Yorkshire & Humber Neonatal ODN (South) Clinical Guideline
Title: Chronic Neonatal Lung Disease- Management of Author: Aiwyne Foo
Date written: 10 November 2011, Updated July 2017
Date ratified:
Review date: December 2020

This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire & Humber Neonatal ODN (South). The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

Best practice recommendations represent widely used evidence-based practice and high quality standards that all Neonatal Units across the Network should implement. Subsequent suggested recommendations may be put into practice in local units. However, alternative appropriate local guidelines may also exist.

A. Summary page

- To provide, as far as possible, an evidence based approach to the management of evolving chronic neonatal lung disease.

- The terms chronic lung disease (CLD) and bronchopulmonary dysplasia (BPD) are both used in this guideline according to where the evidence originated from.

- Where prevention is not possible, to treat or minimize the risk factors contributing to the development and worsening of CLD:
  - Respiratory distress syndrome
  - Positive pressure ventilation
  - Supplemental oxygen use
  - Patent ductus arteriosus
  - Infection
  - Growth failure

Therapeutic options are as follow:
1. Commence caffeine early (B)
2. Intramuscular Vitamin A (B) not for routine use
3. Postnatal corticosteroids:
   - In general, use will be in tertiary neonatal unit, to promote extubation, and to reduce mortality and CLD.
   - Use dexamethasone as choice of steroid as limited evidence of other forms of steroids.
o Avoid use in first two weeks of life (A)
o Identify and treat other causes for continued ventilator dependence before use.
o Cautious use in extreme preterm infants > 2 w of life with high requirement of mechanical ventilation, and those re-ventilated who remain ventilator-dependent for a significant length of time. (A) Consider discussion with tertiary neonatologist/respiratory specialist before use.
o Discuss risks and benefits with parents (D) (refer to appendix 2)
o Consider the DART or the Mini-dex regime (see below 4.1.3.5)
o Consider discussion with respiratory specialist/tertiary neonatologist the use of steroids, in infants >36 w PMA with CLD who are still nCPAP or high flow oxygen dependent to lessen detrimental effects on neuro-development and facilitate discharge home. (D)

3. Consider a short term trial of diuretics – thiazide and spironolactone, and possibly a longer course if necessary. (A)

Infants >36 w PMA with CLD requiring oxygen therapy should have their oxygen saturation kept ≥ 93%, and to avoid <90% as far as possible.

Refer to Long Term Oxygen Therapy in Children Guideline for:
  • Low flow oxygen use
  • Oxygen titration and pulse oximetry
  • Discharge planning

B. Full guideline

1.0 Background
Bronchopulmonary dysplasia (BPD) is the most common form of chronic lung disease in infancy (CNLD/CLD) (1). BPD currently occurs primarily in extremely premature infants (23-28 weeks gestation) born in the late canalicular/early saccular stage of lung development. BPD today is conceptualized as a consequence of disrupted and impaired lung development (38).

Major risk factors include preterm birth per se, supplemental oxygen and positive pressure ventilation, patent ductus arteriosus, and infection.

Enhanced susceptibility to a variety of infections and inflammation play a large role in early and prolonged lung disease following premature birth (32). CLD is associated with increased mortality, poor neurodevelopmental outcome, significant long term cardiorespiratory sequelae including pulmonary hypertension, decreased lung volume in the neonatal period, poor airway function and limited exercise tolerance in later childhood and adulthood.

CLD is defined as a requirement for supplemental oxygen for 21 of the first 28 days of life, and identifies three grades of severity (mild, moderate or severe) depending on the level of
supplemental oxygen and mechanical ventilatory support at 36 weeks post menstrual age (PMA) (1,2).

The use of different definitions for BPD has been an on-going challenge and it is recognized that an evidence based definition needs to be developed for benchmarking and prognostic use (33).

2.0 Aim
To provide, as far as possible, an evidence-based guide to the management of evolving CLD, with emphasis on a multimodal approach- including adequate nutrition, careful fluid management, effective and safe pharmacotherapy, and respiratory support aiming at minimal lung injury.

3.0 Areas outside remit
Investigations including pulmonary function testing.
Details of home oxygen and long term oxygen therapy.

4.0 Core guideline

4.1 Pharmacological Treatment

4.1.1 Caffeine
Reduces the risk of CLD and improves the primary outcome of survival without neurodevelopmental impairment at 18 to 21 months corrected age (3).
Caffeine is shown in high quality studies to prevent BPD without the risk of clinically important adverse effects (34).
Recommendation:
Commence caffeine early – this can be before extubation is considered and for all infants <30 week's gestation.

4.1.2 Vitamin A
10 RCTs compared vitamin A supplementation with a control where supplementation appeared to have a small benefit in reducing the risk of death and oxygen requirement at 1 month of age (NNTB 20) and the risk of CLD at 36 weeks PMA (NNTB 11) (4).
4.1.2.2 No adverse effects of vitamin A were reported, but it was noted that intramuscular injections of vitamin A were painful (5).
Neurodevelopmental assessment of surviving infants showed no difference between the groups at 18-22 months of corrected age (6).
Recommendation:
At present not considered for regional use.

4.1.3 Postnatal corticosteroids
Early (<8 days) systemic use to prevent CLD: 29 RCTs with 3750 infants where reviews showed a decreased risk of death and BPD at 28 days and 36 weeks PMA, PDA and ROP, GI bleeding and intestinal perforation were adverse effects, alongside increased risk of hyperglycaemia, hypertension, hypertrophic cardiomyopathy and growth failure. Late outcomes were reported in 12 trials- severe adverse neurological effects (developmental delay, cerebral palsy and abnormal neurological examination) were found at follow-up (7).
Delayed (>7 days) systemic use facilitated extubation, reduced the risk of BPD and death or BPD at both 28 days and 36 weeks PMA. Short term adverse effects include hyperglycaemia and hypertension and a trend towards an increased risk of infection and GI bleeding. There was no effect on the combined rate of death or cerebral palsy at follow-up (8).

Moderately early (7-14 days) systemic use showed similar results to delayed systemic use with limited data on long term outcome (9).

Inhaled corticosteroids: reviews of 10 qualified trials of inhaled corticosteroids administered to preterm infants with birth weight up to 1500g beginning in the 1st 2 weeks after birth – showed increasing evidence that early administration of inhaled steroids in VLBW neonates is effective in reducing the incidence of CLD at 36 weeks PMA. The long term follow up of the Bassler 2015 study may affect the conclusion of this review. Further studies are needed (38).

Low dose dexamethasone after 1st week of life facilitates extubation and shortens duration of ventilation in very preterm/extremely low birth weight infants without any obvious short term complications. (DART) - Doses used were 0.15mg/kg for 3 days, followed by 0.10mg/kg for 3 days, then 0.05mg/kg for 2 days and 0.02mg/kg for 2 days (11). At 2-year follow-up, although sample size was small and unable to provide definitive evidence on long term effects, low dose dexamethasone was not associated with long term morbidity (12).

A small non-randomised controlled trial showed that low dose dexamethasone 0.05mg/kg/day for 10 days followed by alternated day- doses for 6 days facilitated extubation without significant short term side effects (31).

A 5-year observational study also reported similar results with very low dose dexamethasone – starting at 0.05mg/kg/day, reducing over 9 days with a cumulative dose of 24mg/kg (32).

The NPEU multicentre Minidex Trial will be looking at the efficacy and safety of very low dose dexamethasone used to facilitate the extubation of ventilator dependent preterm babies who are at high risk of BPD. Higher cumulative dexamethasone doses administered after the 1st week of life may decrease the risk for BPD without the risk of increasing the risk for neuro-developmental sequelae in ventilated preterm infants (13).

Recommendation:

- Use dexamethasone as choice of steroid as limited evidence with other forms of steroid
- Avoid use in first two weeks of life
- Identify and treat other causes for continued ventilator dependence
- Cautious use in extreme preterm infants > 2 weeks of life with high requirement of mechanical ventilation, and those re-ventilated for whatever reason and remain ventilator-dependent for a significant length of time.
- Discuss with parents risks and benefits of steroids (refer to parental information appendix 2).
- Consider a repeat course with or without a prolonged wean for infants who initially responded to therapy but relapsed or deteriorated on withdrawal.
- Discussion with respiratory specialist/tertiary neonatologist the use of steroids, in infants >36 weeks PMA with CLD who are still nCPAP or high flow oxygen dependent to lessen detrimental effects on neuro- development and facilitate discharge home.
4.1.4 Diuretics
In preterm infants >3 weeks of age with CLD, a 4 week treatment course with thiazide and spironolactone improved lung compliance and reduced the need for frusemide. A single study showed this combination decreased the risk of death (14).

In preterm infants <3 weeks of age developing CLD, frusemide has either inconsistent effects or no detectable effect. In infants >3 weeks of age with CLD, frusemide improves lung compliance and oxygenation. However, there is lack of data on important clinical outcomes (15).

Recommendation:
- A short-term trial (2-4 weeks) of diuretics e.g. combined thiazide and spironolactone may be used in preterms with evolving or established CLD.
- A longer course many be needed in some infants.
- Side effects eg. hyponatraemia must be monitored and treated.

4.1.5 Bronchodilators
Data are insufficient for reliable assessment of the use of salbutamol for prevention of CLD. One trial of poor quality reported a reduction in the incidence of CLD and shorter duration of supplementary oxygen with prophylactic aminophylline. There were no trials identified using bronchodilator therapy for treatment of CLD (16).

In a review of 2 studies with 64 infants given prophylactic inhaled cromolyn sodium there was no evidence of prevention of CLD (17).

Recommendation:
- Insufficient evidence to support the routine use of bronchodilators in CLD.

4.1.6 Pulmonary Vasodilators
Inhaled nitric oxide is used in babies with pulmonary hypertensive crises (18). However, in infants with evolving BPD ventilated between 7 and 21 days of life, long term administration of iNO did not decrease rate of death or BPD at 36 weeks PMA (19).

Early use of nitric oxide in very preterm infants did not improve survival without BPD or brain injury in a large RCT involving 800 infants (20).

Sildenafil is the medication most commonly used in neonatal units for pulmonary hypertension associated with CLD, but there are many side effects (36).

Recommendation:
- Discuss management of pulmonary hypertension with tertiary neonatologist/respiratory paediatrician
- Screening for early development of pulmonary hypertension, as well as periodic screening with established CLD, will help diagnose and allow early treatment if indicated.

4.1.7 Antibiotics
Respiratory tract colonization with *Ureaplasma parvum* and *U. urealyticum* in preterm infants is a significant risk factor for BPD, but causality has not been established (35).

Animal studies have shown Ureaplasma can establish a chronic infection with inflammation in the intrauterine compartment and alter fetal lung development (35).

Recommendation:
Currently insufficient data concerning the benefit/risk ratio of antibiotics therapy to recommend treatment to prevent BPD in preterm infants at-risk or with confirmed Ureaplasma infection.

4.2 Oxygen administration
Treating hypoxia whilst limiting oxygen toxicity is the goal (21-22). The BOOST and STOP-ROP RCTs assessed oxygen saturations targets in preterm infants after 28 days: the former found the high saturation group received oxygen for longer but no difference in primary outcome at 1 year corrected, the latter found a trend towards a beneficial effect of a higher oxygen saturation target (23,24).
In extremely preterm infants, targeting lower (85% to 89%) SpO\textsubscript{2} compared to higher (91% to 95%) had no significant effect on the composite outcome of death or major disability or on major disability alone, but increased the average risk of mortality by 28 per 1000 infants treated (25).
The SUPPORT trial showed that a lower target range of oxygenation (85-89%) as compared to a higher one (91-95%), did not significantly decrease the composite outcome of severe retinopathy or death, but resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors (33).

Recommendation:
• Target oxygen saturation for <36 weeks PMA between 91-95%.

4.3 Patent Ductus Arteriosus and Fluid Management
The presence of a PDA and a high fluid intake are associated with an increased risk of BPD likely due to pulmonary fluid overload (26).
Prophylactic indomethacin and ibuprofen are equally effective in closing PDA but do not prevent BPD (27). There is no evidence to support the practice of fluid restriction in infants with early or established BPD (37).

Recommendation:
• Avoid excessive fluid intake in the presence of a significant PDA.
• Refer to Y&H Neonatal ODN (South) guideline on Management of the Patent Ductus Arteriosus.

4.4 Nutrition
BPD is associated with a low lean mass and low functional residual capacity is associated with intrauterine growth restriction and duration of supplemental oxygen (28).

Recommendation:
• Optimum nutrition from as early on as possible.
• In some cases the use of high energy formula in reduced quantities to avoid fluid overload and gastroesophageal reflux may be beneficial whilst maintaining and promoting growth e.g. SMA High Energy 130ml/kg/day or Infatrini 120ml/kg/day has the same calories as 150ml/kg/day of preterm formulae. However, the majority of babies with CLD will be preterm and it must be remembered that these formulas are not designed for preterm infants and may not meet other dietary requirements (e.g. phosphate).

4.5 Respiratory Support Strategies and Surfactant
Refer to Y&H Neonatal ODN (South) Ventilation and RDS guidelines.
4.6 Long term oxygen therapy
Hypoxaemia causes pulmonary hypertension, a complication of CLD with up to 30% mortality. Low oxygen saturations are also associated with poor growth and poor sleep quality (29). Oxygen titration should be done using pulse oximetry including periods of different activities. Weaning of supplemental oxygen should only be done based on satisfactory recordings during a trial of lower flow.

There is insufficient evidence to say weaning for increasing hours a day or step-wise weaning to a continuous lower flow is a better method (29). Discharge planning and management of home oxygen in infants with CLD is extensively covered in Long Term Oxygen Therapy in Children Guideline (30).

Recommendation:
Infants >36 w PMA with CLD requiring oxygen therapy should have their oxygen saturation kept ≥ 94%, and to avoid <90% as far as possible.
• Refer to Long Term Oxygen Therapy in Children Guideline (30).

6) Audit criteria
• Routine use of caffeine in preterms <1250g
• At 36 weeks PMA - maintenance of oxygen saturations > 94%

7) References
Vitamin A supplementation to prevent mortality and short and long term morbidity in very low birth weight infants
8. Halliday HL, Ehrenkranz RA, Doyle LW. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane database Syst Rev 2014 May 13; CD001145
9. Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev 2011;CD001144
10. (a) Shah VS, Ohlsson et al. early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates. Cochrane Database Syst Rev 2007;CD001969
12. Doyle LW Davis PG et al. Outcome at 2 years of age Infants from the DART 1 study. Pediatrics 2007;119:716-21
15. Stewart A, Brion LP. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Cochrane database syst Rev 2011; CD001453
31. Yates HL, Newell SJ. Mini-dex: Very low dose dexamethasone (0.05mg/kg/day) in chronic lung disease. ADC 2011;96(3):F190-4

C. Appendices
1. Evidence grading
2. Parent Information Leaflet

Appendix 1 Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Requires at least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>B</td>
<td>Requires a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
</tr>
<tr>
<td>C</td>
<td>Requires a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
</tr>
</tbody>
</table>

Appendix 2 Parent Information Leaflet

See next page
Using steroid treatment for Neonatal Lung Disease

Background
Chronic lung disease of prematurity occurs in some babies who have been born early. It is likely to happen if the baby has been born prematurely (less than 30 weeks gestation) and has required ventilation following birth.

The lungs of premature babies lack a chemical called surfactant. Chronic lung disease usually develops gradually due to the effects of ventilation and also infection which lead to damage to these lungs.

Sometimes chronic lung disease is severe enough to make it difficult for a baby to come off the breathing machine or in extreme circumstances the baby may die.

Dexamethasone is a steroid medicine which reduces chronic lung disease and improves the baby’s breathing and, as a result in most cases the baby is able to come off the ventilator and in lower amounts of oxygen (1).

Why is Dexamethasone treatment suggested for my baby?
Your baby requires a significant amount of breathing support and a high oxygen level and is amongst those babies who are at risk of severe chronic lung disease. To help your baby come off the ventilator it is felt that they would benefit from treatment with Dexamethasone.

What are the advantages of Dexamethasone treatment for my baby?
In most cases, the use of Dexamethasone will help your baby come off the ventilator, although your baby may well still need some support in oxygen given though the nose or by a special machine call a CPAP machine (Continuous Positive Airway Pressure). It is hoped that once your baby is off the ventilator, the lungs can begin that long process of repair and healing.

What are the disadvantages for my baby?
Dexamethasone is a powerful medication which can cause other problems on its own. Some of these are listed below:-

Bleeding in the stomach. We treat this by using another medication that reduces the production or effect of acid on the stomach walls.

It can also cause a temporary increase in blood sugar and the baby’s blood pressure. These would be monitored regularly and if necessary treated or the medication stopped altogether (2).

There is a small chance of an increased risk of infection. If there is any suspicion of infection, we would be sending some blood samples to the laboratory and then starting your baby on antibiotics.

Poor weight gain and head growth. Because of this we would also be monitoring your baby’s weight and head circumference regularly.
While some studies have suggested that there may be an increased risk of cerebral palsy (movement difficulties associated with some degree of brain damage) (3), other studies have suggested that there is no increased risk (4, 5, 6, 7, 8).

It is however important that you know about this. If a baby is extremely premature and requires long periods on the breathing machine then they also do have an increased risk of having cerebral palsy. In these situations, we do need to weigh the risks of continued stay on the breathing machine with those of giving your baby Dexamethasone.

**What if my baby does not receive the treatment?**
If your baby does not receive treatment with Dexamethasone, it may well be that your baby will either require a longer period on the breathing machine or may die as they will not be able to come off the ventilator.

**What does the course of treatment consist of?**
The course of treatment in our unit currently consists of twice daily doses of Dexamethasone starting with an initial dose treatment for 3 days, followed by reduced intermediate dose treatment for another 3 days and then low dose treatment for 3 days and the treatment is then stopped. This means your baby would have this treatment for 9 days in total. Usually only one course of treatment is given, but very occasionally it may be necessary to give a second course of treatment or continue on a low dose treatment on alternate days in severe cases of chronic lung disease.

**How quickly does the treatment work?**
Usually by the second to third day of starting treatment we would normally see a response to the steroid treatment and most babies would be able to come off the ventilator during the treatment’s first week.

There is still a chance that your baby may need to be put back on the ventilator after successfully coming off but any period of time your baby spends off the ventilator would also contribute to the healing and repair process. In some cases the Dexamethasone may only have a short term benefit to your baby or the treatment may not be successful and your baby will need to remain on the ventilator.

**Do I have to agree to this treatment?**
The doctors have discussed this with you because they think that this right for your baby to have this treatment. You do not have to agree if after this discussion, you feel that it is not the right time for your baby to have this treatment.

If my baby does not have the treatment now can my baby have this later? Yes, your baby can, although the doctors will advise you when they believe is the right time to think about giving this treatment.

**Who do I ask for more information?**
Please ask to speak to one of the senior doctors if you have any questions.
REFERENCES
6. Steven J. Gross, Ran D. Anbar, and Barbara B. Mettelman Follow-up at 15 Years of Preterm Infants From a Controlled Trial of Moderately Early Dexamethasone for the Prevention of Chronic Lung Disease Pediatrics, Mar 2005; 115: 681 - 687.
7. Michael O'Shea, Lisa K. Washburn, Patricia A. Nixon, and Donald J. Goldstein. Follow-up of a Randomized, Placebo-Controlled Trial of Dexamethasone to Decrease the Duration of Ventilator Dependency in Very Low Birth Weight Infants: Neurodevelopmental Outcomes at 4 to 11 Years of Age Pediatrics, Sep 2007; 120: 594 - 602.