KN, Roberts CT, Manley BJ, Davis PG. Interventions to Improve Rates of Successful Extubation in Preterm Infants: A Systematic Review and Meta-analysis. JAMA Pediatr. 2017 Feb 1;171(2):165-174. doi: 10.1001/jamapediatrics.2016.3015. Review. PubMed PMID: 27918754.
2. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev. 2017 Feb 1;2:CD003212. doi: 10.1002/14651858.CD003212.pub3. Review. PubMed PMID:28146296.
3. Buzzella B, Claure N, D'Ugard C, Bancalari E. A randomized controlled trial of two nasal continuous positive airway pressure levels after extubation in preterm infants. J Pediatr. 2014 Jan;164(1):46-51. doi: 10.1016/j.jpeds.2013.08.040. Epub 2013 Oct 1. PubMed PMID: 24094879.
4. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2016 Feb 22;2:CD006405. doi: 10.1002/14651858.CD006405.pub3. Review. PubMed PMID: 26899543.

Lung Health Working Group
"BPD Bundle" Revision

Repeat Doses of Surfactant

Derek Kowal, Jonathan Wong, Shivali Lekhi

Currently in the Bundle

Surfactant administration	Exact timing controversial: • If baby requires intubation for resuscitation – consider surfactant • If oxygen requirement becomes higher than 30% - 50% on nCPAP • Early-selective surfactant	1a and physiological sense to avoid lung injury 1a
	Avoid aggressive hand ventilation for administering surfactant	Physiological sense, no evidence

Clinical Question

- Does administration of repeated doses of exogenous surfactant in preterm infants decrease the risk of bronchopulmonary dysplasia?

- P: Preterm infants
- I: >1 dose of surfactant
- C: 1 dose of surfactant
- O: Bronchopulmonary dysplasia

Search Strategy (Search terms and databases)

- Search Terms:
  - PUBMED: Surfactant, bronchopulmonary dysplasia
    (if added repeat = 0 results)
  - Limit: humans, newborn, English, date

  - EMBASE: surfactant
  - Limit: humans, English, clinical trial, date

- Databases:
  - Cochrane, MEDLINE, EMBASE

List of exclusion criteria

- Abstract-only results.
- Results prior to June 2008.

Results of Search Strategy

- Total number of articles identified: Pubmed 325, Embase 71 (Total 396)
- Articles remaining after screening of titles/abstracts: 41
- Articles included after full text review:
- Additional articles identified (e.g. from references):

- Final number of articles in this review: 3 + Cochrane

Classify Level of Evidence for each article

Levels of Evidence for Therapeutic Interventions
LOE 1: Randomised Controlled Trials (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomisation (eg. “pseudo”-randomised) (or meta-analyses of such studies)
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Specific quality items are listed below for each type of intervention study (http://www.cebm.net/index.aspx?o=1157). For further information, including quality for diagnosis and prognosis questions, see separate document: Defining Quality of Evidence.doc).

Meta-analysis (of LOE 1 or LOE 2 studies) [Scott 2006]

- Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were identified)
- Was study design defined?
- Were selection criteria stated for studies to be included (based on trial design and methodological quality)?
- Were inclusive searches undertaken (using appropriately crafted search strategies)?
- Were characteristics and methodological quality of each trial identified?
- Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?

Randomised Controlled Trials (LOE 1) (http://www.cebm.net/index.aspx?o=1157)

- Was the assignment of patients to treatment randomised?
- Was the randomisation list concealed?
- Were all patients who entered the trial accounted for at its conclusion?
- Were the patients analysed in the groups to which they were randomised?
- Were patients and clinicians "blinded" to which treatment was being received?
- Aside from the experimental treatment, were the groups treated equally?
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Methodological quality for each article (cont'd)

- **Studies using controls without randomisation (concurrent LOE 2, or retrospective LOE 3) (http://www.cebm.net/index.aspx?o=1157)**
- Were comparison groups clearly defined?
- Were outcomes measured in the same (preferably blinded) objective way in both groups?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete?
- **Studies without controls (LOE 4)**
- Were outcomes measured in an objective way?
- Were known confounders identified and appropriately controlled for?
- Was follow-up of patients sufficiently long and complete?
- **Studies not directly related to the specific patient/population (LOE 5)**
- Studies not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.) should have their methodological quality allocated to the type of study (ie. RCTs = good, studies without randomised controls = fair, and studies without controls = poor). Animal studies should also be designated using *italics*.

Morley, P. 2007. Instructions for completion of the C2010 evidence evaluation worksheet. (August 15, 2007).

Summary of evidence based on LOE and methodological quality

Each study will go into one of these boxes

Summary of evidence

Evidence Supporting Clinical Question

Good					
Fair					
Poor					
	1	2	3	4	5
Level of evidence					

Cochrane

Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants (2012)

- Although the early trials of prophylactic surfactant administration to infants judged to be at risk of developing RDS compared with selective use of surfactant in infants with established RDS demonstrated a decreased risk of air leak and mortality, recent large trials that reflect current practice (including greater utilization of maternal steroids and routine post delivery stabilization on CPAP) do not support these differences and demonstrate less risk of chronic lung disease or death when using early stabilization on CPAP with selective surfactant administration to infants requiring intubation.

Cochrane

Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (2012)

- Early selective surfactant administration given to infants with RDS requiring assisted ventilation leads to a decreased risk of acute pulmonary injury (decreased risk of pneumothorax and pulmonary interstitial emphysema) and a decreased risk of neonatal mortality and chronic lung disease compared to delaying treatment of such infants until they develop worsening RDS.

Cochrane

Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants (2015)

- Significant differences in clinical outcome were noted in the comparison trials of modified minced lung surfactant extract (beractant) compared with porcine minced lung surfactant extract (poractant alfa) including a significant increase in the risk of mortality prior to discharge, death or oxygen requirement at 36 weeks' postmenstrual age, PDA requiring treatment and "receiving > 1 dose of surfactant" in infants treated with modified bovine minced lung surfactant extract compared with porcine minced lung surfactant extract. The difference in these outcomes was limited to studies using a higher initial dose of porcine minced lung surfactant extract. It is uncertain whether the observed differences are from differences in dose or from source of extraction (porcine vs. bovine) because of the lack of dose-equivalent comparison groups with appropriate sample size. No differences in clinical outcomes were observed in comparative trials between bovine lung lavage surfactant and modified bovine minced lung surfactants.

Cochrane

Animal derived surfactant compared to protein-free synthetic surfactant preparations in preterm infants that have or are at high risk for respiratory distress syndrome (2015)

- Both animal derived surfactant extracts and protein free synthetic surfactant extracts are effective in the treatment and prevention of respiratory distress syndrome. Comparative trials demonstrate greater early improvement in the requirement for ventilator support, fewer pneumothoraces, and fewer deaths associated with animal derived surfactant extract treatment. Animal derived surfactant may be associated with an increase in necrotizing enterocolitis and intraventricular hemorrhage, though the more serious hemorrhages (Grade 3 and 4) are not increased. Despite these concerns, animal derived surfactant extracts would seem to be the more desirable choice when compared to currently available protein free synthetic surfactants.

Cochrane

Multiple vs. single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome (2009)

- In infants with established respiratory distress, a policy of multiple doses of animal derived surfactant extract resulted in greater improvements regarding oxygenation and ventilatory requirements, a decreased risk of pneumothorax and a trend toward improved survival.
- In infants at high risk of respiratory distress, a policy of multiple doses of synthetic surfactant resulted in greater improvements regarding oxygenation and ventilatory requirements, a decreased risk of NEC and decreased mortality.
- The ability to give multiple doses of surfactant to infants with ongoing respiratory insufficiency leads to improved clinical outcome and appears to be the most effective treatment policy.

AAP/CPS Statements

Repeat doses of surfactant:

- AAP (2014):
  - Refers to Cochrane review

- CPS (2015, Reaffirmed 2017)
  - Infants with RDS who have persistent or recurrent oxygen and ventilatory requirements within the first 72h of life should have repeated doses of surfactant. Administration of more than 3 doses has not been shown to be of benefit (Grade A).
  - Retreatment should be considered when there is persistent or recurrent oxygen requirements of 30% or more, as early as 2h after the initial dose (Grade A).

Summary of Findings from each study

Use and timing of surfactant administration: impact on neonatal outcomes in extremely low gestational infants born in Canadian NICUs (Stritzke, 2018)

- Surfactant administration within 30 min of life was not associated with increased risk of the primary composite outcome, but had decreased rates of late onset sepsis and ROP.

Surfactant utilization and short-term outcomes in an era of non-invasive respiratory support in Canadian NICUS (Raghuram, 2017)

- NRS did not increase overall use of surfactant.
- Therapeutic surfactant rates were higher in the later period group with a decrease in rates of BPD.

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Surfactant

INSURE vs nasal CPAP

- Evidence: Meta-analysis of 6 RCTs ($n = 1250$) reporting the outcome of BPD or death at 36 weeks PMA[71]
- Results: Neither INSURE or nasal CPAP was superior to reduce the risk of BPD/death.
- Treatment effect: Relative risk 0.88 (95% CI: 0.76 to 1.02)

Early (< 2 h of life) vs Late ($\geqslant 2$ h of life) administration among infants receiving invasive mechanical ventilation

- Evidence: Cochrane meta-analysis of 3 RCTs ($n = 3050$) reporting the outcome of BPD or death at 36 weeks PMA[64]
- Results: Early compared with late surfactant reduced the risk of BPD/death.
- Treatment effect: Relative risk 0.83 (95% CI: 0.75 to 0.91)
- Number needed to treat: 16 (95% CI: 11 to 34)

Less-invasive surfactant administration (LISA) vs all control therapies

- Evidence: Meta-analysis of 5 RCTs ($n = 857$) reporting the outcome of BPD or death at 36 weeks PMA (Figure 2)
- Results: LISA compared with control therapy reduced the risk of BPD/death.
- Treatment effect: Relative risk 0.74 (95% CI 0.58 to 0.94).
- Number needed to treat: 15 (95% CI 8 to 70)

Less-invasive surfactant administration (LISA) vs INSURE

- Evidence: Meta-analysis of 3 RCTs ($n = 426$) reporting the outcome of BPD or death at 36 weeks PMA (Figure 2)
- Results: LISA compared with INSURE reduced the risk of BPD/death.
- Treatment effect: Relative risk 0.63 (95% CI 0.42 to 0.93)
- Number needed to treat: 12 (95% CI 6 to 66)

Foglia, 2017

Reviewer's final comments and assessment based on available literature

- Overall, no new data regarding the use of surfactant and outcomes, specifically BPD.

- Increasing evidence on the use of surfactant via MIST/LISA and improved outcomes.

Overall recommendation

- Recommendation statement: As per CPS...
    - Infants with RDS who have persistent or recurrent oxygen (>30%) and ventilatory requirements within the first 72h of life should have repeated doses of surfactant. There insufficient data to describe the effects of repeat doses and BPD.
- Grade A Evidence.