CHRONIC LUNG DISEASE
Supporting information

This guideline has been prepared with reference to the following:

Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. Neonatology. 2014; 105:55-63

https://www.karger.com/Article/FullText/356561

BOOST II United Kingdom Collaborative Group, BOOST II Australia Collaborative Group, BOOST II New Zealand Collaborative Group et al. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013;368:2094-104

https://www.nejm.org/doi/full/10.1056/NEJMoa1302298

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target Ranges of Oxygen Saturation in Extremely Preterm Infants. N Engl J Med. 2010;362:1959–69

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2891970/

What is the definition of chronic lung disease (CLD)?
Definitions of CLD (or bronchopulmonary dysplasia) have in the past been "…broad and hazy, with several competing definitions in the literature" (Charafeddine, 1999). The original description of the condition (Northway, 1967) indicated that oxygen dependency at 28 days of age was diagnostic, and this definition is still widely accepted (Baraldi, 2007; Panickar, 2004). Other definitions include oxygen dependence at 28 days of age with at least 21 days of oxygen supplementation and consistent chest x-ray findings (Bancalari, 1979), and oxygen at 36 weeks corrected gestational age (Shennan, 1988). The National Institutes of Health (2005) recommend a severity based criteria definition for diagnosis:

- Mild BPD defined as need for supplemental oxygen for at least 28 days but not at 36 weeks postmenstrual age or discharge
- Moderate BPD defined as need for supplemental oxygen for at least 28 days plus treatment with < 30% oxygen at 36 weeks postmenstrual age
- Severe BPD defined as need for supplemental oxygen for at least 28 days plus treatment with ≥ 30% oxygen and/or positive pressure at 36 weeks postmenstrual age

Bancalari E, Abdenour GE, Feller R, et al. Bronchopulmonary dysplasia: clinical presentation. J Pediatr 1979;95: 819-23

Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med 2007;357:1946-55

Charafeddine L, D'Angio CT, Phelps DL. Atypical chronic lung disease patterns in neonates. Pediatrics 1999;103: 759-65

Northway WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease: bronchopulmonary dysplasia. N Engl J Med 1967;276:357-68

Panickar J, Scholefield H, Kumar Y, et al. Atypical chronic lung disease in preterm infants. J Perinat Med 2004;32:162-7

Shennan AT, Dunn MS, Ohlsson A, et al. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32

Evidence Level: IV

How do different dexamethasone dosing regimes compare in terms of risks v benefits?
A 2019 RCT in 57 extremely preterm infants compared the pulmonary and neurodevelopmental outcomes of 42-day course of dexamethasone or 9-day course (Marr, 2019). Infants in the 42-day group had shorter duration of ventilation (25 vs 37 days), P < .005, received fewer transfusions (2 vs 3.5), P < .01, and reached full enteral feeds earlier (40 vs 46 days), P < .05. Intact survival at school age was significantly increased in the 42-day group (75%) compared with the 9-day group (34%), P < .005. The authors concluded that a 42-day tapering course of dexamethasone in extremely preterm

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infants at high risk for bronchopulmonary dysplasia decreased hospital morbidities and increased rate of survival without handicap compared with a treatment protocol that attempted to minimise steroid exposure.
Three Cochrane systematic reviews (Doyle, 2014; Doyle, 2014a; Halliday, 2003) have concluded that the benefits of early (<96 hours), moderately early (7-14 days) and late (>3 weeks) treatment with corticosteroids may not outweigh the actual or potential adverse effects. In particular, no study to date has been sufficiently powered to detect important adverse long-term neurosensory outcomes (Halliday, 2004i). In view of this, the recommendation is to reserve treatment for those infants who cannot be weaned from mechanical ventilation, and to minimise the dose and duration of any course of treatment.
A further Cochrane review of 5 trials comparing inhaled versus systemic corticosteroids (Shah, 2012) found no advantage for inhaled steroids, either in effectiveness or in side-effect profiles.
Significant adverse effects, in terms of spontaneous gastrointestinal perforation, cessation of weight gain, and smaller head circumference have been recorded at moderate dose levels (0.15-0.02mg/kg over 10 days) (Stark, 2001).
A retrospective, two-centre study (van der Heide-Jalving, 2003) compared 25 hydrocortisone-treated patients (tapering dose of 5-1mg/kg for 22 days) and 25 controls with 23 dexamethasone-treated patients (tapering dose of 0.5-0.1 mg/kg for 21 days) and 23 controls. Effectiveness was found to be equal, but both short and long term adverse effects were significantly fewer in the hydrocortisone group.

Doyle L, Ehrenkranz R, Halliday H. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database of Systematic Reviews 2014. Art. No.: CD001146
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001146.pub4/pdf/standard

Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. The Cochrane Database of Systematic *Reviews* 2003, Issue 1. Art. No.: CD001144
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001144/full

Doyle L, Ehrenkranz R, Halliday H. Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants. The Cochrane Database of Systematic Reviews. 2014. Art. No.: CD001145
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001145.pub3/full

Marr BL, Mettelman BB, Bode MB et al. Randomized Trial of 42-Day Compared with 9-Day Courses of Dexamethasone for the Treatment of Evolving Bronchopulmonary Dysplasia in Extremely Preterm Infants. J Pediatr. 2019;211:20-6

Shah SS, Ohlsson A, Halliday H, et al. Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants. The Cochrane Database of Systematic Reviews 2012. Art. No.: CD002057
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002057.pub3/full

Stark AR, Carlo WA, Tyson JE, et al. Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. N Engl J Med 2001;344:95-101
http://www.nejm.org/doi/full/10.1056/NEJM200101113440203#t=articleTop

van der Heide-Jalving M, Kamphuis PJ, van der Laan MJ, et al. Short-and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? Acta Paediatr 2003;92:827-35

Evidence Level: I

What is the role of diuretics?
There is some evidence from small trials of diuretics in neonates with bronchopulmonary dysplasia (BPD) suggesting an improvement in short term lung mechanics and oxygenation (Donn, 2017), although a larger observational trial did not show short term respiratory improvement (Blaisdell, 2018). A large observational study showed marked variation in use of loop diuretics in infants with BPD. No differences in mortality or age at discharge were seen between low-use and high-use centres (Bamat, 2021). Additionally, there are several potential risks of diuretic use, such as hyponatraemia, hypokalaemia, increased calcium loss and hypochloraemic metabolic alkalosis, and the long term effects on bone growth and mineralisation are not yet understood (Donn, 2017). Furosemide also stimulates renal prostaglandin production, which may promote patency of the ductus arteriosus (Thompson, 2018). A 2021 review concluded that it would seem prudent to avoid routine use of

diuretics since they have failed to show a level of benefit that would outweigh possible harms (Zayegh, 2021).

Lung disease in preterm infants is often complicated with lung oedema. A Cochrane review of 6 small studies (Stewart, 2011i) found that, in preterm infants > 3 weeks of age with CLD, acute and chronic administration of distal diuretics improved pulmonary mechanics. The authors warn that "positive effects should be interpreted with caution as the numbers of patients studied are small in surprisingly few randomized controlled trials."

Another Cochrane review by the same team (Stewart, 2011ii) concluded that:" In view of the lack of data from randomized trials concerning effects on important clinical outcomes, routine or sustained use of systemic loop diuretics in infants with (or developing) CLD cannot be recommended based on current evidence. Randomized trials are needed to assess the effects of furosemide administration on survival, duration of ventilatory support and oxygen administration, length of hospital stay, potential complications and long-term outcome.

Bamat NA, Nelin TD, Eichenwald EC et al. Loop Diuretics in Severe Bronchopulmonary Dysplasia: Cumulative Use and Associations with Mortality and Age at Discharge. J Pediatr. 2021;231:43-9

Blaisdell CJ, Troendle J, Zajicek A et al. Acute responses to diuretic therapy in extremely low gestational age newborns: results from the prematurity and respiratory outcomes program cohort study. J Pediatr 2018; 197:42-7

Donn SM. Bronchopulmonary dysplasia: myths of pharmacologic management. Semin Fetal Neonatal Med 2017;22:354-58

Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD001817 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001817.pub2/full

Stewart A, Brion LP. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD001453 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001453.pub2/full

Thompson EJ, Greenberg RG, Kumar K et al Association between furosemide exposure and patent ductus arteriosus in hospitalized infants of very low birth weight. J Pediatr 2018;199:231-6

Zayegh AM, Davis PG. BPD treatments: The never-ending smorgasbord. Semin Fetal Neonatal Med. 2021;26:101223

Evidence Level: I

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