

Bronchopulmonary Dysplasia (BPD) BUNDLE – Infants <29 weeks GA		
Domain	Comments	Recommendation
Threatened preterm labour	Antenatal steroid administration	1a (good evidence of improving survival, no evidence that this improves BPD)
Delivery room management of spontaneously breathing neonate	Trial of continuous positive airway pressure (CPAP) of 5-8 cm H ₂ O.	1b (Schmolzer et al, 2013)
	Initiate resuscitation using FIO ₂ 0.21-0.30 and titrate O ₂ to achieve pre-ductal saturation of >85% by 7- 10 minutes of age	1b
Surfactant administration Revised!	<p>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</p> <p>Preterm infants with RDS who are managed with non-invasive respiratory support as an initial mode should receive early selective surfactant at a FiO₂ threshold of greater than 0.3 and no later than 0.5. Clinical considerations such as the work of breathing, radiologic evidence of RDS and the non-invasive mean airway pressure used may justify an earlier threshold for surfactant therapy.</p>	<p>1a</p> <p>2b</p>
Methods of Surfactant Administration New!	<p>Minimally Invasive Surfactant Therapy (MIST) or Less Invasive Surfactant Administration (LISA) is the preferred mode of surfactant administration for spontaneously breathing babies on non-invasive respiratory who are greater than or equal to 26 weeks gestation, provided that clinicians are experienced with this technique.</p> <p>Preterm infants who cannot be treated with MIST/LISA and require intubation solely for surfactant administration should be evaluated for rapid extubation back to non-invasive respiratory support (Intubate, surfactant, Extubate-INSURE) as opposed to routine mechanical ventilation to reduce duration of</p>	<p>1b</p> <p>1b</p>

Revised February 2020

	invasive mechanical ventilation.	
Repeat Doses of Surfactant New!	Infants with evidence of RDS on chest x-ray and who have persistent or recurrent oxygen (>30%) and ventilatory requirements within the first 72h of life should have repeated doses of surfactant.	1 b (CPS)
Use of Macrolides New!	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.	1a
Systemic Steroids New!	<p>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)</p> <p>Dexamethasone in the first week of life to prevent BPD should not be given. (Level 1 evidence, good quality)</p> <p>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)</p> <p>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)</p> <p>Hydrocortisone to treat infants at high risk of BPD, after the first week of life, or infants</p>	<p>1a</p> <p>1a</p> <p>1</p> <p>1</p> <p>1</p>

	with prolonged ventilator dependence is not recommended. (Level 1 evidence)	
Inhaled Steroids New!	The routine use of inhaled corticosteroids to prevent BPD is not recommended. (Level 1 evidence)	1
Use of distending pressure post resuscitation	Maintain <u>consistent</u> CPAP to prevent lung de-recruitment	1c
	Continue use of appropriate distending pressure to maintain Functional Residual Capacity (FRC)	No evidence, clinical and physiological sense
Mode of Mechanical Ventilation and Tidal Volume Targets Revised!	Volume targeted ventilation is recommended over pressure limited ventilation to minimize risk of BPD	1b
	Tidal Volume Targets <ul style="list-style-type: none"> • Birth weight less than 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). 	4C 4C, BPD rates were not reported with this strategy.
	Appropriate use of High Frequency Ventilation (HFV) – criteria to be developed locally	
Avoid lung de-recruitment	Use in-line suction No routine suctioning, suction only as clinically indicated Avoid ventilator disconnects	No evidence, physiological sense
Extubation Revised!	Daily assessment of infants eligible for extubation: criteria to be developed locally. Extubate as early as clinically appropriate to minimize duration of invasive ventilation.	1b
Immediate post-extubation management Revised!	Non-invasive positive pressure ventilation (NIPPV) or CPAP should be used as post extubation support to reduce risk of re-intubation in preterm infants	1b
	If using CPAP as primary post extubation support; use higher CPAP levels (greater than	1b

	6cmH20) with escalation to NIPPV (via a ventilator) as rescue therapy to reduce risk of re-intubation.	
	Do not use high flow nasal cannula (HFNC) in the immediate post extubation period, insufficient evidence on use in infants less than 28 weeks gestation	Wilkinson et al, 2016
Oxygen therapy (oxygen is a DRUG)	Always use blenders when on oxygen therapy	1b
	Use daily histogram to guide respiratory support and oxygen therapy to aim for maintaining SpO2 within alarm limits for greater than 70% of time	2C, physiological plausibility
	Enforce high alarm setting on monitor when infant is receiving oxygen	1b
	Oxygen saturation alarm limits	No absolute recommendations can be given at this time for BPD prevention
Medical Therapy	Caffeine for apnea of prematurity	1a
	Early caffeine	1b
	Monitor weight change closely in first 7 days to optimize fluid and sodium intake	2b, physiological sense
	Vitamin A	1b; however, availability is an issue in Canada
Optimizing Early Nutrition	TPN within 4 hours of life if < 1500 g	1b
Prevention of Unplanned Extubation New!	Implement standardized practices to reduce unplanned extubation.	Patient Safety
Patient Care Plans	Daily discussion regarding respiratory management and O2 therapy status	No evidence, clinical sense
	Multidisciplinary discussions regarding respiratory management of difficult patients	No evidence, clinical sense

Reference List for BPD Bundle

Threatened Preterm Labour

1. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev.* 2017 Mar 21;3:CD004454. doi: 10.1002/14651858.CD004454.pub3. Review. PubMed PMID: 28321847; PubMed Central PMCID: PMC6464568.

Delivery Room Management of Spontaneously Breathing Infant

2. Schmölzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ.* 2013 Oct 17;347:f5980. doi: 10.1136/bmj.f5980. Review. Erratum in: *BMJ.* 2014;348:g58. PubMed PMID: 24136633; PubMed Central PMCID: PMC3805496.

Surfactant Administration/ Repeat Doses of Surfactant

3. Davis DJ, Barrington KJ Canadian Paediatric Society, Fetus and Newborn Committee. Recommendations for neonatal surfactant therapy. *Paediatr Child Health.* 2005 Feb;10(2):109-16. PubMed PMID: 19668609; PubMed Central PMCID: PMC2722820.
4. 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.
5. 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.
6. Dargaville PA, Aiyappan A, De Paoli AG, Dalton RG, Kuschel CA, Kamlin CO, et al. Continuous positive airway pressure failure in preterm infants: incidence, predictors and consequences. *Neonatology.* 2013;104((1)):8–14.
7. Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. *Cochrane Database Syst Rev.* 2009 Jan 21;(1):CD000141. doi: 10.1002/14651858.CD000141.pub2. Review. PubMed PMID: 19160177.
8. 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;3:CD000510.

Minimally Invasive Surfactant Therapy

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

Surfactant Application vs Conventional Therapy in Extremely Preterm Infants. *JAMA Pediatrics*, 169(8), 723. doi: 10.1001/jamapediatrics.2015.0504

10. Aldana-Aguirre, J. C., Pinto, M., Featherstone, R. M., & Kumar, M. (2016). Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, 102(1). doi: 10.1136/archdischild-2015-310299
11. Rigo, V., Lefebvre, C., & Broux, I. (2016). Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis. *European Journal of Pediatrics*, 175(12), 1933–1942. doi: 10.1007/s00431-016-2789-4
12. Göpel, W., Kribs, A., Ziegler, A., Laux, R., Hoehn, T., Wieg, C., ... Herting, E. (2011). Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *The Lancet*, 378(9803), 1627–1634. doi: 10.1016/s0140-6736(11)60986-0

Intubate, Surfactant, Extubate (INSURE)

13. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007 Oct 17;(4):CD003063. Review. PubMed PMID: 17943779.
14. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, Ferrelli K, O'Connor J, Soll RF; Vermont Oxford Network DRM Study Group. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics*. 2011 Nov;128(5):e1069-76. doi: 10.1542/peds.2010-3848. Epub 2011 Oct 24. PubMed PMID: 22025591.
15. Rojas MA, Lozano JM, Rojas MX, Laughon M, Bose CL, Rondon MA, Charry L, Bastidas JA, Perez LA, Rojas C, Ovalle O, Celis LA, Garcia-Harker J, Jaramillo ML; Colombian Neonatal Research Network. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics*. 2009 Jan;123(1):137-42. doi: 10.1542/peds.2007-3501. PubMed PMID: 19117872.

Macrolides

16. 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.
17. 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.
18. 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.
19. Ozdemir, R., et al. (2011). "Clarithromycin in preventing bronchopulmonary dysplasia in *Ureaplasma urealyticum*-positive preterm infants." *Pediatrics* **128**(6): e1496-1501.
20. 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.

Revised February 2020

Systemic Steroids

21. Peltoniemi O, Kari MA, Heinonen K, Saarela T, Nikolajev K, Andersson S, Voutilainen R, Hallman M. Pretreatment cortisol values may predict responses to hydrocortisone administration for the prevention of bronchopulmonary dysplasia in high-risk infants. *J Pediatr*. 2005 May;146(5):632-7. PubMed PMID: 15870666.
22. Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, Zupan-Simunek V, Coursol A, Beuchée A, Bolot P, Andrini P, Mohamed D, Alberti C; PREMIOLOC trial study group. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMIOLOC): a double-blind, placebo-controlled, multicentre, randomised trial. *Lancet*. 2016 Apr 30;387(10030):1827-36. doi: 10.1016/S0140-6736(16)00202-6. Epub 2016 Feb 23. PubMed PMID: 26916176.
23. Shaffer ML, Baud O, Lacaze-Masmonteil T, Peltoniemi OM, Bonsante F, Watterberg KL. Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis. *J Pediatr*. 2019 Apr;207:136-142.e5. doi: 10.1016/j.jpeds.2018.10.004. Epub 2018 Nov 8. PubMed PMID: 30416014.
24. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev*. 2017 Oct 24;10:CD001145. doi: 10.1002/14651858.CD001145.pub4. Review. PubMed PMID: 29063594; PubMed Central PMCID: PMC6485440.
25. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev*. 2017 Oct 24;10:CD001146. doi: 10.1002/14651858.CD001146.pub5. Review. PubMed PMID: 29063585; PubMed Central PMCID: PMC6485683.

Inhaled Steroids

26. Shah VS, Ohlsson A, Halliday HL, Dunn M. Early administration of inhaled corticosteroids for preventing chronic lung disease in very low birth weight preterm neonates. *Cochrane Database Syst Rev*. 2017 Jan 4;1:CD001969. doi: 10.1002/14651858.CD001969.pub4. Review. PubMed PMID: 28052185; PubMed Central PMCID: PMC6464720.

Volume Targeted versus Pressure Limited Ventilation

27. Klingenberg C, Wheeler KI, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in neonates. *Cochrane Database Syst Rev*. 2017 Oct 17;10:CD003666. doi: 10.1002/14651858.CD003666.pub4. Review. PubMed PMID: 29039883.
28. 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.

Revised February 2020

29. 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.
30. 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.
31. 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.

Extubation and Post Extubation Management

32. Shalish, Wissam, et al. "Predictors of extubation readiness in preterm infants: a systematic review and meta-analysis." *Archives of Disease in Childhood-Fetal and Neonatal Edition* 104.1 (2019): F89-F97.
33. Danan C, Durrmeyer X, Brochard L, Decobert F, Benani M, Dassieu G. A randomized trial of delayed extubation for the reduction of reintubation in extremely preterm infants. *Pediatric Pulmonology*. 2008 Feb;43(2):117-24. PubMed PMID:18092355.
34. Fischer HS, Buhner C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013;132:e1351-1360
35. Robbins M, Trittman J, Martin E, Reber KM, Nelin L, Shepherd E. Early extubation attempts reduce length of stay in extremely preterm infants even if re-intubation is necessary. *J Neonatal Perinatal Med*. 2015;8(2):91-7. doi: 10.3233/NPM-15814061. PubMed PMID: 26410431.
36. Jensen EA, DeMauro SB, Kornhauser M, Aghai ZH, Greenspan JS, Dysart KC. Effects of Multiple Ventilation Courses and Duration of Mechanical Ventilation on Respiratory Outcomes in Extremely Low-Birth-Weight Infants. *JAMA Pediatr*. 2015 Nov; 169(11):1011-7. doi: 10.1001/jamapediatrics.2015.2401. PubMed PMID: 26414549; PubMed Central PMCID: PMC6445387.
37. 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.
38. 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.
39. Buzzella B, Claire 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.
40. 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.

Oxygen Therapy

41. Askie LM, Darlow BVA, Finer N, Stenson B, Vento M, Whyte R. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database Syst Rev* 2017;4:CD011190
42. Askie LM, Darlow BA, Davis PG, Finer N, Stenson B, Vento M, Whyte R. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database Syst Rev*. 2017 Apr 11;4:CD011190. doi: 10.1002/14651858.CD011190.pub2. Review. PubMed PMID: 28398697; PubMed Central PMCID: PMC6478245.
43. Manja V, Saugstad OD, Lakshminrusimha S. Oxygen Saturation Targets in Preterm Infants and Outcomes at 18-24 Months: A Systematic Review. *Pediatrics*. 2017 Jan;139(1). pii: e20161609. doi: 10.1542/peds.2016-1609. Epub 2016 Dec 5. Review. PubMed PMID: 27940510; PubMed Central PMCID: PMC5192090.
44. Escobedo MB, Aziz K, Kapadia VS, Lee HC, Niermeyer S, Schmölzer GM, Szyld E, Weiner GM, Wyckoff MH, Yamada NK, Zaichkin JG. 2019 American Heart Association Focused Update on Neonatal Resuscitation: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Pediatrics*. 2019 Nov 14. pii: e20191362. doi: 10.1542/peds.2019-1362. [Epub ahead of print] PubMed PMID: 31727863.

Medical Therapy

45. Schmidt B, Roberts RS, Davis P, Doyle L, Barrington KJ, Olhsson A et al for the Caffeine for Apnea of Prematurity Trial Group. *New Engl J Med* 2006;354:2113-2121
46. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birth weight infants. *Cochrane Database Syst Rev* 2007;4:CD000501

Optimizing Early Nutrition

47. Ehrenkranz RA, Das A, Wrage LA, Pointdexter BB, Higgins RD, Stoll BJ et al. Early nutrition mediates the influence of severity of illness on extremely low birth weight infants. *Pediatric Research* 2011;69:522-529