Guideline for the Prevention of Bronchopulmonary Dysplasia and Assessment of Evolving Bronchopulmonary Dysplasia

Toronto Centre for Neonatal Health

Research • Innovation • Education • Outreach

Founding Partners: Neonatologists at Mount Sinai, SickKids, Sunnybrook and St. Michael’s Hospital
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<th>Summary of Recommendations:</th>
<th>Target Population: neonates born &lt; 30 weeks gestation</th>
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</thead>
</table>
| **Non-invasive Monitoring**   | ■ Target SpO2 for preterm infants requiring supplemental oxygen in the range of 90 to 95% (as per unit specific guideline).  
                                ■ Alarms should be set to maximize time spent within the designated oxygen saturation target range.  
                                ■ Use non-invasive CO2 monitoring for mechanically ventilated infants. |
| **Surfactant**                | ■ Consider early selective surfactant administration for infants requiring intubation.  
                                ■ For infants on CPAP during transition (first 1 – 2 hours) to extra-uterine life who have worsening respiratory distress or oxygen requirements >30% on optimized non-invasive CPAP, recommend intubation and surfactant administration as the earlier surfactant is given when there is RDS, the better the outcome.  
                                ■ Use of a natural surfactant is preferred due to its superior effectiveness. |
| **Caffeine**                  | ■ Start caffeine on day 1 of life for infants at high risk of needing mechanical ventilation or non-invasive respiratory support (e.g. <1,250 g birth weight and/or less than 30 weeks gestation at birth). |
| **Conventional Ventilation**  | ■ **Initial mode of ventilation for infants born greater than or equal to 27 weeks gestational age**  
                                ■ Use volume targeted ventilation.  
                                ■ Provide 4 – 6 ml/kg for volume targeted ventilation.  
                                ■ Initially, use a minimum positive end expiratory pressure (PEEP) of 5 cmH2O and then advance PEEP if required based on clinical response.  
                                ■ Target adequate recruitment to avoid atelectrauma while avoiding overdistension.  
                                ■ Consider high frequency oscillation ventilation (HFOV) or high frequency jet ventilation for infants who require increased peak inspiratory pressures or increased positive end expiratory pressures to achieve targeted volume. |
| **High Frequency Oscillation Ventilation (HFOV)** | ■ **Strongly consider as initial mode of ventilation for infants born less than 27 weeks gestational age.**  
                                ■ Recommend using HFOV – volume targeted mode.  
                                ■ **Initial Settings**  
                                ▪ Target volume: 1 - 2 ml/kg. Higher volumes may be required due to deadspace. Assess for adequate shake and CO2 clearance as an additional measure of effectiveness.  
                                ▪ Start mean airway pressure (MAP): 2 cm above the conventional ventilation MAP.  
                                ▪ Frequency 8-10 Hz.  
                                ▪ Obtain chest x-ray to assess for adequate aeration (or overdistension) within a few hours post commencement of HFOV. |
| **High Frequency Jet Ventilation (HFJV)** | Consider HFJV for the following infants:  
                                ■ **Initial mode of ventilation for infants with concerns of pulmonary hypoplasia.**  
                                ■ Tidal volumes targets approaching set upper pressure limits/ranges on conventional ventilation.  
                                ■ Air-leaks (including pulmonary interstitial emphysema – PIE).  
                                ■ Non-homogenous lung disease (e.g. pneumonia or meconium aspiration syndrome).  
                                ■ Evolving or established bronchopulmonary dysplasia.  
                                ■ **Initial settings**  
                                ▪ Inspiratory time = 0.02 seconds.  
                                ▪ Rate: 240 - 360 breaths per minute: air leak, gas trapping, significant spontaneous breathing.  
                                ▪ 300 breaths per minute: lung disease with short time constants (ie RDS).  
                                ▪ Mean airway pressure (MAP): match MAP of conventional ventilation to calculated MAP of HFJV.  
                                ▪ If air trapping or air leak present in non-atelectatic lungs, consider a lower mean airway pressure (MAP) to achieve adequate aeration and acceptable oxygen saturations and FiO2 delivery. |
| **Extubation**                | **Infants born < 24 weeks gestation:** if intubated, provide invasive ventilation for at least 72 hours, then extubate as soon as possible.  
                                ■ **Extubate as soon as possible to reduce further ventilator induced lung injury.**  
                                ■ Extubate to non-invasive respiratory support to maintain distending pressure (NIPPV/CPAP/NI-HFOV)*  
                                ■ Consider extubation if:  
                                1. **Blood gases are acceptable on low ventilator settings**  
                                   HFOV: < 11 cmH2O mean airway pressure  
                                   CMV: 8-9 cmH2O mean airway pressure  
                                2. **FiO2 is less than 40%**  
                                3. **Respiratory drive is adequate**
## Summary of Recommendations

### Hydrocortisone

**< 28 weeks GA on day 1 of life**

1. **Use of early low-dose prophylactic hydrocortisone for the prevention of BPD (see dosing suggestion within guideline)**
   
   Initiation of low-dose hydrocortisone on **day 1 of life in infants less than 28 weeks gestation** for the prevention of bronchopulmonary dysplasia may be considered when there are significant concerns for the development of bronchopulmonary dysplasia (such as but not limited to: infants born to mothers with suspected/confirmed chorioamnionitis; infants born to mothers who did not receive antenatal steroids).

2. **Avoid the combined use of indomethacin and systemic steroids (e.g. hydrocortisone, dexamethasone)**
   
   The combined use of indomethacin (treatment or prophylaxis) and systemic steroids should be avoided due to the increased risk of gastrointestinal perforations.

3. **Late-onset sepsis and early hydrocortisone**
   
   Close monitoring for late sepsis is essential due to an increased risk for late onset sepsis.

### Dexamethasone

**> 7 days of age**

- While routine dexamethasone therapy for all ventilated infants is not recommended and the benefits of late corticosteroid therapy (> 7 days of age) may not outweigh the actual or potential adverse effects, clinicians may consider late dexamethasone use for infants at high risk for bronchopulmonary dysplasia or with bronchopulmonary dysplasia who are unable to wean from mechanical ventilation using a regime that minimizes the dose and duration of therapy (refer to dosing suggestion within guideline).

- Prior to initiating treatment with dexamethasone for the management of evolving or established BPD, a discussion between the staff neonatologist and the baby’s parents to review the potential risks and benefits of dexamethasone should occur and permission for treatment obtained.

### Diuretics

- **Loop diuretics (e.g. furosemide)**
  
  - In preterm infants > 3 weeks of age with BPD or developing BPD and clinical and radiographic signs of pulmonary edema, a single dose or short course of diuretic therapy (up to one week) may be considered to improve oxygenation and lung compliance.
  
  - Evidence is lacking demonstrating benefits of loop diuretic use in the first few weeks of life for infants developing BPD.

- **Thiazide diuretics (e.g. hydrochlorothiazide and spironolactone)**
  
  - Infants who require and benefit clinically from single-doses or short courses of loop diuretics may benefit from chronic therapy.
  
  - In preterm infants > 3 weeks of age with evolving or established BPD and clinical and radiographic signs of pulmonary edema, treatment with distal renal tubule diuretics may be considered to improve pulmonary mechanics recognizing that the effects may be variable and transient.
Clinical Practice Guideline for the Prevention and Management of Infants with Evolving Bronchopulmonary Dysplasia (BPD)

Clinical Practice Guideline: Cardiorespiratory, pharmacologic, nutrition and neurodevelopmental support strategies for the prevention and management of (BPD) of evolving and established BPD. This clinical practice guideline aims to provide lung protective ventilation and pharmacologic strategies in preterm infants at high risk for developing BPD based on the current state of the evidence. As new evidence develops, alternate care plans may be considered.

Target Population: neonates born < 30 weeks gestation.

Purpose: The purpose of this clinical practice guideline is to prevent and decrease rates of bronchopulmonary dysplasia and to optimize and standardize the care of preterm infants with established or evolving bronchopulmonary dysplasia to improve their short-term and long-term outcomes.

Primary Goals
1. Prevent the development of BPD
2. Optimize nutrition for growth and nutrition
3. Prevent infection
4. Prevent the development of cor pulmonale
5. Support neurodevelopment

Background
Bronchopulmonary dysplasia is marked by lung inflammation and abnormal growth and development of the alveoli that typically develops in preterm infants treated with oxygen and positive-pressure mechanical ventilation. BPD remains a major cause of mortality and early morbidity in extremely low birth weight infants, with a concomitant increase in later neurodevelopmental impairment. BPD is one of the most common complications of extreme preterm birth. However, since the increased survival of the extremely preterm infant through advancements including the routine use of antenatal steroids, surfactant therapy and “gentler” ventilation strategies, the incidence of BPD has not changed significantly. Furthermore, the prevalence, or total number of infants with BPD, has increased because of improved survival. In addition, infants who subsequently develop severe BPD often have severe complications including pulmonary hypertension, poor growth and neurodevelopmental problems.

Definitions
- **Bronchopulmonary Dysplasia:** defined as a need for supplemental oxygen at 36 weeks’ postmenstrual age
  - Canadian Neonatal Network: chronic lung disease is defined as respiratory support given at 36 weeks’ post menstrual age
- **Evolving Bronchopulmonary Dysplasia:** the ongoing need for invasive or non-invasive respiratory support and/or supplemental oxygen in preterm babies between postnatal day 28 and 36 weeks post menstrual age
- **Etiologies:**
  - Lung injury caused by high shear forces from cyclic opening and collapse of atelectatic but recruitable lung units
  - Volutrauma: lung injury caused by alveolar overdistension

Mechanical Ventilation and BPD: Respiratory failure due to lung immaturity is a major cause of mortality in preterm infants. Although the use of invasive ventilation in neonates with respiratory failure saves lives and is necessary for the survival of many preterm infants, its use is associated with lung injury and BPD.

BPD: An Arrest in Pulmonary Development
- **BPD** has evolved since it was first described by Northway and Colleagues in 1967. They first described the characteristic features of BPD as an evolving radiograph pattern of lung injury in moderately preterm infants (infants in the late saccular stage of lung development) managed with pressure-limited time-cycled ventilators and high levels of supplemental oxygen.
- A new form of BPD developed with the increased survival of extremely preterm infants (22-25 weeks gestation) and advances in neonatal care. The “new” BPD is associated with an arrest in pulmonary development. This arrest in pulmonary development occurs in preterm infants born during the late canalicular stage and throughout the saccular stage of lung development.
- The new BPD is characterized by an interruption in airway septation and vessel growth. The arrest in lung development may be due to early exposure of the immature lung to breathing in a gas environment and/or the effects of oxygen toxicity and volutrauma.
Morphologic Changes of BPD\(^3\-^7\)
- Arrest in lung development that impairs alveolarization and vascularization
- Large simplified alveolar structures; ↓ number of alveoli; ↓ alveolar septation
- Abnormal vascular development with abnormally muscularized distal vessels
- Increased lung fluid, inflammation
  - Less severe epithelium airway injury than “old BPD”; variable smooth muscle airway hyperplasia and interstitial fibrosis

### Principal stages of lung development

![Diagram of lung development stages](image)

Fig. 1. Principal stages of lung development in humans. Diagrammatic representations of the time-line and developmental organization of trachea, primary bronchi, intrapulmonary bronchi and acinus in the mammalian respiratory system. Kajekar, R. Pharmacology & Therapeutics 114 (2007) 129–145.

### Pathogenesis of BPD: multifactorial disease occurring in an immature lung due to a combination of factors

![Diagram of pathogenesis](image)

Clinical interventions and occurrences that contribute to BPD. Jobe, H. Neoreviews 2006;7:e531-e545
## Pathogenesis of BPD

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Genetics</strong></td>
<td>- Genetics likely influences gene expression for surfactant synthesis, vascular development and inflammatory regulation.&lt;br&gt;- Infants with a genetic predisposition for airway reactivity (i.e. a strong family history of atopy and asthma) may be more likely to develop BPD.</td>
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<tr>
<td><strong>Hyperoxia and oxidant injury</strong></td>
<td>- Free oxygen radical production due to oxygen exposure is a principal factor contributing to the development of BPD. Free radicals are molecules with extra electrons in their outer ring and that leads to lipid peroxidation of cellular membranes throughout the body.&lt;br&gt;- Antioxidant concentrations in premature infants may be inadequate to protect against oxidative injury.&lt;br&gt;- Hyperoxia may induce inflammation, edema, and cellular dysfunction; impairment of mucociliary function and antiproteases inactivation.</td>
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<tr>
<td><strong>Hypoxia</strong></td>
<td>- Hypoxia may delay alveolar development and chronic hypoxia is associated with pulmonary hypertension, cor pulmonale and poor growth.</td>
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<td><strong>Ventilator induced lung injury (VILI)</strong></td>
<td>- Mechanical ventilation is a lifesaving intervention. However, it promotes lung injury through the initiation of an inflammatory process contributing to the development of BPD.&lt;br&gt;- The inflammatory process leads to the development of edema and potentially surfactant inactivation.&lt;br&gt;- The surfactant-deficient lung results in alveolar over-distention or primitive lung structure destruction, contributing further to lung injury.&lt;br&gt;- Conversely, failure to maintain adequate alveolar distention (i.e., alveolar atelectasis) can result in a repetitive cycle of alveolar collapse and recruitment, resulting in lung parenchymal injury.</td>
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<tr>
<td><strong>Inadequate Respiratory Drive and Apnea</strong></td>
<td>- An inadequate respiratory drive in preterm infants necessitates the need for mechanical ventilation, thus increasing the risk of ventilator-induced lung injury. Early use of caffeine is indicated.</td>
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<td><strong>Inflammatory Responses</strong></td>
<td>- Inflammation appears to be a significant factor in the development of BPD.&lt;br&gt;- Inflammatory processes may be initiated by the production of oxygen free radicals, mechanical ventilation, trauma, and infection.</td>
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<tr>
<td><strong>Infection</strong></td>
<td>- Infection may initiate an inflammatory process and may contribute to the development of BPD.&lt;br&gt;- Chorioamnionitis has been shown to be associated with an increased risk of BPD.</td>
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<tr>
<td><strong>Nutrition</strong></td>
<td>- Adequate nutrition is essential for lung development (and overall growth and development).&lt;br&gt;- Animal models have demonstrated that nutritional restriction results in reduced alveolar genesis.</td>
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<tr>
<td><strong>Aspiration Structural Lesions</strong></td>
<td>- Persistent or recurrent respiratory exacerbations may also be as the result of structural complications of prolonged mechanical support in susceptible populations such as tracheomalacia, subglottic stenosis, bronchomalacia and/or chronic aspiration secondary to gastroesophageal reflux or swallowing dysfunction.</td>
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</table>
Ventilation Management Goals

1. Avoid unnecessary intubation and mechanical ventilation to prevent secondary ventilator associated lung injury
   A. Provide mechanical or non-invasive respiratory support that maintains an open lung strategy while achieving the following:
      - Adequate oxygenation: adjust FiO2 to target SpO2 ~ 90-95%.
      - Provide acceptable blood gas exchange (see below).
      - Moderate permissive hypercapnia after the first week of life which aims to maintain gas exchange while reducing lung injury by avoiding high tidal volumes, pulmonary over-distention and hypocapnia.
      - Hypercapnia (PCO2 >60 mmHg), is a risk factor for acute brain injury in ELBW infants that may impair cerebral autoregulation and cause vasodilatation. RCTs have evaluated infants managed with permissive hypercapnia PCO2 or with PCO2 levels above the typical hypercapnia range (PCO2 55 mmHg to 65 mmHg), compared with normocapnia (PCO2 35 mmHg to 45 mmHg). Authors found no difference in the incidence of severe IVH with ventriculomegaly, intraparenchymal lesions or long-term neurodevelopmental outcomes. Median PCO2 levels > 72 mmHg or < 32 mmHg were associated with acute brain injury. Both extreme hypercapnia appear to cause brain injury and should be avoided.
   B. Avoid fluctuations in CO2 to reduce the risk of intraventricular hemorrhage, particularly during the first 72 hours of life. Use of transcutaneous CO2 probes when possible as they can facilitate timely adjustment in ventilation to achieve targets. Fluctuations of hypocapnia and hypercapnia increases the risk of IVH. pCO2 has a more profound effect on cerebral blood flow as buffering does not occur because the blood brain barrier limits HCO3 diffusion into the perivascular space. Hypocapnia in preterm infants compared to term infants causes marked cerebral blood vessel vasoconstriction, risking cerebral hypoperfusion and ischemic brain injury.

2. Minimize lung injury with the use of gentle ventilation
   - Recruit atelectatic lung by inflation and optimize lung volume for even distribution.
   - Avoid overinflation that increases the risk of air leaks (e.g. pneumothorax and pulmonary interstitial emphysema) and the development of air leak associated BPD and IVH.
   - Avoid underinflation that risks recurrent lung atelectasis that can lead to inflammation (atelectrauma).
   - Target low tidal volumes with increased positive end expiratory pressure (PEEP) for lung recruitment without overdistention.

Target blood gas values for infants < 30 weeks gestation

| Days 1-6 of life | pCO2 | 45 – 55 mm Hg | Avoid fluctuations in pCO2 (especially during the first 72 hours of life due to an increased risk of IVH) |
| Days 7–14 of life | pCO2 | 50 – 60 mm Hg |
| Days > 14 days of life | pCO2 | 50 – 60 mm Hg |

Values outside these parameters may be accepted at the discretion of the medical team, for example (but not exclusively) the acceptance of increased hypercarbia in the chronically ventilated infant.


References
Delivery room management for infants born < 29 weeks gestation: general guidelines

- Provide CPAP for spontaneously breathing preterm infants. Provide gentle positive pressure ventilation (PPV) for apnea or bradycardia
- Reserve intubation for babies who have not responded to optimized CPAP
- If intubation and FiO2 > 0.21 required for stabilization, surfactant should be given (early selective surfactant)

Delivery room management for infant born less than 24 weeks gestation

1. Initially provide CPAP or positive pressure ventilation as required
2. Establish vascular access if infant stable
3. Intubate. Consider short-acting opiate, muscle relaxant and atropine for intubation
4. Administer natural surfactant
5. Maintain mechanical ventilation using lung protective strategies
6. For brain protection continue invasive ventilation for 72 hours unless persistent hypocapnia

- Intubation and surfactant is recommended as local data demonstrates that almost all infants born < 24 weeks gestation require intubation.
- Occasionally CPAP can be considered for vigorous infants < 24 weeks. Frequent monitoring is required with a low threshold for intubation and surfactant administration.

Delivery room management for infants born 24 weeks gestation (≥ 24 weeks) to < 30 weeks

- perinatal centres may use higher CPAP levels

Pre-ductal SpO2 Target

<table>
<thead>
<tr>
<th>Time</th>
<th>Target (%)</th>
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<tbody>
<tr>
<td>1 min</td>
<td>60% - 65%</td>
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<tr>
<td>2 min</td>
<td>65% - 70%</td>
</tr>
<tr>
<td>3 min</td>
<td>70% - 75%</td>
</tr>
<tr>
<td>4 min</td>
<td>75% - 80%</td>
</tr>
<tr>
<td>5 min</td>
<td>80% - 85%</td>
</tr>
<tr>
<td>10 min</td>
<td>85% - 95%</td>
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*Ventilation Corrective Steps (“MR. SOPA”)*

**M** Mask adjustment
Reapply the mask. Consider 2 hand technique.

**R** Reposition airway
Place head neutral or slightly extended

Try PPV and reassess chest movement

**S** Suction mouth and nose
Use a bulb syringe or suction catheter

**O** Open mouth
Open the mouth and lift the jaw forward

Try PPV and reassess chest movement

**P** Pressure increase
Increase pressure in 5 to 10 cm H₂O increments. Max 30 cm H₂O

**A** Alternate airway
Place an endotracheal tube

If unable to wean FiO2 quickly despite optimal nasal CPAP, recommend intubation and surfactant

**YES**

Spontaneously Breathing?

NO

Heart rate > 100 bpm AND SpO₂ in target?

NO

Increase CPAP to max 10 cm H₂O*

YES

Heart rate > 100 bpm AND SpO₂ in target?

YES

1. Provide or maintain heated humidified CPAP to prevent atelectasis
2. Establish vascular access
3. Give caffeine

NO

FiO2 > 0.30?

NO

Wean CPAP to achieve SpO₂ targets

YES

FiO2 > 0.21?

NO

Administer surfactant

YES

FiO2 > 0.21?

NO

Wean ventilation to achieve SpO₂ targets

NO

Heart rate > 100 bpm AND SpO₂ in target?

NO

Use ventilation corrective steps (MR. SOPA)

YES

Intubate

NO

Heart rate > 100 bpm AND SpO₂ in target?

NO

Provide positive pressure ventilation with either:
Bag and Mask OR T-piece (Neopuff)

YES

Provide or maintain heated humidified CPAP to prevent atelectasis

NO

If unable to wean FiO2 quickly despite optimal nasal CPAP, recommend intubation and surfactant

*perinatal centres may use higher CPAP levels*
## Ventilation Management Guidelines

### Oxygen saturation targets beyond stabilization

<table>
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<td>Target SpO2 for preterm infants requiring supplemental oxygen in the range of 90 to 95% (as per unit specific guideline).</td>
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<td>Alarms should be set to maximize time spent within the designated oxygen saturation target range.</td>
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<td>Use non-invasive CO2 monitoring for mechanically ventilated infants.</td>
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</tbody>
</table>

### Non-invasive CO2 monitoring

**Rationale**
- NeOProM meta-analysis (of 5 large scale RCTs) confirmed that the lower target range (85–89%) was associated with an increased risk of death but there was no difference between the 2 target ranges in terms of disability at 18–24 months and the lower target range did not reduce BPD or severe visual impairment but it did increase the risk of NEC requiring surgery or causing death. Stenson BJ: Oxygen saturation targets for extremely preterm infants after the NeOProM trials. Neonatology 2016; 109: 352–358.
- Lower saturation targets in SGA infants has been shown to be associated with an increase in mortality and this may be related to their higher risk of developing pulmonary hypertension with BPD. JAMA 2018 Jun 5;319(21):2190-2201. Doi:10.1001/jama.2018.5725

### Threshold for intubation and surfactant administration

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<td>Consider early selective surfactant administration for infants requiring intubation.</td>
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<td>For infants on CPAP during transition (first 1 – 2 hours) to extra-uterine life who have worsening respiratory distress or oxygen requirements &gt;30% on optimized non-invasive CPAP, recommend intubation and surfactant administration as the earlier surfactant is given when there is RDS, the better the outcome.</td>
</tr>
<tr>
<td>Use a natural surfactant as it is more effective than protein-free synthetic surfactant.</td>
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<tr>
<td>Optimized non-invasive CPAP can vary between 5-10 cmH2O.</td>
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### Rationale
- Surfactant has changed the severity of BPD and improved the survival of premature infants but has not been shown to consistently reduce the incidence of BPD.
- European Consensus Guideline; Neonatology 2017;111:107–125
## Ventilation Management Guidelines

### Conventional Ventilation

**Recommendations**
- Initial mode of ventilation for infants born greater than or equal to 27 weeks gestational age.
- Use volume targeted ventilation.
- Provide 4 – 6 ml/kg for volume targeted ventilation.
- Initially, use a minimum positive end expiratory pressure (PEEP) of 5 cmH2O and then advance PEEP if required based on clinical response.
- Target adequate recruitment to avoid atelectrauma and overdistension.
- Consider high frequency oscillation ventilation (HFOV) or high frequency jet ventilation for infants who require increased peak inspiratory pressures or increased positive end expiratory pressures to achieve targeted volume.

**Rationale**
- Volume targeted ventilation may shorten the duration of ventilation and reduce BPD and intraventricular haemorrhage.
- Volume targeted ventilation may reduce BPD or death and IVH and shorten the duration of mechanical ventilation.
- PEEP/MAP increases functional residual capacity (FRC) allowing for more uniform air distribution and decreases the potential for volutrauma. PEEP/ MAP should be the primary method of recruitment and maintaining airway stability.

### High Frequency Oscillation Ventilation (HFOV)

**High frequency oscillatory ventilation (HFOV):**
- Uses small tidal volumes and a constant distending pressure (mean airway pressure) delivered at high frequencies with the goal of maintaining a constant lung recruitment to prevent lung injury from overdistension and loss of recruitment (atelectrauma).
- Delivers tidal volume (Vt) smaller than the dead space through an electronically controlled piston-diaphragm unit at rates of 300 to 900 breaths/min (5 to 15 Hz). MAP is adjusted to achieve the target lung volume.
- Optimal continuous distending pressure on HFOV is approximately 1–2 cmH2O above the closing pressure as identified by deterioration of oxygenation during stepwise reductions in airway pressure after full lung recruitment.

**Recommendations**
- Consider as initial mode of ventilation for infants born less than 27 weeks gestational age.
- Consider using HFOV – volume targeted mode.

**Initial Settings**
- Target volume: 1 - 2 ml/kg. Higher volumes may be required due to deadspace. Assess for adequate shake and CO2 clearance as an additional measure of effectiveness.
- Start mean airway pressure (MAP): 2 cm above the conventional ventilation MAP.
- Frequency 8-10 Hz.
- Obtain chest x-ray to assess for adequate aeration or overdistension within a few hours post commencement of HFOV.

**Lung Recruitment Measures**
1. Refer to local lung recruitment measure guidelines.
2. The safety of lung recruitment measures for infants < 25 weeks with immature lung development has not been established.
3. Infants 25 weeks gestational age or greater: consider performing lung recruitment measures if there are concerns of poor aeration (clinically or radiographically).

**Rationale**
- High frequency ventilation may reduce BPD but there is an increased risk for air leaks if not used carefully.
- Pressure amplitude and frequency can result in differing tidal volumes due to changes in lung mechanics. Although there are very few published studies on HFOV-VG, improved maintenance of tidal volume and CO2 have been reported.
Ventilation Management Guidelines

High Frequency Jet Ventilation (HFJV)

- **High frequency jet ventilation (HFJV):** uses the jet ventilator in conjunction with a conventional ventilator.
- A flow interrupter with a pinch valve, placed proximal to the ETT adaptor, is used to deliver high frequency gas pulses at frequencies of 240 to 660 breaths/min (4 to 11 Hz).
- Lung volume is maintained by positive end expiratory pressure (PEEP) generated by the conventional ventilator with or without sigh breaths. HFJV offers theoretical benefits through its passive expiration, along with lower MAP, when compared with HFOV.
- May be more beneficial in non-homogenous lung disease and air leak, as it allows for passive expiration and adjustment of inspiratory time, and it enables adequate gas exchange with lower mean airway pressures.

### Recommendations

**Consider HFJV for the following infants:**
- Initial mode of ventilation for infants with concerns of pulmonary hypoplasia (ie prolonged premature rupture of membranes).
- Tidal volumes targets approaching set pressure upper limits/ranges on conventional vent.
- Air-leaks (including pulmonary interstitial emphysema – PIE).
- Non-homogenous lung disease (e.g. pneumonia, meconium aspiration syndrome).
- Evolving or established bronchopulmonary dysplasia.

#### Initial settings

- **Inspiratory time = 0.02 seconds.**
- **Rate:**
  - 240 - 360 breaths per minute: air leak, gas trapping, significant spontaneous breathing.
  - 300 breaths per minute: lung disease with short time constants (ie RDS).
- **Mean airway pressure (MAP):** match MAP of conventional ventilation to calculated MAP of HFJV.
- If air trapping or air leak present in non-atelectatic lungs, consider a lower mean airway pressure (MAP) to achieve adequate aeration and acceptable for oxygen saturations and oxygen delivery.

Extubating from Mechanical Ventilation

### Post Extubation Management Principles

- Maintain an open lung and avoid airway de-recruitment.
- Use an adequate distending pressure to maintain functional residual capacity (FRC).

**Recommendations**

**Infants born < 24 weeks gestation:**
- If intubated, provide invasive ventilation for at least 72 hours, then extubate as soon as possible.

**Infants born greater than or equal to 24 weeks gestational age:**

- **Extubate as soon as possible to reduce further ventilator induced lung injury.**
- Extubate to non-invasive respiratory support to maintain distending pressure (NIPPV/CPAP/NI-HFOV)*
- Consider extubation if:
  1. **Blood gases are acceptable on low ventilator settings**
     - HFOV: < 11 cmH2O mean airway pressure
     - CMV: 8-9 cmH2O mean airway pressure
  2. **FiO2 is less than 0.40**
  3. **Respiratory drive is adequate**

Although unit specific, completion of a spontaneous breathing trial prior to extubation may be considered.

### Spontaneous breathing trials use objective criteria for assessing adequate respiratory drive to better predict successful extubation.

**Rationale**

- Approximately 50% of extremely preterm babies with RDS will require mechanical ventilation after management with non-invasive respiratory support.
- Premature infants ≤ 32 weeks: Of 41 babies who passed SBT, only 5 infants failed extubation. SBT had 92% sensitivity, 50% specificity, 88% positive predictive, and 63% negative predictive value for successful extubation. Extubation was considered successful if patients remained extubated for >72 hr. Chawla S, Natarajan G, Gelmini M, Kazzi SN. Role of spontaneous breathing trial in predicting successful extubation in premature infants. Pediatr Pulmonol. 2013;48:443-8.
## Postnatal Corticosteroids

- Glucocorticoids: regulate metabolism and inflammation.
- Mineralocorticoids: regulate sodium and water levels.
- Cortisol is naturally produced by adrenal gland and its production is regulated by adrenocorticotropic hormone (ACTH).
- Corticosteroids major effects are anti-inflammatory and immunosuppressive.
  - Glucocorticoids cross cell membranes and bind to steroid receptors, altering gene transcription and protein production and reducing the synthesis and/or release of inflammatory mediators.
  - Glucocorticoids inhibit certain aspects of leukocyte function leading to an immunosuppressant effect.
- Glucocorticoids affect bone mineralization by inhibiting calcium absorption in the GI tract stimulating bone resorption.
- The major differences between formulations are potency (dose), duration, and mineralocorticoid (salt-retaining) activity.

## Systemic Steroids Use in Preterm Infants

- Inflammation is implicated in the pathogenesis of bronchopulmonary dysplasia.\(^3\)\(^4\)
- The anti-inflammatory effects of corticosteroids have been demonstrated to be effective in facilitating extubation and reducing bronchopulmonary dysplasia in randomized controlled trials.\(^1\)

### Adverse Effects

- There are several short- and long-term adverse effects associated with the use of systemic corticosteroids including hyperglycemia, hypertension, hypertrophic obstructive cardiomyopathy, gastrointestinal haemorrhage and perforation, growth failure, increased neutrophil and platelet counts and hypothalamic-pituitary-adrenal (HPA) axis suppression.\(^7\)
- Why corticosteroids induce myocardial thickening and which dose and duration are safe remain unclear. At a cellular level, cardiac hypertrophy usually results from hypertrophy of myocytes by the synthesis of various intracellular cardiac proteins.\(^2\)
- Most concerning are the potential effects on brain growth and neurodevelopment, specifically an increased rate of cerebral palsy (CP).\(^5\) Animal studies have shown that steroids can permanently affect brain cell division, differentiation and myelination and cerebral cortical development.\(^5\)\(^6\)
- Despite the uncertainty, guidance is needed in balancing the risk and benefits of corticosteroid use in preterm infants.

## Neonatal BPD Outcome Estimator

The NICHD Neonatal Research Network provides a web-based BPD estimator that predicts the risk of bronchopulmonary dysplasia (BPD)-defined according to the Eunice Kennedy Shriver National Institute of Child Health and Human Development consensus definition of no, mild, moderate, and severe BPD (Jobe 2001) - as well as the competing outcome of death, by postnatal day. The population includes infants 23-30 weeks gestation and 501-1250 grams birth weight. The tool may help identify patients most likely to benefit from postnatal treatment. The BPD outcome estimator can be accessed at: https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency Compared to Hydrocortisone</th>
<th>Form</th>
<th>Administration Route</th>
<th>Activity</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>-</td>
<td>Natural</td>
<td>Intravenous</td>
<td>Glucocorticoid</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mineralocorticoid</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25 times as potent</td>
<td>Synthetic</td>
<td>Intravenous</td>
<td>Glucocorticoid</td>
<td>Long</td>
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<tr>
<td></td>
<td></td>
<td>Enteral</td>
<td></td>
<td>Mineralocorticoid</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>4 times as potent</td>
<td>Synthetic</td>
<td>Enteral</td>
<td>Glucocorticoid</td>
<td>Intermediate</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 times as potent</td>
<td>Synthetic</td>
<td>Enteral</td>
<td>Glucocorticoid</td>
<td>Intermediate</td>
</tr>
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<td></td>
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<td>Mineralocorticoid</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5 times as potent</td>
<td>Synthetic</td>
<td>Intravenous</td>
<td>Glucocorticoid</td>
<td>Intermediate</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mineralocorticoid</td>
<td></td>
</tr>
</tbody>
</table>

## References

3. Jobe H. Clinical interventions and occurrences that contribute to BPD. Neoreviews 2006;7:e531-e545
## Postnatal Systemic Steroids: Infants less than or equal to 7 days of age

### Hydrocortisone

**Infants born < 28 weeks gestation on day 1 of life**

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use of early low-dose prophylactic hydrocortisone for the prevention of BPD: initiation of low-dose hydrocortisone on day 1 of life in infants less than 28 weeks gestation for the prevention of BPD may be considered when there are significant risks for the development of BPD (such as but not limited to: infants born to mothers with suspected/confirmed chorioamnionitis; infants born to mothers who did not receive antenatal steroids).</td>
</tr>
<tr>
<td>2. Avoid the combined use of indomethacin and systemic steroids (e.g. hydrocortisone, dexamethasone) The combined use of indomethacin (treatment or prophylaxis) and systemic steroids should be avoided due to the increased risk of gastrointestinal perforations.</td>
</tr>
<tr>
<td>3. Late-onset sepsis and early hydrocortisone: close monitoring for late sepsis is essential due to an increased risk for late onset sepsis.</td>
</tr>
</tbody>
</table>

### Clinicians may consider the dosing used in used in the early low-dose hydrocortisone study (PREMILOC)

[http://dx.doi.org/10.1016/S0140-6736(16)00202-6](http://dx.doi.org/10.1016/S0140-6736(16)00202-6)

It is recommended that dosing is verified with official pharmacy resources and/or the published reference

<table>
<thead>
<tr>
<th>Hydrocortisone hemisuccinate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg per day divided into two doses per day for 7 days, followed by,</td>
</tr>
<tr>
<td>one dose of 0·5 mg/kg per day for 3 days</td>
</tr>
</tbody>
</table>

### Rationale

- **PREMILOC study**: In extremely preterm infants, the rate of survival without bronchopulmonary dysplasia at 36 weeks of postmenstrual age was significantly increased by prophylactic low-dose hydrocortisone. Infants < 28 weeks of gestation received either intravenous low-dose hydrocortisone or placebo during the first 10 postnatal days. Infants randomly assigned to the hydrocortisone group received 1 mg/kg of hydrocortisone per day divided into two doses per day for 7 days, followed by one dose of 0·5 mg/kg per day for 3 days. Infants born 24–25 weeks gestational age treated with hydrocortisone had a higher rate of sepsis (40% vs 23%: sub-hazard ratio 1·87, 95% CI 1·09–3·21, p = 0·02). Indomethacin was associated with a statistically significant improvement in neurodevelopmental outcomes at 2 years of age. \[1\] Lancet 2016; 387: 1827–1836.


### Meta-Analysis of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: Early low-dose hydrocortisone therapy is beneficial for survival without BPD in very preterm infants. Among 5 eligible studies, 4 randomized controlled trials had individual patient data available (96% of participants identified; n = 982). Early low-dose hydrocortisone treatment for 10–15 days was associated with a significant increase in survival without BPD (OR, 1.45; 95% CI, 1.11–1.90; P = 0.007; I² = 0%). Decreases in medical treatment for patent ductus arteriosus (OR, 0.72; 95% CI, 0.56–0.93; P = 0.01; I² = 0%). Decreases death before discharge (OR, 0.70; 95% CI, 0.51–0.97; P = 0.03; I² = 0%). The therapy was associated with an increased risk of spontaneous gastrointestinal perforation (OR, 2.50; 95% CI, 1.33–4.69; P = 0.004; I² = 31.9%) when hydrocortisone was given in association with indomethacin exposure. The incidence of late-onset sepsis was increased in infants exposed to hydrocortisone (OR, 1.34; 95% CI, 1.02–1.75; P = 0.04; I² = 0%). No adverse effects were reported for either death or 2-year neurodevelopmental outcomes as assessed in an aggregate meta-analysis. Shaffer MI, 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. 2018 Nov 8; pii: S0022-3476(18)31416-1.

### Early treatment with low-dose hydrocortisone in extremely low birth weight infants increased the likelihood of survival without CLD. The benefit was particularly apparent in infants with chorioamnionitis. Randomized, double-masked, placebo-controlled pilot study to test whether early treatment with low-dose hydrocortisone for 12 days (1 mg/kg/day for 9 days followed by 0·5 mg/kg/day for 3 days), begun before 48 hours of life, would increase the likelihood of survival without CLD. Watterberg KL, Gerdes JS, Gifford KL, Lin HM. Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. Pediatrics 1999; 104:1258–63.

**Postnatal Systemic Steroids: Infants greater than 7 days of age**

**Dexamethasone Infants > 7 days of age**

- Although postnatal dexamethasone is associated with an increased risk of cerebral palsy, bronchopulmonary dysplasia is also associated with adverse neurological outcomes and there may be greater potential benefit from a course of postnatal steroids.

**Recommendations**

- While routine dexamethasone therapy for all ventilated infants is not recommended and the benefits of late corticosteroid therapy (> 7 days of age) may not outweigh the actual or potential adverse effects, clinicians may consider late dexamethasone use for infants at high risk for bronchopulmonary dysplasia or with bronchopulmonary dysplasia who are unable to wean from mechanical ventilation using a regime that minimizes the dose and duration of therapy.

- Prior to initiating treatment with dexamethasone for the management of evolving or established BPD, a discussion between the staff neonatologist and the baby’s parents to review the potential risks and benefits of dexamethasone should occur and permission for treatment obtained.

**Clinicians may consider the dosing used in the Dexamethasone: A Randomized Trial (DART protocol).**

*Pediatrics* 2006;117(1):75-83. DOI: 10.1542/peds.2004-2843

**It is recommended that dosing is verified with official pharmacy resources and/or the published reference**

> 7 days postnatal age: (total cumulative dose 0.89 mg/kg)

- 0.075 mg/kg/dose PO/IV q12h x 3 days
- 0.05 mg/kg/dose PO/IV q12h x 3 days
- 0.025 mg/kg/dose PO/IV q12h x 2 days
- 0.01 mg/kg/dose PO/IV q12h x 2 days

**Rationale**

- Doyle et al Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: A multicenter, international, randomized, controlled trial. *Pediatrics* 2006;117(1):75-83. The DART protocol used a lower initial dose of 0.15 mg/kg/day, tapered over 10 days for a cumulative exposure of 0.89 mg/kg, and compared this to placebo. This lower dose facilitated extubation and shortened the duration of intubation for ventilator-dependent infants. More infants were extubated successfully by 10 days of treatment in the dexamethasone group (60%, 21 of 35 patients) than in the control group (12%, 4 of 34 patients) (odds ratio [OR]: 11.2; 95% confidence interval [CI]: 3.2-39.0). Ventilator and oxygen requirements improved substantially, and the duration of intubation was shorter.

- Doyle et al. Outcome at 2 Years of Age From the DART Study: A Multicenter, International, Randomized, Controlled Trial of Low-Dose Dexamethasone. *Pediatrics* 2007;119(4):716. The trial was abandoned well short of its target sample size because of recruitment difficulties. There was little evidence for a difference in the major end point, the rate of the combined outcome of death, or major disability at 2 years of age (dexamethasone group: 46%; controls: 43%). Rates of mortality before follow-up (11% vs 20%), major disability (41% vs 31%), cerebral palsy (14% vs 22%), or of the combined outcomes of death or cerebral palsy (23% vs 37%) were not substantially different between the groups.

- Canadian Paediatric Society Statement: After seven days of life, dexamethasone has been shown to decrease the rate of CLD at 36 weeks’ postmenstrual age with less impact on neurodevelopmental outcome. While routine dexamethasone therapy of all ventilated infants is not recommended, clinicians may consider a short course of low-dose dexamethasone for individual infants at high risk of or with severe CLD. Jefferies AI: Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Paediatr Child Health* 2012; 17: 573–574.

- Very preterm (gestational age: <28 weeks) or extremely low birth weight (birth weight: <1000 g) infants who were ventilator dependent after the first 1 week of life were eligible and were assigned randomly to receive masked dexamethasone (0.89 mg/kg over 10 days) or saline placebo. More infants were extubated successfully by 10 days of treatment in the dexamethasone group (60%, 21 of 35 patients) than in the control group (12%, 4 of 34 patients) (odds ratio [OR]: 11.2; 95% confidence interval [CI]: 3.2-39.0). Ventilator and oxygen requirements improved substantially, and the duration of intubation was shorter. There was little evidence for a reduction in either the mortality rate (dexamethasone group: 11%; control group: 20%; OR: 0.52; 95% CI: 0.14-1.95) or the rate of oxygen dependence at 36 weeks (dexamethasone group: 85%; control group: 91%; OR: 0.58; 95% CI: 0.13-2.66). Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB; DART Study Investigators. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: A multicenter, international, randomized, controlled trial. *Pediatrics* 2006;117(1):75-83.

- Cochrane Database: Although there continues to be concern about an increased incidence of adverse neurological outcomes in infants treated with postnatal steroids, this review of postnatal corticosteroid treatment for chronic lung disease initiated after seven days of age suggests that late therapy may reduce neonatal mortality without significantly increasing the risk of adverse long-term neurodevelopmental outcomes. Given the evidence of both benefits and harms of treatment, and the limitations of the evidence at present, it appears prudent to reserve the use of late corticosteroids for infants who cannot be weaned from mechanical ventilation and to minimise the dose and duration of any course of treatment. Doyle LW, Ehrenkranz RA, Halliday HL. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev 2014; 5:CD001145.

- After seven days of life, dexamethasone has been shown to decrease the rate of CLD at 36 weeks’ postmenstrual age with less impact on neurodevelopmental outcome. Oxygen dependency at 36 weeks’ PMA has been shown to be one of three independent predictors of poor neurodevelopmental outcome at 18 to 24 months. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sause RS, Whitfield MF; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: Results from the trial of indomethacin prophylaxis in preterms. *JAMA* 2003;289(9):1124-9.

- Infants at higher risk of bronchopulmonary dysplasia had increased rates of survival free of cerebral palsy after postnatal corticosteroid treatment in a previous meta-regression of data from 14 randomized controlled trials. The relationship persists and is stronger in an updated analysis with data from 20 randomized controlled trials. Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC: 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
Postnatal Systemic Steroids: Infants less than or equal to 7 days of age

Dexamethasone
Infants ≤ 7 days of age

Dexamethasone is **NOT recommended** for the prevention bronchopulmonary dysplasia in the first 7 days of life as it is associated with an increased risk of cerebral palsy.

**Rationale**
- The benefits of early postnatal corticosteroid treatment (≤ 7 days), particularly dexamethasone, may not outweigh the adverse effects of this treatment. Although early corticosteroid treatment facilitates extubation and reduces the risk of chronic lung disease and patent ductus arteriosus, it causes short-term adverse effects including gastrointestinal bleeding, intestinal perforation, hyperglycaemia, hypertension, hypertrophic cardiomyopathy and growth failure. Long-term follow-up studies report an increased risk of abnormal neurological examination and cerebral palsy. Hydrocortisone in the doses and regimens used in the reported RCTs has few beneficial or harmful effects and cannot be recommended for the prevention of chronic lung disease. Doyle LW, Ehrenkranz RA, Halliday HL. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database of Systematic Reviews 2014; Issue 5. Art. No.: CD001146.
- Canadian Paediatric Society Statement: As both dexamethasone and hydrocortisone administration within the first seven days of life is associated with an increased risk of cerebral palsy, early postnatal corticosteroid therapy is not recommended to prevent CLD. Jefferies AL: Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. Paediatr Child Health 2012-reaffirmed 2017; 17: 573–574.

Other Pharmacologic Strategies

**Caffeine**
- Caffeine is effective for the prevention or treatment of apnea and to facilitate extubation from invasive ventilation. Caffeine reduces the incidence of cerebral palsy and cognitive delay at 18 months of age.

**Recommendation**
Start caffeine on day 1 of life for infants at high risk of needing mechanical ventilation or non-invasive respiratory support (e.g. <1,250 g birth weight and/or less than 30 weeks gestation at birth).

**Rationale**
- The Caffeine for Apnea of Prematurity (CAP) study showed that caffeine facilitated earlier extubation with a significant reduction in BPD, and follow-up at 18 months showed a reduction in neuro-disability.
- Large cohort studies support the use of early caffeine for improving outcomes such as BPD (although relationship cannot be assumed to be cause and effect).

See next page for diuretic recommendations
**Diuretics**

- Interstitial alveolar edema may lead to decreased pulmonary compliance secondary to increased fluid administration, capillary leak due to inflammation secondary to infection or ventilator-induced lung injury inflammation.

- Evidence is lacking that diuretics improve clinically significant outcomes such as duration of mechanical ventilation, oxygen dependence and length of stay, loop diuretics (furosemide) and thiazide diuretics (e.g. Hydrochlorothiazide and Spironolactone) transiently improve pulmonary compliance and are frequently used to treat the manifestations of evolving or established BPD to increase reabsorption of lung fluid and reduce interstitial alveolar edema.

**Loop Diuretics** *(e.g. furosemide)*: decrease interstitial edema by inhibiting reabsorption of sodium and chloride in the ascending loop of Henle and proximal and distal renal tubules and blocking chloride transport. In addition, can cause pulmonary vasodilation via local prostaglandin production and inhibiting bronchial smooth muscle contraction resulting in bronchodilation.

**Major adverse effects**: volume depletion, metabolic alkalosis, hyponatremia, hypokalemia, hypercalciuria (kidney stones, osteopenia).

**Thiazide diuretics** *(e.g. hydrochlorothiazide and spironolactone)*

- The risk of electrolyte abnormalities with distal tubule diuretics is less compared to loop diuretics due to the small amount of sodium absorption occurring in the distal tubule.

- **Hydrochlorothiazide**: inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water and potassium, hydrogen, magnesium, phosphate, calcium and bicarbonate ions.

- **Spironolactone**: competes with aldosterone for receptor sites in the distal renal tubules, increasing sodium chloride and water excretion while conserving potassium and hydrogen ions.

### Recommendations

**Loop diuretics** *(e.g. furosemide)*

- In preterm infants > 3 weeks of age with BPD or developing BPD and clinical and radiographic signs of pulmonary edema, a single dose or short course of diuretic therapy (up to one week) may be considered to improve oxygenation and lung compliance.

- Furosemide is the preferred for short duration diuretic therapy.

- Evidence is lacking demonstrating benefits of loop diuretic use in the first few weeks of life for infants with developing BPD.

- Care should be taken to avoid electrolyte disturbances by providing appropriate supplementation.

**Thiazide diuretics** *(e.g. hydrochlorothiazide and spironolactone)*

- Infants who require and benefit clinically from single-doses or short courses of loop diuretics may benefit from chronic therapy.

- In preterm infants > 3 weeks of age with evolving or established BPD and clinical and radiographic signs of pulmonary edema, treatment with distal renal tubule diuretics may be considered to improve pulmonary mechanics recognizing that the effects may be variable and transient.

- A defined clinical endpoint should be established to limit exposure to the adverse effects of chronic diuretic therapies.

- Care should be taken to avoid electrolyte disturbances by providing appropriate supplementation.

### Rationale

- Cochrane Review: Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease (Review). Review of six trials assessing the effects of furosemide: inconstant/no detectable effect in preterm infants <3 weeks of age. In infants > 3 weeks with BPD, furosemide (single dose or chronic use) improves lung compliance and oxygenation and/or lung compliance. Due to the lack of randomized trials, routine use of systemic loop diuretics in infants with or developing BPD cannot be recommended based on the current evidence. 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. DOI: 10.1002/14651858.CD001453.pub2.

- Cochrane Review: Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. Review of six small studies that assessed diuretics acting on distal segments of the renal tubule (distal diuretics) in preterm infants with or developing chronic lung disease (CLD). In preterm infants > 3 weeks of age with CLD, a four week treatment with thiazide and spironolactone improved lung compliance and reduced the need for furosemide. A single study showed thiazide and spironolactone decreased the risk of death and tended to decrease the risk for remaining intubated after eight weeks in infants who did not have access to corticosteroids, bronchodilators or aminophylline. In preterm infants > 3 weeks of age with CLD, acute and chronic administration of distal diuretics improve pulmonary mechanics. 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. DOI: 10.1002/14651858.CD001817.pub2.
### Appendix A: Additional therapies that may be considered but further studies are required before they can be recommended as a standard of care

<table>
<thead>
<tr>
<th><strong>Prednisolone</strong></th>
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<tbody>
<tr>
<td><strong>Rationale</strong></td>
<td>Retrospective study to determine whether oral prednisolone is effective in weaning infants with bronchopulmonary dysplasia, after 36 weeks' postmenstrual age, off supplemental oxygen and to identify factors associated with successful weaning. Of those in the oral prednisolone group, 63% responded to treatment. Pulmonary acuity score and PCO2 were the only parameters that remained significant on multiple logistic regression analyses. The oral prednisolone-responsive group had a lower pulmonary acuity score compared with the oral prednisolone-nonresponsive group. Capillary PCO2 values were significantly lower in the oral prednisolone-responsive group compared with the oral prednisolone-nonresponsive group. Oral prednisolone therapy is effective in weaning off supplemental oxygen in a post-term infant with oxygen-dependent bronchopulmonary dysplasia who has a pulmonary acuity score of &lt;0.5 and PCO2 of &lt;48.5 mm Hg. In addition, if a single course of prednisolone fails, there is no clear benefit of using multiple courses. Bhandari, A., et al., Effect of a short course of prednisolone in infants with oxygen-dependent bronchopulmonary dysplasia. Pediatrics, 2008. 121(2): p. e344-9.</td>
</tr>
</tbody>
</table>
| **Recommendations** | - After 36 weeks post menstrual age, preterm infants with BPD who have not responded to a trial of dexamethasone, hydrocortisone and/or diuretic therapy, and continue to require invasive or non-invasive ventilation, may benefit from a short-course of prednisolone therapy.  
- Prior to initiating treatment with prednisolone for the management of evolving or established BPD, a discussion between the staff neonatologist and the baby's parents to review the potential risks and benefits should occur and permission for treatment obtained. |

<table>
<thead>
<tr>
<th><strong>Hydrocortisone</strong></th>
<th>Infants &gt; 7 days of age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>Hydrocortisone use after 7 days of age to prevent BPD or prolonged ventilator dependence is <strong>NOT</strong> recommended due to a lack of evidence in reducing BPD at 36 weeks' postmenstrual age.</td>
</tr>
</tbody>
</table>

Hydrocortisone has been proposed as an alternate treatment for BPD due to its less potent glucocorticoid effects, fewer side effects and concerns of the long-term neurodevelopmental effects with dexamethasone use. In a large randomized control trial (Onland et al. BMC Pediatrics 2011, 11:102) hydrocortisone initiated between 7 – 14 days of age has not been shown to reduce the incidence of BPD or the composite outcome of death or BPD at 36 weeks' postmenstrual age but has been shown to reduce the rate of mortality and increase the rate successful extubation. Hydrocortisone use after 7 days of age for the management of evolving or prolonged ventilator dependence is **NOT** recommended due to a lack of evidence in reducing BPD at 36 weeks' postmenstrual age.

- **Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants (the SToP-BPD study); a multicenter randomized placebo controlled trial.** Trial included preterm infants with a gestational age of less than 30 weeks and/or birth weight of less than 1250 g who were ventilator dependent between 7 and 14 days of life. Infants were randomly assigned to receive a 22-day course of systemic hydrocortisone (cumulative dose, 72.5mg/kg) (n = 182) or placebo (n = 190). Twenty-one outcomes showed non-significant differences, including BPD (55.2% with hydrocortisone vs 50.0% with placebo; risk difference, 5.2% [95%CI, -4.9% to 15.2%]; odds ratio, 1.24 [95%; 0.82-1.86]; P = .31). Hyperglycemia requiring insulin therapy was the only adverse effect reported more often in the hydrocortisone group (18.2%) than in the placebo group (7.9%). Among mechanically ventilated very preterm infants, administration of hydrocortisone between 7 and 14 days after birth, compared with placebo, did not improve the composite outcome of death or BPD at 36 weeks' postmenstrual age. These findings do not support the use of hydrocortisone for this indication. Significantly more infants were successfully extubated in the hydrocortisone than in group the placebo on day 3 (84.4% vs 92.9%; crude risk difference, -8.5% [95% CI, -15.3% to -1.9%]; crude odds ratio,0.41 [95%CI,0.21-0.83]; P = .01), day 7 (54.4% vs 78.1%; crude risk difference, -23.7% [95% CI, -32.9% to -13.8%]; crude odds ratio, 0.34 [95% CI, 0.21-0.54]; P < .001), and day 14 (33.7% vs 51.2%; crude risk difference, -17.5% [95%CI, -27.5% to -6.9%]; crude odds ratio,0.49 [95%CI,0.31-0.76]; P = .001) after initiating therapy. Onland et al. Systemic Hydrocortisone to Prevent Bronchopulmonary Dysplasia in preterm infants (the SToP-BPD study); a multicenter randomized placebo controlled trial. BMC Pediatrics 2011, 11:102.  
- **Neonatal magnetic resonance imaging performed at eight years of age on infants treated with hydrocortisone showed that although, overall, children born preterm had significantly reduced grey matter volumes compared to term children, there were no differences in the intracranial volumes, grey matter volumes or white matter volumes between children who did and did not receive hydrocortisone for treatment of CLD. Lodygensky GA, Rademaker K, Zimine A, et al. Structural and functional brain development after hydrocortisone treatment for neonatal chronic lung disease. Pediatrics 2005;116(1):1-7.**
Appendix A: Additional therapies that may be considered but further studies are required before they can be recommended as a standard of care

**Inhaled Corticosteroids**

- Inhaled corticosteroid are directly delivered to lungs with less systemic absorption and may reduce the adverse effects associated with corticosteroid use. However, uncertainty remains over the effectiveness, optimal method of delivery, timing of treatment, dosage, systemic absorption and long-term effects of inhaled corticosteroids.

- In the European study of inhaled steroids (budesonide) started within 24 hours of birth, there was a small effect on reducing BPD, however, there was a higher mortality rate among infants who received inhaled corticosteroids. Among surviving extremely preterm infants, the rate of neurodevelopmental disability at 2 years did not differ significantly between treatment vs placebo infants. A Cochrane review of inhaled corticosteroids started after the first week of life did not did not show a beneficial effect on death or BPD and the safety of inhalation corticosteroids was assessed in only a small number of trials. More studies are needed.

**Recommendation**

Inhaled corticosteroids may be considered for infants with evolving or with bronchopulmonary dysplasia who are unable to wean from invasive or non-invasive respiratory support ventilation recognizing the limitations of evidence.

**Rationale**

**Early Use of Inhaled corticosteroids**

Assessed impact of inhaled corticosteroids in preterm infants with birth weight up to 1500 grams (VLBW) beginning in the first two weeks after birth for the prevention of CLD as reflected by the requirement for supplemental oxygen at 36 weeks' postmenstrual age (PMA). There was no significant reduction in the rate of chronic lung disease at 36 weeks' postmenstrual age. A significant reduction in the combined outcome of death or chronic lung disease at 36 weeks' postmenstrual age among all randomized neonates and among survivors was noted. Even though the results were significant, the upper confidence interval was infinity (i.e. we would have to treat every baby with inhaled steroid to prevent one baby dying or developing chronic lung disease at 36 weeks' postmenstrual age). A lower rate of reintubation was noted in the steroid group compared with the control group in one large study. 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 of Systematic Reviews 2017, Issue 1. Art. No.: CD001969. DOI: 10.1002/14651858.CD001969.pub4.

**Inhaled Corticosteroids Started Within 24 hours after birth**

In gestational age infants 23 weeks 0 days to 27 weeks 6 days compared early (within 24 hours after birth) inhaled budesonide or placebo until they no longer required oxygen and positive-pressure support or until they reached a postmenstrual age of 32 weeks 0 days. The incidence of bronchopulmonary dysplasia was 27.8% in the budesonide group versus 38.0% in the placebo group (relative risk, stratified according to gestational age, 0.74; 95% CI, 0.60 to 0.91; P = 0.004); death occurred in 16.3% and 13.6% of the patients, respectively (relative risk, stratified according to gestational age, 1.24; 95% CI, 0.91 to 1.69; P = 0.17). The proportion of infants who required surgical closure of a patent ductus arteriosus was lower in the budesonide group (relative risk, stratified according to gestational age, 0.55; 95% CI, 0.36 to 0.83; P = 0.004), as was the proportion of infants who required reintubation (relative risk, stratified according to gestational age, 0.58; 95% CI, 0.35 to 0.96; P = 0.03). Bassler D, Plavka R, Shinwell ES, Hallman M, Jarreau PH, Carnielli V, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med. 2015;373(16):1497–506.

**Long-Term Effects of Inhaled Budesonide for Bronchopulmonary Dysplasia**

Infants randomly assigned (gestational age, 23 weeks 0 days to 27 weeks 6 days) to receive early (within 24 hours after birth) inhaled budesonide or placebo. Among surviving extremely preterm infants, the rate of neurodevelopmental disability at 2 years did not differ significantly between infants who received early budesonide for the prevention of bronchopulmonary dysplasia and those who received placebo, but the mortality rate was higher among those who received budesonide. Bassler D, Shinwell ES, Hallman M, Jarreau PH, Plavka R, Cernielli V, Meisner C, Engel C, Koch A, Kreutzer K, van den Anker NJ, Schwab M, Halliday HL, Poets CF; Neonatal European Study of Inhaled Steroids Trial Group. Long-Term Effects of Inhaled Budesonide for Bronchopulmonary Dysplasia. N Engl J Med. 2018 Jan 11;378(2):148-157.

**Inhaled Corticosteroid Use (≥7 days)**

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 (typical RR (TRR) 0.80, 95% CI 0.66 to 0.98; 5 studies, 79 infants) and at the latest reported time point after treatment onset (TRR 0.60, 95%CI 0.45 to 0.80; 6 studies, 90 infants). Furthermore, 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 (TRR 0.51, 95% CI 0.26 to 1.00; 4 studies, 74 infants; very low-quality evidence). Our results should be interpreted with caution because the total number of randomized participants is relatively small, and most trials differed considerably in participant characteristics, inhalation therapy, and outcome definitions. The included trials did not show a beneficial effect of inhalation corticosteroids on death or BPD. In addition, the safety of inhalation corticosteroids was assessed in only a small number of trials. Based on these results, inhalation corticosteroids initiated after the first week of life cannot be recommended for preterm infants at risk of BPD. More studies are needed. Onland W, Oftringa M, van Kaam A. Late (≥7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD002311.
APPENDIX B

The management of infants with established bronchopulmonary dysplasia (BPD)

This section of the guideline is specific to SickKids Neonatal Intensive Care Unit
Appendix B: Respiratory Management Guidelines – For Infants with Established BPD at 36 weeks post menstrual age or greater

○ Infants who remain ventilator-dependent have severe complications including pulmonary hypertension, poor growth and neurodevelopmental problems.
○ In severe BPD the lung is characterized with different levels of airway resistance and altered compliance leading to varying time constants.
○ In severe BPD to achieve gas exchange, reduce the risk of atelectasis, and decrease dead space ventilation, the ventilator support strategy changes from a fast-rate, low tidal volume strategy during the early course to a slow-rate, high tidal volume and extended inspiratory time.
○ Although generally counterintuitive in the setting of hyperinflation, positive end expiratory pressure (PEEP) should be relatively high (> 6-8 cm H2O) to optimize gas exchange, maintain functional residual capacity, avoid regional atelectasis, and avoid the adverse effects of “inadvertent PEEP.” In some patients with significant airways closure especially with tracheomalacia or bronchomalacia, PEEP may need to be even higher to keep airways open during active exhalation.

Respiratory support for infants with established BPD at 36 weeks post menstrual age or greater

- Target oxygen saturation 36 weeks and above: 92% to 95%
- Provide oxygen supplementation to maintain consistent saturation in target ranges
  ○ Example: Avoid weaning the oxygen supplementation in an infant who is receiving 150- 200 mL/min low flow oxygen and the oxygen saturations are consistently maintained 92% to 95% at rest AND with activity (i.e. feeding, activity to support developmental needs).
- Provision of respiratory support that avoids atelectasis and establishes an acceptable work breathing (determined by tolerance of age-appropriate activities)
- For infants with severe BPD who remain ventilator-dependent near a post-menstrual age of 36 weeks or greater, the following ventilation strategies may be considered.(see schematic below)
  - Larger tidal volumes are often required (10-12 mL/kg)
    ○ allows for improved gas distribution into distal lung
    ○ avoid over-distension – may increase agitation and paradoxically worsen ventilation
  - Longer inspiratory times (≥0.6 seconds)
    ○ Permissive hypercapnia to facilitate weaning
  - Slower rates allow for better emptying, especially with larger tidal volumes (10-20 bpm)
    ○ allows for sufficient emptying of lung to avoid hyperinflation/”breath stacking”.
  - Higher PEEP may be required for infants with dynamic airway collapse

Recommended:

- For infants 36 weeks or greater post-menstrual age, provide respiratory support that allows for weaning while also preventing the development or progression of established pulmonary hypertension. Specifically, to minimize strain on the right heart and promote pulmonary vasculature relaxation, provide respiratory support that allows ongoing developmental progress, growth and adequate oxygenation.


PEEP – positive end expiratory pressure
Appendix B: Recommendations for BPD-associated pulmonary hypertension at 36 weeks post menstrual age or greater

- Pulmonary vascular disease and pulmonary hypertension contribute to the pathogenesis and pathophysiology of BPD and significantly influence the outcomes of preterm infants with BPD.
- Persistent echocardiographic evidence of pulmonary hypertension beyond the first few months of life has been associated with high mortality, especially in infants with severe disease who require prolonged support with mechanical ventilation.
- Ongoing care of infants with BPD-associated pulmonary hypertension requires comprehensive and consistent management.

### 1. Echocardiogram surveillance recommendations for BPD associated pulmonary hypertension

<table>
<thead>
<tr>
<th>Premature Infants born ≤ 28 weeks gestation</th>
<th>Indication for echocardiogram</th>
<th>Additional comments and actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 7 of life</strong></td>
<td>Infant who continue to require invasive respiratory support.</td>
<td>Echocardiogram evidence of pulmonary hypertension at day 7 suggests high risk for BPD and may identify acute pulmonary hypertension that may benefit from therapy (e.g. potential for inhaled nitric)</td>
</tr>
<tr>
<td><strong>At any age</strong></td>
<td>Severe respiratory disease and/or manifestations of pulmonary hypertension, especially if recurrent hypoxemia events.</td>
<td></td>
</tr>
<tr>
<td><strong>36 weeks PMA</strong></td>
<td>Diagnosis of BPD at 36 weeks post menstrual age.</td>
<td><strong>BPD definition:</strong> need for supplemental oxygen at 36 weeks’ postmenstrual age (i.e. oxygen supplementation or respiratory support)</td>
</tr>
<tr>
<td><strong>IUGR/SGA infants at 36 - 38 weeks PMA</strong></td>
<td>IUGR or SGA infant – born &lt; 10th percentile irrespective of respiratory support requirements due to risk of pulmonary hypertension. Depending on echocardiogram findings the following may be indicated: 1. Initiation of oxygen or other treatments 2. Consultation with SickKids pulmonary hypertension team 3. Follow-up echocardiograms.</td>
<td>• IUGR/SGA infants are at increased risk of developing BPD. Premature infants who are SGA/IUGR have abnormal alveolar and pulmonary vascular development that increases their risk of developing early and late pulmonary hypertension. • IUGR/SGA infants who do not require oxygen may still develop pulmonary hypertension with growth and increasing postnatal age and should have echocardiogram screening at 36 – 38 weeks postmenstrual age.</td>
</tr>
<tr>
<td><strong>Transferring to level 2 unit at &lt; 33 weeks PMA and remains on respiratory support</strong></td>
<td>Provide level 2 unit with recommendation to complete an echocardiogram at 36 weeks PMA if infant continues to require respiratory support to assess for pulmonary hypertension.</td>
<td><strong>Script for discharge letter:</strong> It is recommended that an echocardiogram be completed to evaluate for pulmonary hypertension if infant continues to require oxygen, non-invasive respiratory support, or treatment for lung disease (inhaled steroids, diuretics) at 36 weeks postmenstrual age, or if the infant was born ≤ 28 weeks gestation and is &lt; 10% percentile at birth with or without need for oxygen. If there are findings of pulmonary hypertension on echocardiogram, consultation with SickKids cardiology/pulmonary hypertension team is recommended. If required, the echocardiogram can be done as an outpatient at Sickkids - cardiology 416-813-5848.</td>
</tr>
<tr>
<td><strong>For transfer to level 2 unit at 33 – 35 weeks PMA and remains on respiratory support</strong></td>
<td>Complete echocardiogram prior to transfer to assess for pulmonary hypertension.</td>
<td><strong>Consult cardiology pulmonary hypertension team</strong> if there is echocardiogram evidence of pulmonary hypertension to provide ongoing recommendations including: • timing of next echocardiogram • if transferred, follow-up recommendations</td>
</tr>
</tbody>
</table>

PMA = post menstrual age; SGA = small for gestational age; IUGR = intrauterine growth restriction
Appendix B: Recommendations for BPD-associated pulmonary hypertension at 36 weeks post menstrual age or greater

2. An echocardiogram for pulmonary hypertension screening in preterm infants should be completed as per SickKids Pulmonary Hypertension Echocardiogram protocol. This protocol includes several measurements including but not limited to the following:

- A complete anatomic evaluation, to identify and characterize the physiologic contribution of structural abnormalities, shunts and pulmonary veins
- Assessment of right and left ventricular size, hypertrophy, systolic, and diastolic function
- Systolic and diastolic interventricular septal position
- Tricuspid and pulmonary regurgitation jet velocities (when present)
- Simultaneous systemic blood pressure documentation

3. Establish a multidisciplinary team

A multidisciplinary team of neonatologists, pulmonologists, cardiologists and pulmonary hypertension specialists should be involved in the care of infants with BPD-associated pulmonary hypertension to ensure a comprehensive and consistent approach.

4. Consult cardiology

Consult cardiology pulmonary hypertension team for infants with echocardiogram evidence of pulmonary hypertension at 36 weeks post menstrual age. Cardiology will provide recommendations regarding management (e.g. consideration for pulmonary arterial hypertension (PAH)-targeted therapy or diuretic use). Consider consultation prior to 36 weeks post menstrual age for infants with severe BPD and echocardiogram evidence pulmonary hypertension.

5. Oxygen saturation targets

Provide supplemental oxygen with the goal of maintaining oxygen saturations between 92% to 95% for infants with BPD associated pulmonary hypertension at 36 weeks post menstrual age or greater. For infants with severe BPD associated pulmonary hypertension at 36 week post menstrual age or greater whose retina is fully vascularized, in consultation with cardiology, consider targeting oxygen saturations between 95% to 98%.

Rationale:

a) Provide respiratory support that minimizes strain on the right heart and promotes pulmonary vasculature relaxation.

b) Reduce air hunger, optimize growth, minimize hypoxemia events and improve tolerance of activity and feeding.

c) Aims to avoid intermittent or chronic hypoxemia that can increase the severity or delay resolution of pulmonary hypertension.

Mild degrees of oxygen desaturation can elevate pulmonary artery pressure in BPD infants with pulmonary hypertension.

d) Minimize hyperoxia events in premature infants who have not achieved retinal vascularization.

e) Theoretically, high levels of oxygen to maintain oxygen saturation beyond the recommended range may contribute to airway inflammation.

6. Further evaluation and treatment of comorbidities that impact the severity of lung disease should be undertaken with the diagnosis of BPD-pulmonary hypertension infants before the initiation of pulmonary arterial hypertension (PAH)-targeted therapy and may include:

- Computerized tomography (CT) scan to: 1) assess lung parenchyma and 2) assess for the presence of pulmonary artery and vein stenosis
- Cardiac catheterization and/or echocardiogram to assess for left ventricular diastolic dysfunction and aorto-pulmonary collaterals
- ENT consultation for potential laryngoscopy/bronchoscopy to assess for structural airways disease
- Studies to assess degree of intermittent or sustained hypoxemia (example: overnight oximetry; sleep studies)
- Studies to assess for aspiration and gastroesophageal reflux disease (example: radiological feeding study)

7. Arrange long-term follow-up with multi-disciplinary pulmonary hypertension team

Infants with pulmonary hypertension and BPD should have outpatient follow-up with the multidisciplinary pulmonary hypertension team for ongoing treatment of their chronic lung disease and pulmonary hypertension at regular intervals (e.g. every 3-4 months) with use of echocardiography, biomarkers, hemodynamic studies, and sleep studies when indicated during follow-up, depending on disease severity and clinical progress.

References

BPD-associated Pulmonary Hypertension

Clinical approach for the evaluation and treatment of pulmonary hypertension (PH) in infants with BPD

Figure. Clinical approach for the evaluation and treatment of PH in BPD infants. ECHO, echocardiogram; LVDD, LV diastolic dysfunction; O₂, oxygen; SAP, systemic arterial pressure.

Echocardiogram findings of pulmonary hypertension and its severity

- **None**: RVSP <1/3 systemic pressure by TR gradient; septal position rounded and committed to LV; no RVH; normal RV size and function; if present, large VSD or PDA gradients suggesting <1/3 systemic RV pressures (Ao pressure − gradient = PA pressure)

- **Mild**: RVSP 1/3-1/2 systemic pressure; septal flattening in systole, mild RVH and RV dilatation, RV function may be normal.

- **Moderate**: RVSP 1/2-2/3 systemic pressure; septum flat or with late systolic posterior bowing, moderate RVH or dilatation, RV may have reduced function.

- **Severe**: RVSP >2/3 systemic pressure; if present, shunt with predominant R-L gradient, pansystolic posterior septal bowing, Severe RVH, RV dysfunction, RV dilatation, “low-velocity” shunting across PDA or VSD.

Note: Dilated right atrium, right to left atrial shunt, posterior bowing of the atrial septum, dilated inferior vena cava and dilated coronary sinus are also evidence of RA hypertension and RV diastolic dysfunction.

References:
## Appendix B: Nutrition management for infants with established BPD

### Nutrition

- Growth in the NICU is an important determinant of neurodevelopment outcomes for very preterm infants.
- Adequate nutrition is critical for lung growth and development, lung function and tissue repair.
- Infants with established BPD commonly demonstrate poor postnatal growth.
- Infants with severe BPD have increased resting energy expenditure due to increased work of breathing and generalized growth suppression from a chronic stress and inflammation. Furthermore, therapeutic interventions such as diuretics, systemic steroids and fluid restriction often place these infants at higher risk of energy and protein deficits.
- Infants with severe BPD are prone to pulmonary edema and often are managed with conservative fluid intakes. This needs to be balanced with providing adequate nutrients to meet physiological requirements.
- Energy needs for an infants with BPD have been estimated to be up to 25% greater.

### Recommendations

- Close monitoring of growth and nutrition by team members including nursing, medical staff (MD/NP) and dietitians.
- Regular assessments of growth using Fenton preterm growth charts
  - Linear growth is regarded as the best measure of assessing adequacy of dietary intake and is associated with lean body mass accretion and organ growth and development.
  - To improve accuracy, use a length board to measure crown-heel length.
- Goal weight gain
  - < 37 weeks PMA: 15-20 g/kg/day
  - ≥ 37 weeks PMA: 20-30 grams per day (total, not per kg)
- Close monitoring of growth is essential to avoid overfeeding and underfeeding.
- Calories: provide 120 – 150 kcal/kg/day
  - Usually requires fortified breast milk (especially if using donor milk) or high calorie formula
- Total fluid intake: 110 – 140 ml/kg/day

### References

Appendix B: Neurodevelopmental support for infants with established BPD

Supporting Neurodevelopment

- Infants with established BPD are at risk of development delays as a result of prematurity, underlying respiratory disease and prolonged hospital stays.
- Optimizing neurodevelopment in severe BPD requires an overall state of the infant whereby all needs are being met in an age-appropriate manner.
- An interdisciplinary team with a focus on achieving not only survival, but the best possible neurodevelopmental outcome is required. Improved neurodevelopmental outcomes have been demonstrated using a interdisciplinary team approach.

Recommendations to support neurodevelopment in infants with established BPD

1. **Provide adequate physiology-based respiratory care:** An infant needs to feel comfortable and secure in their environment. To support the developmental progress of infants with established BPD, provide respiratory support that is sufficient to avoid air hunger and to provide adequate oxygenation.

2. **Support neuroregulation and avoid or decrease the use of sedation and analgesia as the developing brain is vulnerable to these medications.**
   - Aim to decrease or eliminate comfort medication exposure by non-pharmacological means:
     - Learning and reading infant cues
     - Encouraging skin-to-skin holding
     - Encourage family presence
     - Use family voice recordings when not family not available
     - During care and stressful/painful interventions use containment

3. **Utilize an interdisciplinary model of care with a neurodevelopmental focus**
   - If not already involved, consult occupational therapy for infants with moderate – severe BPD who continue to require respiratory support beyond 32 – 34 week post-menstrual age.
   - **Occupational Therapy Goals**
     - To collaborate with nursing and medical in the provision of developmentally supportive care
     - Perform standardized assessment and evaluate development progress
     - Provide family education and guide family participation during routine handling
     - Provide individualized neurodevelopmental program for acquisition of age appropriate milestones
     - Incorporate therapeutic activities into routine care

4. **Facilitate maintenance of physiological and behavioral stability during routine handling and while performing age appropriate developmental skills.**

5. **Modulate sensory inputs and facilitate age appropriate external environment.**

6. **Promote guided movement, muscle strengthening, and proper positioning for musculoskeletal alignment, postural control, and breathing mechanics.**

Appendix B: Oral feeding for infants with established BPD

- Infants with established BPD are at risk of feeding delays and disorders (e.g. oral aversion, aspiration) as a result of prematurity, underlying respiratory disease, prolonged intubation or respiratory support, and prolonged hospitalizations. In addition, consider the possibility of vocal cord paresis in infants who have had a PDA ligation as this is also a risk factor for aspiration.

Recommendations
- If there are manifestations suggestive of aspiration and/or airway compromise during oral feeding (e.g. cough, increased congestion, oxygen desaturation, apnea, bradycardia, failure to progress with oral feeding), recommend holding oral feeding and consulting occupational therapy for an oral feeding assessment. If there are clinical concerns of aspiration, a radiologic feeding study may be required to objectively evaluate swallow and aspiration risk.
- Infants on low flow oxygen or no oxygen supplementation: may be fed when physiologically stable (refer to SickKids NICU Oral Feeding Decision Tree – Appendix C).
- Infants on non-invasive respiratory support are to be fed as per the Non-Invasive CPAP Respiratory Support and Establishing Safe Nipple Feeding for Preterm and High Risk Infants (breastfeeding, bottle feeding and non-nutritive sucking at the breast while on non-invasive CPAP) (Appendix D).

Appendix B: Discharge planning for infants with BPD (includes involvement of respiratory medicine)

1. Discharge planning for infants with established BPD being discharged on home oxygen supplementation requires a multidisciplinary team to coordinate discharge.
2. Discharge planning requires an individualized approach based on the needs of the family and community support.
3. Discharge preparations should start a few weeks prior to discharge.
4. Referral to Respiratory Medicine’s Chronic Respiratory Care Clinic at SickKids is recommended for infants who require oxygen supplementation upon discharge from hospital. This clinic provides multidisciplinary team care (i.e. dietitians, nursing, physicians etc.) for monitoring oxygen requirements and screening for the development of pulmonary hypertension.
   - Infants using oxygen should go home with a saturation monitor.
   - Respiratory medicine to provide guideline for 1) target oxygen saturations and 2) amount of oxygen supplementation.
   - The minimum suggested flow rate for home oxygen is 100 to 125 mL/minute.
5. Prior to discharge from hospital
   - A recent echocardiogram is recommended to assess for pulmonary hypertension
   - Consider a baseline chest radiograph and a capillary blood gas OR end tidal CO2 measurement.
6. If there are individuals who smoke in the household to which the infant is being discharged, provide counselling on the importance of avoiding environmental smoke (even on adults’ clothes, skin, etc if smoking occurs outside) as this can exacerbate the infant’s symptoms and offer resources whereby individuals can obtain support via a smoking cessation program.
7. Criteria for safe discharge to home include:
   - A safe and stable oxygen requirement
   - Ability to orally feed or alternate feeding plan established
   - Close coordination with home care resources
   - Involvement of neurodevelopment team
   - Coordination with a primary care physician
8. Prior to discharge from hospital
   - A recent echocardiogram is recommended to assess for pulmonary hypertension
   - Consider a baseline chest radiograph and a capillary blood gas OR end tidal CO2 measurement.
**SickKids NICU Oral Feeding Decision Tree**

**Purpose:** To support decision-making for initiating and advancing oral feeding

### Box 1: Risk factors for aspiration during feeding
- Tachypnea (RR >60) or WOB
- Surgical PDA ligation or cardiac repair
- Structural airway anomaly (e.g. laryngeal cleft)
- Respiratory distress syndrome (RDS) with respiratory distress
- Vocal cord dysfunction, stridor, or hoarse voice
- Pierre Robin sequence
- Genetic conditions
- Abnormal neurologic exam
- Clinical swallowing concerns
- Inability to manage secretions

### Box 2: Manifestations of aspiration or decompenation during feeding
1. Bradycardia or desaturations even after:
   - Repositioning-side-lying and/or upright
   - If bottle feeding, breast tried
   - External pacing
2. Poor feeding = unable to initiate or sustain suckling, weak suck
3. Negative behaviors = gagging, retching, arching, pushing nipple out, refusing to suck

### Box 3: Feeding Readiness Scale
1. Alert or fussy prior to care.
2. Rooting and/or hands to mouth.
4. Alert once handled. Some rooting or takes pacifier.
5. Briefly alert with care.
6. No hunger behaviors (i.e. rooting, sucking).
7. Adequate tone.
8. Sleeping throughout care.
9. No hunger cues.
10. No change in tone.
11. Significant change in HR, RR, O2, or work of breathing beyond baseline.

If #1 or #2 from above: Infant is ready for oral feeding

- Discuss options: breast versus bottle.
- Attempt breastfeeding first, if able.
- Consult LC as needed (i.e. if large milk supply).
- Use an extra slow flow nipple (purple ring) for initial bottle feeding assessment.
- Bottle feed using side-lying (preferred for breastfeeding morn).

### Semi-Demand Feeding Protocol

- At each feeding:
  1. Gently wake infant and offer a soother or finger for non-nutritive sucking.
  2. If possible, allow infant to suck for a few minutes prior to assessing for oral feeding.
     - If infant responds by remaining in alert/awake state (even if eyes are closed) and/or presents with non-nutritive sucking, (scores 1 or 2 on feeding readiness scale), offer the breast or bottle.
     - If the infant does not stay awake, (scores 3 or 4 on feeding readiness scale), feed by NG.
  3. Feed orally until infant stops sucking/swallowing and does not voluntarily resume sucking/swallowing or up to their TFI or for no longer than 20 minutes.
  4. Give remainder of feed (if any) by NG.
  5. Repeat the process at infant’s next feed or prior if the infant shows signs of feeding readiness (rooting, sucking).
  6. If infant is being breast fed and has a maximum allowed intake, weigh before and after breast feeding.
  7. If taking near full TFI by mouth, discuss demand feeding with medical team.
Appendix D

Non-Invasive CPAP Respiratory Support and Establishing Safe Nipple Feeding for Preterm and High Risk Infants
(Breastfeeding, bottle feeding and non-nutritive sucking at the breast while on non-invasive CPAP)

- Infants may require the extended use of non-invasive continuous positive airway pressure (CPAP) for the management of chronic lung disease, apnea of prematurity or due to other conditions (e.g., cardiac, surgical). Many of these infants remain on non-invasive respiratory support at the age when oral feeding would typically be introduced.
- To establish oral feeding, infants need to coordinate their suck, swallow and breathing, a process that is acquired through maturation and experience. The risk of aspiration due to poor suck, swallow and breathe coordination can be mediated with proper feeding techniques such as positioning, external prompting, and the use of slow flow nipples (Luo et al. 2012).
- Historically, the introduction of oral feeding has been delayed until CPAP support is no longer required because of concerns that infants are unable to coordinate their nutritive suck, swallow and breathing, risking aspiration or worsening their respiratory status. Although CPAP does increase glottal opening, it has been found not to affect nutritive swallowing (Boudrias et al., 2013). Recent experiences and literature suggest that the controlled introduction of oral feeding for infants on CPAP can be safe and may accelerate their attainment of oral feeding skills and the achievement of full oral feeding (Hanan et al., 2015, Shetty et al., 2016).

Assessment of Infants Readiness for Oral Feeding or Non-Nutritive Sucking (NNS) at the breast while on Non-Invasive CPAP

Eligibility Criteria
1. Infant ≥ 32 weeks post menstrual age
2. Infant on non-invasive CPAP
3. Physiologically stable
   a. Does not decompensate* if non-invasive CPAP is temporarily displaced
   b. Able to suck on soother without decompensating*
4. Enteral feeds a minimum of 10 ml/hr per feed
5. Able to swallow and manage secretions
6. No plan for transfer within the next 2 days

*Decompensation = bradycardia, apnea and/or SpO2 < 90%

Medical team discusses (MD/NP) order for OT feeding assessment

Medical team orders OT consult for oral feeding assessment on CPAP

OT consulted and one of the following plans established

- NO ORAL FEEDING
  - Non-nutritive sucking (NNS) at pumped breast and/or with soother

- OT ONLY ORAL FEEDING
  - SAFE FOR ORAL FEEDS
    - Nursing and/or parents to use OT Individualized plan for feeding

Irrespective of oral feeding plan, continue:
1. Oral immune therapy (OIT)
2. Non-nutritive sucking (NNS) on soother

General guidelines for OT approved nursing and/or parent feeding on CPAP
1. Refer to Individualized OT plan
2. REVIEW ELIGIBILITY CRITERIA PRIOR TO EACH FEED
3. Provide support for fragile feeders
   - Position side-lying, hands in midline
   - Provide non-nutritive sucking (NNS) prior to offering bottle
   - Use Dr. Brown’s preemie nipple
   - Monitor suck, swallow, breathing coordination and provide external pacing as needed
4. Stop oral feeding, notify medical team and OT if during feeding there is:
   - Tachycardia, tachypynes or oxygen desaturation
   - Aspiration signs (e.g. cough, bradycardia) or signs of distress such as arching or gagging
5. Breastfeeding
   - For the mom who is able, breastfeeding should be the first mode offered
   - At every opportunity, breast is best
   - Breastfeeding stages will frequently be ahead of bottle feeding stages
   - Breast weights may be considered for assessment of milk transfer
   - Milk transfer volume can be also be assessed by comparing post-feed pumping volumes to usual pumping volumes
6. Discharge: SickKids OT will contact the accepting units OT to discuss oral feeding plan. If no OT is available, discussion with the accepting physician is recommended. Inform parents that oral feeding on CPAP may be discontinued post transfer and is unit dependent.