Bronchopulmonary Dysplasia Care Bundle
Northern Neonatal Network

1. Introduction

Bronchopulmonary dysplasia (BPD) is the most common complication of preterm birth, and is associated with adverse respiratory and neurodevelopmental outcomes throughout childhood and into adult life[1]. BPD is defined in preterm infants born at <32 weeks gestation as requiring oxygen or positive pressure respiratory support at 36 weeks post menstrual age. The National Neonatal Audit Report (NNAP) shows BPD rates in the Northern region are consistently higher than the national average, even when adjusted for population characteristics[2]. In 2020-2022, the rate of death or BPD in preterm infants <32 weeks gestation receiving neonatal care in the Northern region was 47.1%, compared to 39.7% nationally, with rates ~5% higher than similar populations, highlighting this as a key area for improvement (figure 1).

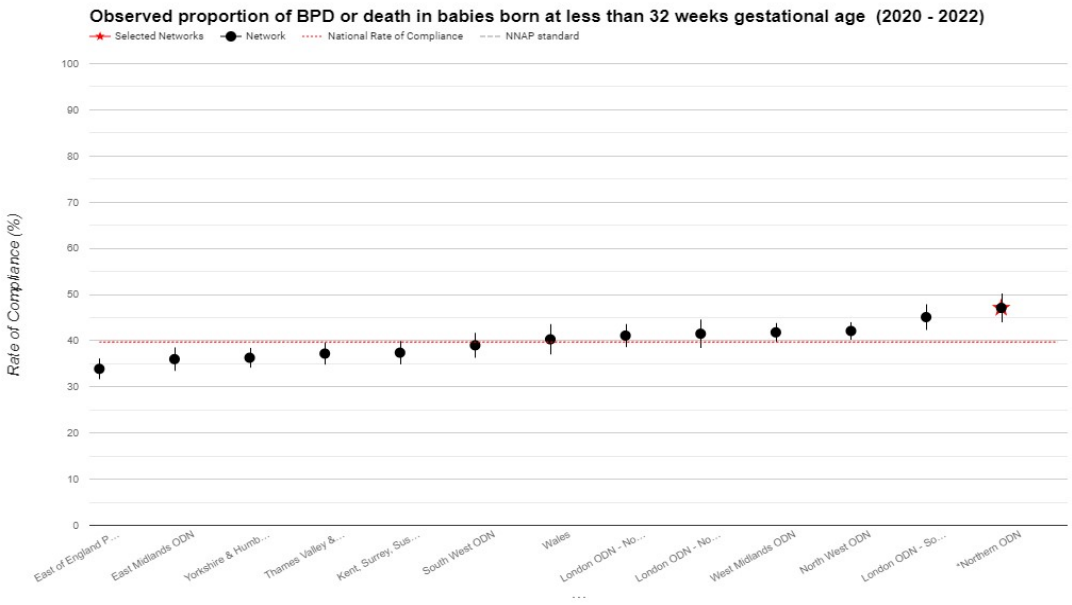

Figure 1: Network rates of BPD or death in very preterm babies 2020-2022 (NNAP).

BPD is a multifactorial disease, with arrested/dysregulated lung development, abnormal vascularisation, and inflammation as key factors contributing to its pathogenesis. As a result, a number of interlinked strategies are required to support preterm infants from birth, promote growth, prevent inflammation and ultimately reduce rates of BPD (figure 2).

Antenatal	Delivery Suite	Early Postnatal	Later Postnatal
Preventing preterm birth	Normothermia	Early caffeine	Targeted dexamethasone
Reduced maternal smoking	Early CPAP	Lung protective respiratory support	Pulmonary hypertension management
Antenatal steroids	Selective surfactant	Prophylactic hydrocortisone	
		LISA	

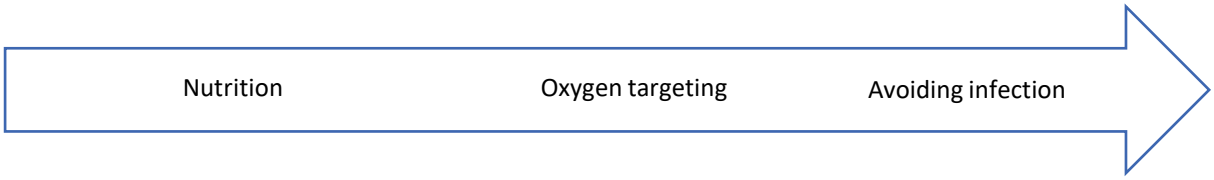

Figure 2: Strategies to reduce BPD

2. Guideline Scope

The aim of this guideline is to support provision of care based on best practice and best available evidence to reduce rates of bronchopulmonary dysplasia. It is intended for use by neonatal professionals involved in the care of preterm infants.

Antenatal optimisation is outside the scope of this guideline, but is covered elsewhere in the NENC Management of Preterm Birth guideline[3].

Key areas covered include:

- Maintenance of normothermia
- Early respiratory support
- Surfactant administration
- Mechanical ventilation strategies
- Caffeine use
- Prophylactic hydrocortisone
- Targeted dexamethasone

3. Normothermia

Recommendations

a) All preterm infants should have a documented first temperature of 36.5-37.5°C within one hour of birth.

- Hypothermia is associated with a significantly increased risk of BPD, in addition to other morbidities including hypoglycaemia, necrotising enterocolitis, intraventricular haemorrhage and death[4].
- Numerous strategies can be used to minimise heat loss and promote normothermia, including:
    - Use of an occlusive plastic bag/wrap and a woollen or plastic hat to reduce evaporation of heat from the skin.
    - Use of warm, humidified gases at delivery to reduce loss of moisture and heat from the respiratory tract.
    - Stabilisation under a radiant heat source.
    - Maintain delivery room temperature 23-26°C.
    - Use of a Transwarmer or heated mattress.
- The NENC Preterm Birth Guideline, and British Association of Perinatal Medicine (BAPM) Normothermia Toolkit provide further support for implementing improvement in maintaining normothermia[3,5].

4. Early Respiratory Support

Recommendations

a) Continuous positive airway pressure (CPAP) should be considered the first line mode of respiratory support for spontaneously breathing preterm infants following delivery.

- Routine use of CPAP rather than intubation and ventilation at delivery reduces the incidence of death or BPD at 36 weeks (RR 0.89 [0.79-0.97])[6–8]
- Spontaneously breathing preterm infants should therefore be stabilised using CPAP, rather than intubated in the delivery room wherever possible. Intubation should be reserved for infants not responding to positive pressure ventilation via mask/prongs or CPAP.

- Nasal high flow therapy should **not** be used as the primary mode of respiratory support in preterm infants as it is associated with significantly higher rates of treatment failure than CPAP[9,10].
- Synchronised non-invasive positive pressure ventilation (NIPPV) has been associated with reduced need for mechanical ventilation and re-intubation in preterm infants, therefore may be considered as an alternative to CPAP[11,12].

5. Surfactant Administration

Recommendations

a) Preterm infants requiring intubation and ventilation during stabilisation should receive surfactant immediately.
b) Less invasive surfactant administration should be considered for preterm infants receiving non-invasive respiratory support, provided clinicians are experienced with this technique.

- Surfactant should be considered when FiO_2 is >0.3 with optimal CPAP, and given time to settle (30-60 minutes depending on clinical situation) as this is predictive of CPAP failure[13].
    - Surfactant administration may be considered at a lower FiO_2 if clinically indicated by work of breathing, blood gases or in very premature infants

- Less invasive surfactant administration (LISA) techniques reduce the incidence of BPD (OR 0.49 [0.3-0.79]), exposure to mechanical ventilation, incidence of pneumothorax and significant intraventricular haemorrhage compared to intubation for surfactant administration[14–16].
- LISA should be the preferred method for surfactant administration when an infant is receiving non-invasive respiratory support. Local guidelines for analgesia and/or sedation are required. Side effects have been reported with LISA, notably bradycardia during surfactant installation. This can be effectively managed by temporarily pausing the instillation or slowing the pace of instillation.

- A first dose of 200mg/kg dose of poractant alfa is recommended, as this is associated with lower need for repeat administration than lower doses[17].
- A second dose of 100mg/kg poractant alfa may be considered after 12 hours if the infant remains intubated with persistent high oxygen needs or high ventilatory needs.

Any infant in a level 1 unit requiring surfactant should be discussed with the Northern Neonatal Transport Service (NNeTS) for retrieval. LISA should not be performed in level 1 units; here the priority should be stabilisation with intubation, ventilation, and surfactant administration prior to transfer.

6. Mechanical Ventilation Strategies.

Recommendations

a) For infants requiring invasive ventilation, a synchronised, volume-targeted mode should be used.
b) Rescue high frequency oscillatory ventilation may considered to minimise exposure to high peak inspiratory pressures and/or tidal volumes.

Despite efforts to optimise non-invasive support, a number of preterm infants will require invasive mechanical ventilation. The aim of mechanical ventilation in preterm infants should be to provide acceptable gas exchange, whilst avoiding lung injury due to volutrauma, barotrauma and/or atelectotrauma, for the shortest duration possible.

Volume targeted modes of ventilation are associated with a shorter duration of ventilation, fewer air leaks and lower rates of BPD (RR 0.73 [0.59-0.89], NNT 8) than pressure-targeted ventilation modes, therefore volume targeted ventilation should be used as first line mode of ventilation[18].

High frequency oscillatory ventilation is an alternative strategy, which delivers very small tidal volumes at a very fast rate with the lung held open by a continuous distending pressure to prevent lung injury by overdistention and atelectasis. Studies comparing HFOV to conventional mechanical ventilation show a small reduction in rates of BPD, however these trials compared HFOV to pressure-limited modes of ventilation, rather than the volume modes used today[19]. HFOV may be used to avoid exposure to high peak inspiratory pressures and/or tidal volumes e.g. when peak inspiratory pressure ≥28cmH_2O, tidal volume >6ml/kg.

7. Early Extubation and Weaning Ventilation

Recommendations

a) Ventilation should be proactively weaned.
b) Extubation to optimal CPAP should be attempted as early as possible to minimise duration of mechanical ventilation.
c) Avoid unplanned extubation.

- Cumulative duration of ventilation, rather than courses of ventilation, predicts BPD in preterm infants, therefore ventilation should be actively weaned and extubation to non-invasive respiratory support should occur as soon as possible (figure 3)[20].
- We recommend extubation to CPAP and not high flow nasal cannula therapy, as the latter is associated with higher rates of treatment failure in very preterm infants[21,22].
- Extubation to CPAP 7-9cmH_2O is associated with higher rates of success than lower levels of CPAP[17].

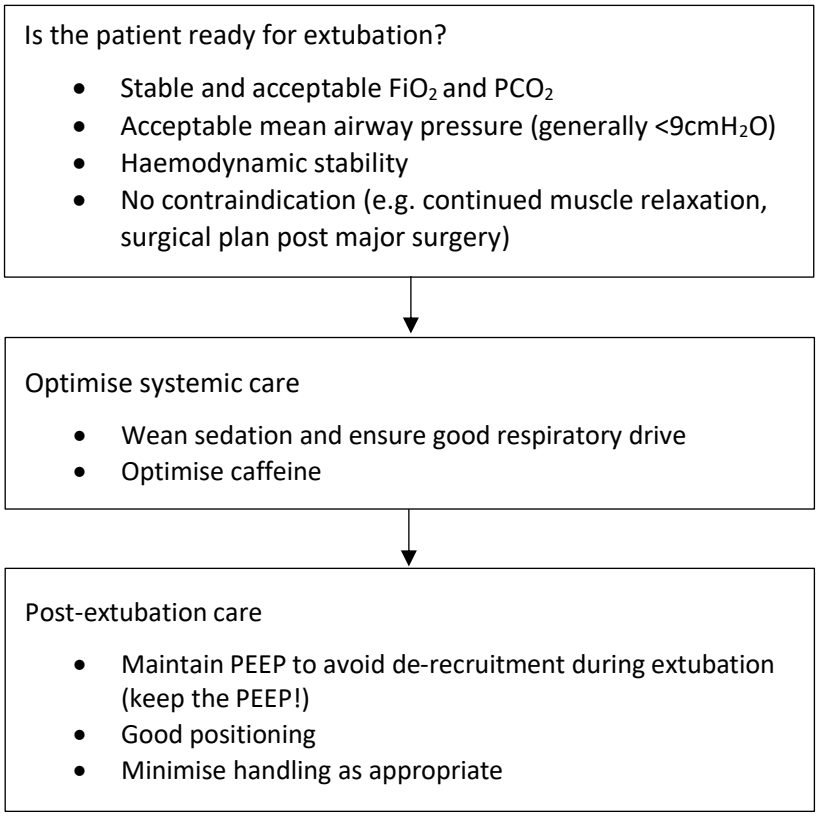

Figure 3: Extubation strategy

- Unplanned extubation should be avoided as it causes cardiopulmonary instability, derecruitment and this may inturn increase the respiratory need and thus BPD[23].

8. Caffeine Administration

Recommendations

a) It is recommended that all preterm infants <30 weeks gestation receive caffeine with in the first 72 hours of life.
b) Consider caffeine for other infants at high risk of needing invasive ventilation or non-invasive respiratory support e.g. 30-32 weeks gestation, <1.25kg, apnoea.

- The Caffeine for Apnoea of Prematurity (CAP) trial showed clear benefits for administration of caffeine, particularly when started within the first 72 hours of admission, namely earlier extubation, reduced BPD (OR 0.63 [0.52-0.76]), improved neurodevelopmental outcome at 18 months and lung function at 11 years[24–26]. Caffeine should therefore be given routinely to all eligible infants.
- Higher maintenance doses of caffeine (up to 20mg/kg/day caffeine citrate in divided doses) may be considered in infants who continue to have apnoea with standard doses[8].
- Caffeine therapy is generally discontinued at 33-35 weeks corrected gestational age, but may be continued beyond this in infants who continue to have apnoea.

9. Prophylactic Hydrocortisone

Recommendations

a) A course of early, low-dose prophylactic hydrocortisone may be considered to reduce BPD in infants born at 24^{+0} – 27^{+6} weeks gestation.
b) The combined use of hydrocortisone and non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with increased risk of gastro intestinal perforation, hence use of NSAIDs along with hydrocortisone must be avoided.

The PREMILOC study randomised >500 extremely preterm infants <28 weeks gestation to prophylactic hydrocortisone or placebo, and reported significantly higher rates of BPD-free survival with hydrocortisone (OR 1.48 [1.02-2.16] NNT=12).

In this study, a subgroup analysis showed that infants born 24-25 weeks gestation, treated with hydrocortisone had a higher rate of late-onset sepsis but no difference in rates of gastrointestinal

perforation was observed. At 2-year follow-up, early hydrocortisone was associated with significantly improved neurodevelopmental outcome in infants born at 24-25 weeks gestation[27–29]. At 5-year follow-up, early hydrocortisone treatment was associated with a significant increase in working memory and retention ability[30].

The PREMILOC study was discontinued early due to lack of funding, however these benefits are also evident in meta-analysis where prophylactic hydrocortisone increases survival without BPD in preterm infants without increasing rates of cerebral palsy[31,32].

- Number needed to treat for survival without BPD = 18
- Number needed to treat for survival without moderate to severe neurodevelopmental impairment = 14.

Hydrocortisone has been associated with increased rates of gastrointestinal perforation; however, this is predominantly associated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs e.g. ibuprofen or indomethacin) for treatment of a patent ductus arteriosus, and is not evidence in studies where infants receiving NSAIDs were excluded (including PREMILOC).

A course of low-dose hydrocortisone using a regime such as that used in PREMILOC (1mg/kg per day for 7 days then 0.5mg/kg/day for 3 days) starting on day 1 of life may be considered in preterm infants at risk of BPD especially premature infants exposed to chorioamnionitis and those who did not receive ANS[33].

The combined use of hydrocortisone and ibuprofen must be avoided to prevent increasing the risk of GI perforation, and infants receiving hydrocortisone should be closely monitor for infection due to potential increased risk of late onset sepsis.

10. Targeted Dexamethasone

Recommendations

a) A targeted course of dexamethasone should be considered moderately early in the postnatal course for infants at high risk of BPD e.g. infants requiring invasive ventilation for respiratory disease at >7 days of age.
b) A tapered, low-dose (0.15-0.2mg/kg/day), short course of dexamethasone should be used.

Dexamethasone used after the first week of life reduces BPD alone and the combined outcome of death/BPD, without evidence of increased cerebral palsy[34]. The likelihood of net benefit of postnatal dexamethasone depends on an individual's baseline risk of BPD, with those at highest risk,

such as those still requiring invasive ventilation for respiratory disease after 1-2 weeks, most likely to benefit[17,35].

Moderately early steroid use (day 8-14) to reduce inflammation, facilitate extubation, and minimise exposure to invasive ventilation appears to be most beneficial on meta-analysis, therefore risk assessment at this timepoint is recommended[36].

A tapered, short-course of low-dose dexamethasone such as that used in the DART regime is recommended as first line treatment as this has been shown to facilitate extubation[37].

11. Nutrition

Recommendations

- Early breast milk should be given to all preterm infants.

- Exclusive mother's own milk feeding significantly reduces risk of BPD (RR 0.74 [0.57-0.96])[38].
- Infants with evolving or established BPD have increased calorie requirements for growth and lung repair (120-150kcal/kg/day). Growth should be closely monitored and energy intake adjusted as required[39].

12. Prevention of Infection

Recommendations

- Meticulous infection control measures are required to prevent nosocomial infection.

- Postnatal infection is an independent risk factor for BPD, therefore careful infection control measures and good antibiotic stewardship are required[40].

13. Management of pulmonary hypertension

Recommendations

- Consider echocardiogram to assess heart function and for evidence of pulmonary hypertension in preterm infants with established BPD at 36 weeks PMA on positive pressure respiratory support.

- Pulmonary hypertension is present in 39% of infants with severe BPD, and is associated with increased risk of death (RR 4.7 [2.7-8.3]) and neurodevelopmental impairment[41,42].
- Pulmonary hypertension may be potentially modifiable with sildenafil. If there is evidence of pulmonary hypertension, sildenafil may be considered.

14. Audit Tool

For infants born at <32 weeks gestation

1. Admission temperature 36.5-37.5°C? Yes No
2. Intubated in delivery room? Yes No
3. Ever intubated during admission? Yes No
4. Total duration of invasive ventilation: _____ days
5. Received LISA? Yes No
6. Received caffeine on day 1? Yes No
7. Received mother's own milk:
    a. As first milk Yes No
    b. Exclusively during admission Yes No
8. For infants < 28 weeks:
    a. Received hydrocortisone within first 48 hours? Yes No
9. Received postnatal dexamethasone? Yes No
    a. If yes, age dexamethasone started: _____ days
    b. If yes, starting dexamethasone dose: _____ mcg/kg/day
10. Requiring positive pressure respiratory support at 36 weeks? Yes No
    a. If yes, echo for pulmonary hypertension performed? Yes No

REFERENCES

1 Thébaud B, Goss KN, Laughon M, *et al.* Bronchopulmonary dysplasia. *Nat Rev Dis Prim* 2019;**5**:78. doi:10.1038/s41572-019-0127-7

2 National Neonatal Audit Programme (NNAP). 2020 annual Report on 2019 data. 2020. https://www.rcpch.ac.uk/work-we-do/quality-improvement-patient-safety/national-neonatal-audit-programme

3 North East and North Cumbria Clinical Network: Management of preterm birth. 2021. doi:10.1007/s00129-018-4227-3

4 Lyu Y, Shah PS, Ye XY, *et al.* Association between admission temperature and mortality and major morbidity in preterm infants born at fewer than 33weeks' gestation. *JAMA Pediatr* 2015;**169**:1–8. doi:10.1001/jamapediatrics.2015.0277

5 Improving Normothermia in Very Preterm Infants: A Quality Improvement Toolkit. British Association of Perinatal Medicine. 2019. www.bapm.org/quality

6 Subramaniam P, Ho J, Davis P. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev* 2016;**6**:1–51. doi:10.1002/14651858.CD001243.pub3

7 Schmölzer GM, Kumar M, Pichler G, *et al.* Non-invasive versus invasive respiratory support in preterm infants at birth: Systematic review and meta-analysis. *BMJ* 2013;**347**:1–8. doi:10.1136/bmj.f5980

8 National Institute for Health and Care Excellence. Specialist neonatal respiratory care for babies born preterm. 2019. doi:10.7748/ncyp.31.3.11.s9

9 Roberts CT, Owen LS, Manley BJ, *et al.* Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants. *N Engl J Med* 2016;**375**:1142–51. doi:10.1056/NEJMoa1603694

10 Manley BJ, Arnolda GRB, Wright IMR, *et al.* Nasal High-Flow Therapy for Newborn Infants in Special Care Nurseries. *N Engl J Med* 2019;**380**:2031–40. doi:10.1056/NEJMoa1812077

11 Ramaswamy VV, More K, Roehr CC, *et al.* Efficacy of noninvasive respiratory support modes for primary respiratory support in preterm neonates with respiratory distress syndrome: Systematic review and network meta-analysis. *Pediatr Pulmonol* 2020;**55**:2940–63. doi:10.1002/ppul.25011

12 Ramaswamy VV, Bandyopadhyay T, Nanda D, *et al.* Efficacy of noninvasive respiratory support modes as postextubation respiratory support in preterm neonates: A systematic review and network meta-analysis. *Pediatr Pulmonol* 2020;**55**:2924–39.

doi:10.1002/ppul.25007

13 Dargaville PA, Aiyappan A, De Paoli AG, *et al.* Continuous positive airway pressure failure in preterm infants: Incidence, predictors and consequences. *Neonatology* 2013;**104**:8–14. doi:10.1159/000346460

14 Aldana-Aguirre JC, Pinto M, Featherstone RM, *et al.* Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome : a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2017;**102**:17–24. doi:10.1136/archdischild-2015-310299

15 Isayama T, Iwami H, McDonald S, *et al.* Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: A systematic review and meta-analysis. *JAMA - J Am Med Assoc* 2016;**316**:611–24. doi:10.1001/jama.2016.10708

16 Mehler K, Broer A, Roll C, *et al.* Developmental outcome of extremely preterm infants is improved after less invasive surfactant application: Developmental outcome after LISA. *Acta Paediatr Int J Paediatr* 2021;**110**:818–25. doi:10.1111/apa.15565

17 Sweet DG, Carnielli V, Greisen G, *et al.* European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. *Neonatology* 2019;**115**:432–50. doi:10.1159/000499361

18 Klingenberg C, Wheeler K, McCallion N, *et al.* Volume-targeted versus pressure-limited ventilation in neonates. *Cochrane Collab* 2017;:1–87. doi:10.1002/14651858.CD003666.pub4.www.cochranelibrary.com

19 Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2015;**19**. doi:10.1002/14651858.CD000104.pub4

20 Jensen EA, DeMauro SB, Kornhauser M, *et al.* Effects of multiple ventilation courses and duration of mechanical ventilation on respiratory outcomes in extremely low-birth-weight infants. *JAMA Pediatr* 2015;**169**:1011–7. doi:10.1001/jamapediatrics.2015.2401

21 Manley BJ, Owen LS, Doyle LW, *et al.* High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med* 2013;**369**:1425–33.

22 Naples R, Harigopal S. Nasal high flow in extremely preterm infants: Current evidence and practice in the United Kingdom. *Acta Paediatr* 2022;**111**:302–4. doi:10.1111/apa.16135

23 Pavlek LR, Dillard J, Ryshen G, *et al.* Short-term complications and long-term morbidities associated with repeated unplanned extubations. *J Perinatol* 2021;**41**:562–70. doi:10.1038/s41372-021-00927-9

24 Schmidt B, Roberts RS, Davis P, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;**354**:2112–21. doi:10.1056/NEJMoa073679

25 Davis PG, Schmidt B, Roberts RS, *et al.* Caffeine for Apnea of Prematurity Trial: Benefits May Vary in Subgroups. *J Pediatr* 2010;**156**. doi:10.1016/j.jpeds.2009.09.069

26 Mürner-Lavanchy IM, Doyle LW, Schmidt B, *et al.* Neurobehavioral outcomes 11 years after neonatal caffeine therapy for apnea of prematurity. *Pediatrics* 2018;**141**:e20174047. doi:10.1542/peds.2017-4047

27 Baud O, Maury L, Lebail F, *et al.* Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): A double-blind, placebo-controlled, multicentre, randomised trial. *Lancet* 2016;**387**:1827–36. doi:10.1016/S0140-6736(16)00202-6

28 Baud O, Trousson C, Biran V, *et al.* Association Between early low-dose hydrocortisone therapy in extremely preterm neonates and neurodevelopmental outcomes at 2 years of age. *JAMA* 2017;**317**:1329–37. doi:10.1001/jama.2017.2692

29 Baud O, Trousson C, Biran V, *et al.* Two-year neurodevelopmental outcomes of extremely preterm infants treated with early hydrocortisone: Treatment effect according to gestational age at birth. *Arch Dis Child Fetal Neonatal Ed* 2019;**104**:30–5. doi:10.1136/archdischild-2017-313756

30 Trousson C, Toumazi A, Bourmaud A, *et al.* Neurocognitive outcomes at age 5 years after prophylactic hydrocortisone in infants born extremely preterm. *Dev Med Child Neurol* 2023;**65**:926–32. doi:10.1111/dmcn.15470

31 Morris IP, Goel N, Chakraborty M. Efficacy and safety of systemic hydrocortisone for the prevention of bronchopulmonary dysplasia in preterm infants: a systematic review and meta-analysis. *Eur J Pediatr* 2019;**178**:1171–84. doi:10.1007/s00431-019-03398-5

32 Doyle LW, Cheong JL, Hay S, *et al.* Early (<7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev* 2021;**2021**. doi:10.1002/14651858.CD001146.pub6

33 Shaffer ML, Baud O, Lacaze-Masmonteil T, *et al.* Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis. *J Pediatr* 2019;**207**:136-142.e5. doi:10.1016/j.jpeds.2018.10.004

34 Doyle LW, Cheong JL, Hay S, *et al.* Late (≥7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev* 2021;**2021**. doi:10.1002/14651858.CD001146.pub6

35 Doyle LW, Halliday HL, Ehrenkranz RA, *et al.* An update on the impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: Effect modification by risk of bronchopulmonary dysplasia. *J Pediatr* 2014;**165**:1258–60. doi:10.1016/j.jpeds.2014.07.049

36 Ramaswamy VV, Bandyopadhyay T, Nanda D, *et al.* Assessment of Postnatal Corticosteroids for the Prevention of Bronchopulmonary Dysplasia in Preterm Neonates: A Systematic Review and Network Meta-analysis. *JAMA Pediatr* 2021;**175**:e206826. doi:10.1001/jamapediatrics.2020.6826

37 Doyle LW, Davis PG, Morley CJ, *et al.* Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: A multicenter, international, randomized, controlled trial. *Pediatrics* 2006;**117**:75–83. doi:10.1542/peds.2004-2843

38 Villamor-Martínez E, Pierro M, Cavallaro G, *et al.* Mother's own milk and bronchopulmonary dysplasia: A systematic review and meta-analysis. *Front Pediatr* 2019;**7**:1–9. doi:10.3389/fped.2019.00224

39 Dani C, Poggi C. Nutrition and bronchopulmonary dysplasia. *J Matern Neonatal Med* 2012;**25**:37–40. doi:10.3109/14767058.2012.712314

40 Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. *Birth Defects Res Part A - Clin Mol Teratol* 2014;**100**:145–57. doi:10.1002/bdra.23235

41 Arjaans S, Zwart EAH, Ploegstra MJ, *et al.* Identification of gaps in the current knowledge on pulmonary hypertension in extremely preterm infants: A systematic review and meta-analysis. *Paediatr Perinat Epidemiol* 2018;**32**:258–67. doi:10.1111/ppe.12444

42 Naples R, Ramaiah S, Rankin J, *et al.* Life-threatening bronchopulmonary dysplasia: a British Paediatric Surveillance Unit Study. *Arch Dis Child - Fetal Neonatal Ed* 2022;**107**:13–9. doi:10.1136/archdischild-2021-322001