**Brochopulmonary Dysplasia**

Dr. Vineet Bhandari  
MBBS, MD, DNB, DM, FAAP  
Chief of Neonatology  
St. Christopher's Hospital for Children  
160 East Erie Avenue  
Philadelphia, PA19134, United States

Dr. PK Rajiv  
MBBS, DCH, MD  
Head of Newborn Service  
NMC Specialty Hospital  
Dubai-UAE

**Definition of bronchopulmonary dysplasia (BPD)**

The proposed criteria to define BPD suggested in a National Institutes of Health (NIH) sponsored workshop in 1979 included a continued oxygen dependency during the first 28 days plus compatible clinical and radiographic changes.

In 2001, a workshop conducted by the NIH proposed a definition that divided BPD into three categories based on duration and level of supplemental oxygen therapy required (1) (2).

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>&lt;32 weeks</th>
<th>&gt;32 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point of assessment</td>
<td>36 weeks postmenstrual age or discharge to home, whichever comes first</td>
<td>&gt; 28d but &lt;56d postnatal age or discharge to home, whichever comes first</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment with oxygen &gt;21% for at least 28 d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild BPD</strong></td>
</tr>
<tr>
<td><strong>Moderate BPD</strong></td>
</tr>
<tr>
<td><strong>Severe BPD</strong></td>
</tr>
</tbody>
</table>

**Incidence**

In developed countries, the bulk of cases today (“new” BPD) is seen in infants <30 weeks’ gestational age (GA) and ≤1200 g birth weight (BW). In a recent study, the incidence of BPD (using the 36 weeks’ postmenstrual age [PMA] definition) was 42% (BW ≥501–750 g), 25% (BW ≥751–1000 g), 11% (BW ≥1001–1250 g), and 5% (BW ≥1251–1500 g) (3)(4). Infants with a BW of ≤1250g account for 97% of all patients with BPD (5). A physiologic definition based on an oxygen-reduction challenge at 36 weeks’ PMA decreased the incidence of BPD by 10% (6).
Etiopathogenesis

Figure 1

![Diagram of Etiopathogenesis of BPD]

**Figure 1.** Etiopathogenesis of BPD. BPD is the culmination of the interaction of genetic and environmental (ventilator-induced lung injury, hyperoxia, ante- and post-natal infection) factors, on the foundation of an immature (with/without surfactant deficiency) lung, resulting in a persistent inflammatory response in the lung leading to enhanced cell death. Since lung development is ongoing with the injurious response, if the healing process does not resolve the lung towards a normal phenotype, the reparative response leads to impaired alveolarization and dysregulated vascularization which is the characteristic pulmonary phenotype of “new” BPD. Prematurity forms the foundation on which the etiopathogenesis of BPD rests. BPD is an end result of the gene-environmental interactions which cause a persistent inflammatory response in the lung leading to enhanced cell death. Since the development of the lung is ongoing with the injurious response, if the healing process does not resolve the lung towards a normal phenotype, the reparative response leads to impaired alveolarization and dysregulated vascularization which is the characteristic pulmonary phenotype of “new” BPD (Figure 1). (7)

The complex processes and interaction of the environmental factors are explained in more detail in Figure 2, with a focused explanation of the pathogenesis of ventilator-induced injury in Figure 3.
Figure 2. Detailed overview of the pathogenesis of BPD. Multiple environmental factors acting on the immature lung leads to breakdown of the alveolar-capillary barrier (causing pulmonary edema) and release of inflammatory mediators. This, in turn, causes airway damage, vascular injury and interstitial damage leading to the characteristic pathology of BPD.

PMN: Polymorphonuclear neutrophils.
Figure 3
Conceptual Model Of Ventilator-Induced Lung Injury

Figure 3: Low positive end expiratory pressure (PEEP) and high peak inspiratory pressure (PIP) to achieve higher mean airway pressure (MAP) to increase oxygenation contributes to the genesis of BPD. Shearing stress of disproportionate high tidal volume facilitates the development of BPD. The deflation-inflation sequence leads primarily to capillary leakage and cytokine release into the alveolar compartment.
Clinical Course:

Figure 4:

Figure 4. Early phase of BPD. After birth, either the infant is placed on CPAP of 5-6 cmH\textsubscript{2}O or administered surfactant via the INSURE technique. If intubated, attempts are usually made to extubate to (S) NIPPV in the first 3 days of postnatal life. If kept successfully extubated over the first postnatal week, such infants usually do well and may have no or mild BPD. However, if they are re-intubated and require high ventilator pressures (MAP \geq 12 cmH\textsubscript{2}O) and FiO\textsubscript{2} \geq 0.50, they may progress to develop moderate-severe BPD.

**CPAP:** continuous positive airway pressure; **INSURE:** intubate, surfactant administration and extubate; (S) NIPPV: synchronized nasal intermittent positive pressure ventilation; FiO\textsubscript{2}: fraction of inspired oxygen; **VENT:** conventional ventilation; **VG:** volume guarantee; **MAP:** mean airway pressure; **HFO:** high frequency oscillator; **PDA:** patent ductus arteriosus.

**Early phase (up to 1 PN week):**

The infant may have severe respiratory distress syndrome (RDS) requiring intubation and one or more doses of surfactant administration. He/she may have a hemodynamically-significant patent ductus arteriosus (PDA), tend to remain intubated for the initial few days of life and have a high likelihood of failed extubation attempts in the first postnatal (PN) week.

Alternatively and less commonly, the infant may present with almost normal lung function requiring minimal respiratory support or minimal or no oxygen. These infants are usually managed with nasal continuous positive airway pressure (NCPAP) of 4-5 cmH\textsubscript{2}O or even high-flow nasal cannula (>2 L/min). Such infants do reasonably well in the first few days of life; however, by day 5-7, they start showing evidence of worsening respiratory distress (increased work of breathing, tachypnea, retractions) necessitating escalation of respiratory support and supplemental fraction of inspired oxygen (FiO\textsubscript{2}).
Figure 5. Evolving phase of BPD. Over the next few weeks of postnatal life, if intubated, attempts are usually made to extubate to (S) NIPPV. If kept successfully extubated, such infants usually do well and may have no or mild BPD. However, if they develop complications (PDA or pneumonia) and require high ventilator pressures (MAP >12 cmH₂O) and FiO₂ (≥0.50), they may progress to moderate-severe BPD.

(S)NIPPV: synchronized nasal intermittent positive pressure ventilation; FiO₂: fraction of inspired oxygen; VENT: conventional ventilation; SIMV: synchronized intermittent mandatory ventilation; MAP: mean airway pressure; HFO: high frequency oscillator; PDA: patent ductus arteriosus.

Evolving phase (>1 PN week to 36 weeks PMA): By the second week of PN life, these infants manifest increasing respiratory distress and FiO₂ requirements. They may get re-intubated, and the radiological picture is characterized by pulmonary edema, low volume lungs and/or atelectasis. The figure shows the development of pulmonary and cardiac events in a complex background of suspected or proven sepsis and the actions taken thereof. Each complication will be dealt subsequently in the chapter.
Figure 6

Established phase of BPD. Beyond 36 weeks of postmenstrual age, infants with mild BPD are usually on minimal respiratory support (nasal cannula). If intubated, continue conventional SIMV. Attempts should be made to extubate to (S)NIPPV, if the ventilator settings can be weaned. Infants who have moderate-severe BPD and are ventilator dependent may require tracheostomy. All infants with BPD should be screened for pulmonary hypertension.

(S)NIPPV: synchronized nasal intermittent positive pressure ventilation; FiO₂: fraction of inspired oxygen; VENT: conventional ventilation; SIMV: synchronized intermittent mandatory ventilation.

Established phase (>36 weeks PMA):

The infants in this phase have tachypnea, dyspnea, crackles, and wheezing on physical examination. In infants with subglottic stenosis secondary to prolonged intubation, there may be presence of a stridor. Noisy breathing exacerbated with high airflow activities such as feeding and agitation may be heard in infants with tracheomalacia and bronchomalacia. Cardiac complications of severe BPD include pulmonary hypertension and cor pulmonale. Poor growth parameters may be related to undiagnosed hypoxia, cardiac disease, gastroesophageal reflux and swallow dysfunction or recurrent aspiration. Osteopenia is common in extremely low birth weight infants. This is secondary to low calcium and Vitamin D intake, exacerbated by the calciuric effect of chronic diuretic therapy. “BPD spells”, episodes of cyanosis, oxygen desaturations and bradycardia, occur due to agitation, and are related to tracheomalacia and bronchomalacia.

Most cases of BPD are mild to moderate, characterized by an initial need for mechanical ventilation followed by days or weeks of O₂ supplementation. Mild BPD is clinically characterized by retractions, generally diminished breath sounds, and crepitant rales on auscultation. Moderate and severe disease is usually associated with significant respiratory and oxygen support.
Acute Episodes Of Respiratory Deterioration

1. Infection
2. Pulmonary edema (secondary to PDA; possibly increased fluid administration or progression of disease)
3. Heart failure
4. Bronchospasm

Radiologic characteristics

Stage 1: Identical to RDS. Diffuse reticulo-granular pattern with air-bronchograms

Figure 7

Stage 2: Virtually homogenous opacification of lungs that obscures cardiac margins. The early radiographic changes seen in mild disease are replaced by coarse, irregularly shaped densities that are confluent and may contain vacuolar radiolucencies.

Figure 8

Stage 3: Lucent vacuole shave expanded and are identifiable as air cysts among dense patches
Figure 9

Stage 4: Lungs appear bubbly on radiography as air cysts or continue to enlarge. Opacities are reduced to strands, streaks and small patches as cysts expand

Figure 10
Management

A) Antenatal interventions

1) **Prevention of BPD** would be ideal. Among antenatal factors, prevention of premature birth is the single most effective preventive measure. Understanding the biology of preterm labor (8) and targeting therapies to inhibit it safely would be important goals. The use of progesterone in prevention of premature labor has shown promise, although the prolongation of gestation with this approach has yet to improve infant outcomes(9).

2) **Antenatal steroids** still remain the single most effective intervention for lung maturation. However, the effect of antenatal glucocorticoids on the incidence of BPD among survivors has been inconsistent, although some studies have demonstrated a benefit. The inconsistent effect of antenatal steroids on BPD may be due to increased survival of higher risk, less mature preterm infants. Betamethasone is preferred over dexamethasone(10)(11).

3) **Antenatal antibiotics**

Considerable research has gone into understanding the role of antenatal and postnatal inflammation in the etiopathogenesis of BPD(12). Although use of maternal antibiotics is recommended when intraamniotic infection is suspected/diagnosed(13) antenatal interventions to treat chorioamnionitis have not decreased BPD; postnatal interventions may be too late to be effective(14).

B) Golden Hour Practices in Infants Younger Than 33 Weeks' Gestation

The golden-hour practices focus on minimizing stress in infants at birth and during the first hour of life.(15) Consistencies in delivery room stabilization practices have been shown to improve patient outcomes.(16-18)

(Refer Delivery Room Resuscitation Chapter)

**Key components:**

1) Initial FiO2 ~0.3 for preterm infants.
2) Oxygenation saturation targets. Adjust FiO2 to maintain O2 saturation 85 - 92%.
3) Oxygen saturation targeting. Have an oxygen blender in delivery room. Early (2-3 min) SpO2 is 60-70%. Place the pulse oximeter probe in the right arm and give O2 only as needed.
4) DAWSONS chart:

![Figure 11. Standard levels of SpO2 at first minutes after delivery.](image-url)
5) USE CPAP or NIPPV, monitor chest rise and measure volume.
6) Intubate for resuscitation, protracted apnea, severe respiratory distress, high FiO\textsubscript{2} requirement and/or to administer surfactant.
7) Early surfactant if intubated (May be less-invasive surfactant administration or LISA technique).
8) SLI or Sustained lung inflation may be useful (application of an inspiratory hold for a 5-second count, followed by the conversion to mask CPAP to sustain a predetermined positive end-expiratory pressure).
9) Use manometry on self inflating bag with positive end expiratory pressure (PEEP) valve.
   Low pressures (16-18 / 5 cm H\textsubscript{2}O)
   Tidal volume monitoring (target 4-6 ml/kg)
   CO\textsubscript{2} monitoring (target pCO\textsubscript{2} of 45-55 mmHg)
   Volume targeting -4-6 ml per kg
10) Avoid Hypothermia and Hyperthermia

![Diagram]

**Figure 12.** Golden first hour after delivery. After birth, consider using SLI to recruit FRC. Place on NCPAP or (S) NIPPV. If requiring intubation, consider INSURE technique or early surfactant administration, followed by extubation to (S) NIPPV.

SLI: sustained lung inflation; FRC: functional residual capacity; (S) NIPPV: synchronized nasal intermittent positive pressure ventilation; NCPAP: nasal continuous positive airway pressure; INSURE: intubate, surfactant administration and extubate.

**C) Postnatal Interventions**

1) **Oxygen Therapy:** In 2005, the National Institute of Child Health and Human Development devised a workshop with the intention to recognize evidence-based practices. As a result, hyperoxia was recognized as a cause for an increase in proliferation of type II alveolar cells and resulted in important alterations in surfactant development and production.\(^{(19)}\) Because higher oxygen saturation ranges provided little to no benefit to premature infants <30 weeks gestation and in turn created oxidative stress, lower target ranges of 85–93% were implemented.\(^{(20)}\) BPD, retinopathy of prematurity, impaired brain development, and infection may be caused by oxygen toxicity.\(^{(20)}\) Hypoxia can have a direct effect on brain growth and development. Maintaining patients in targeted oxygen saturation ranges has been shown to be difficult and thus has resulted in long-term adverse effects of oxygen therapy. Severe hypoxemia in early and late gestation infants further increases the degree of lung disease and mortality.\(^{(21)}\) In established BPD a slightly higher oxygen saturation of 88 –94% is recommended to prevent right-sided heart failure accompanying BPD. It has been difficult to establish a single oxygen saturation variable that can be effectively used to provide optimal management of BPD without major adverse effects. However, saturation around 90% seems to provide the best stability of both heart and lung function in older infants.\(^{(22)}\) However, in patients with severe BPD and cor pulmonale, higher target oxygen saturation is recommended.\(^{(21)}\)
<table>
<thead>
<tr>
<th>Recommended for neurological outcome</th>
<th>90-95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested for BPD outcome</td>
<td>87-93%</td>
</tr>
<tr>
<td>Recommended CO₂ level</td>
<td>55-65 mmHg</td>
</tr>
</tbody>
</table>

**Ventilator strategy**

![Conceptual model to reduce BPD](image)

**Figure 13.** Conceptual model to reduce BPD. Efforts to extubate and keep the infant extubated using the (S) NIPPV mode of non-invasive ventilation in the first few days of life should be made. If unsuccessful, use VG, SIMV or PSV modes of invasive ventilation. Aggressive weaning of the ventilator settings should be attempted in the first postnatal month of life in an effort to extubate the infant to (S) NIPPV mode.

(S)NIPPV: synchronized nasal intermittent positive pressure ventilation; BPD: bronchopulmonary dysplasia; VG: volume guarantee; SIMV: synchronized intermittent mandatory ventilation; PSV: pressure support ventilation; MAP: mean airway pressure; FiO₂: fraction of inspired oxygen.

**Non-Invasive: NCPAP**

Management of infants at risk for or with established BPD should be directed at (1) minimizing ventilator support and over distention while (2) supporting and maintaining adequate functional residual capacity (FRC) with end-expiratory pressure. These goals can best be achieved with the use of nasal CPAP systems (variable-flow or bubble CPAP delivery). Although the primary use of nasal CPAP delivered with the bubble CPAP system is associated with lower rates of BPD, the multicenter COIN Trial did not show a significant benefit on the incidence of BPD at 36 weeks. Successful use of nasal CPAP requires tolerance of permissive hypercapnia (most centers usually limit this to 65 mmHg). There is some controversy regarding the appropriate level of oxygen saturation to be maintained in these infants. While some have recently advocated use of 90-95% SpO₂ as the target range, we and others have suggested maintaining SpO₂ ranges in the 87-93% with alarm limits of 86% and 94% respectively as these values are probably more physiological and have resulted in improved outcomes of BPD.
Nasal intermittent positive pressure ventilation (NIPPV)

Noninvasive ventilation (NIV) with a set frequency, peak pressure, and positive end-expiratory pressure has been used as an escalation technique to avoid invasive mechanical ventilation when CPAP alone is not sufficient. NIV is delivered through nasal prongs or mask interface, in the form of nasal intermittent positive pressure ventilation (NIPPV) through a ventilator, which can be synchronized (SNIPPV). The success of NIV is variable, depending on the device, the understanding and training of the caregiver applying it, and the settings and parameters applied. SNIPPV has been associated with greater tidal volume (TV) delivery, reduced work of breathing, and a reduction in the need for intubation and BPD, especially in infants < 30 weeks gestation. (29-31) Although potential complications of all noninvasive modes include gastric distention or rupture, damage to the nares or occiput by the interface, or apnea, the benefits of NIV are positive and in most cases outweigh the risks. All noninvasive modalities continue to provide an important degree of clinical benefit for infants during many phases of their respiratory illness.

Once the infant is intubated, there is sufficient data to support the use of (S)NIPPV as the primary extubation mode for neonates, as this has been shown consistently to be more successful than NCPAP. (32,33,34,35) However, it is important to note that while smaller studies of NIPPV have shown a reduction in BPD (36), a large “pragmatic” trial did not confirm the earlier results. (37) However, significant concerns have been raised about the design of the “pragmatic” trial, (36) and hence, additional large randomized controlled trials are necessary to confirm or refute the impact of (S)NIPPV on the incidence of BPD.

Invasive: IPPV

In spite of the development of numerous sophisticated ventilators for the newborn, there is still no clear advantage to any one approach to ventilating the preterm infant. The general approach should be one of preventing atelectasis, sustaining FRC, using a minimal TV (usually 4 to 6 mL/kg), and allowing the infant to trigger his or her own ventilation as much as possible.

There is currently no ideal strategy for mechanical ventilation that is optimal for minimizing the risks of pulmonary sequelae. There are also inconsistencies in determining what TV constitutes appropriate gas exchange without alveolar impairment. However, synchronized and patient-triggered modes of tidal ventilation with consistent TV delivery is preferred to prevent auto-triggering and increased work of breathing, especially in infants < 1,000 g. (38) The most commonly employed ventilation in early management of RDS include pressure controlled continuous mandatory ventilation (CMV), pressure controlled intermittent mandatory ventilation (IMV) (with mandatory breathing “synchronized” to patient inspiratory effort, commonly referred to as SIMV). Adaptive pressure controlled (i.e. volume-targeted pressure control) with CMV or IMV is becoming more popular. Pressure support (PSV) of spontaneous breaths is often used with IMV. CMV is employed in the early management of RDS to decrease patient respiratory muscle work, especially during the period of surfactant replacement, while guaranteeing a set peak inspiratory pressure or TV. Adaptive pressure control provides consistent TV delivery, but no proven benefits for gas exchange. (39)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>TV (Tidal Volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early BPD</td>
<td>3.5-4 ml/kg</td>
</tr>
<tr>
<td>Evolving BPD</td>
<td>4-5 ml/kg</td>
</tr>
<tr>
<td>Established BPD</td>
<td>5-6 ml/kg</td>
</tr>
</tbody>
</table>
Patient triggered ventilation (PTV) Mode

Studies performed by using patient-triggered ventilation have not shown any reduction in the incidence of BPD\(^{(35)(36)}\), although it has been suggested that it may be more beneficial for infants with a BW of <1000 g.\(^{(40)}\)

Volume targeted Ventilation (VTV) vs pressure limited ventilation (PLV)

Preterm infants ventilated using VTV modes had reduced duration of mechanical ventilation, incidence of BPD, failure of primary mode of ventilation, hypocarbia, grade 3/4 intraventricular hemorrhage (IVH), pneumothorax and periventricular leukomalacia (PVL) compared with preterm infants ventilated using PLV modes. There was no evidence that infants ventilated with VTV modes had reduced death compared to infants ventilated using PLV modes.\(^{(41)}\)

In 2010 Cochrane review of volume-targeted versus pressure-limited ventilation in the neonate it was concluded that although rates of death and BPD were not significantly different between the two ventilator strategies, statistically significant effects favouring volume targeting were shown for some clinically important outcomes. However, the numbers of trials and infants randomized were small and further studies are required to confirm the role of volume targeting in neonatal ventilation.\(^{(42)}\)

Mandatory minute ventilation (MMV) mode

MMV mode provides backup support of TV and/or a minimal respiratory rate, in the event the patient cannot meet the minute-volume target. However, the inconsistencies in breathing patterns and volumes in neonates have been a barrier for its long-term implementation.\(^{(43)}\)

High frequency oscillatory ventilation (HFOV)

**Indication for HFO:** “Rescue” treatment only. Any evidence of air leak and/or mean airway pressure (MAP) > 12 cmH\(_2\)O.

HFOV was introduced a few decades ago as an alternative strategy for mechanical ventilation. The initial goal of HFOV was focused on reducing the incidence of alveolar stretch and consequent ventilator induced lung injury (VILI).\(^{(44)}\) Many studies conducted over the past decade demonstrate variable outcomes. The practice of utilizing HFOV in neonatal intensive care units for the prevention of BPD remains unpredictable. Proactive strategies and HFOV, noted in a meta-analysis in low-birth weight infants, revealed a minimal reduction in the development of BPD and no significant changes in neurologic outcomes.\(^{(44)}\) Rescue strategies utilized in respiratory failure have not proven to affect or reduce the incidence of BPD in premature infants.\(^{(45)}\) Neither tidal nor high-frequency ventilation strategies have been regarded as optimal for the prevention of BPD. In a number of studies comparing high-frequency and tidal ventilation there were no significant differences in the development of BPD, but complications such as air leak syndromes have been evident in high-frequency modes.\(^{(43)}\) Avoidance of invasive mechanical ventilation is pivotal in BPD prevention. However, when invasive ventilation is used, the focus on minimizing complications must be the objective.
Ventilator strategies to prevent and treat BPD

Basic pathology \(^{(46)}\)

**Figure 14:** This basic process of the abnormalities of lung architecture and the pulmonary pressures evidenced in BPD, was elegantly investigated by Bhutani et al, giving us the physiological basis of the ventilator strategy in disease. (Goldsmith and Karotkin Assisted Ventilation of the Neonate 5th edition chapter 18 page 310)

**Gentle Ventilation**

The strategies are focused on reducing the magnitude and duration of mechanical ventilatory support to the minimum possible to support cellular homeostasis, while achieving adequate gas exchange.

1. Redefining the goals for “adequate gas exchange” leading to reduced use of ventilatory support
   - Targeting Higher PaCO\(_2\) (Permissive Hypercapnia)
   - Tolerating a Lower SpO\(_2\) (Permissive Hypoxemia)

2. Refining the modes of mechanical ventilation
   - Lower Pressures, Faster Rates, Shorter Inspiratory Times (Ti)
   - Volume – Targeted Ventilation
   - Patient – Triggered Ventilation

3. Pathophysiology in BPD and Ventilatory Strategy
   The constant alterations in lung mechanics are another critical feature of BPD. The reactive airways contribute to increased pulmonary resistance. Judicious adjustments such as increasing PEEP and/or airway flow, or by using a modality with variable inspiratory flow, such as pressure control or pressure support are reported to be superior to traditional fixed flow in time cycled pressure limited ventilation (TCPLV). In addition, lung compliance may also show abnormalities. Ventilating the lung at optimal FRC (defined as the range in which, where incremental changes in pressure recruits the most lung volume) is the most difficult ventilatory endpoint to achieve. Assessing compliance at step by step changes in PEEP may be critical to reach this endpoint. Hence, alterations in resistance and compliance will change the time constant, and sufficient expiratory time to avoid gas trapping and inadvertent PEEP is imperative. Careful thought on the strategy, the best mode, or modality to ventilate a baby with BPD is best made on a case to case basis. Regarding strategy, if lung disease is homogeneous, pressure control ventilation may offer an advantage, whereas heterogeneous lung disease may respond better to volume
control ventilation because peak pressure and peak volume delivery occur at the end of inspiration, offering to make gas delivery more uniform throughout the lung.

**STEP 1**

**Levels of FiO₂ and Ventilatory Assistance**

![PEEP Diagram]

**PEEP**

PEEP IS THE BASIC ENGINE IN THE ART OF FINE VENTILATION PIP AND IT ARE THE ADDED LOAD TO BE JUDICIOUSLY ADJUSTED DESPITE CONTRIBUTING TO THE DRIVING FORCE

This fundamental step lays the foundation of the delicate architecture in the evolution of the disease process of BPD. **THIS STEP IS PRIMARILY TO BE OPTIMISED BEFORE PROCEEDING** to change tidal volume or inspiratory time.
STEP 2
Tidal Volume (PEEP)

Figure 15: This pictogram shows the evolution of CO₂ elimination with excessive tidal volumes, and the rationale to use volume targeting in the acute phase of lung recruitment. This step is secondary after optimization of PEEP.
Suggested Ventilator Settings and Targets for Infants with Early, Evolving and Established phases of BPD\(^{(7)}\):

### Ventilatory Parameters In Phases Of Disease

1. Inspiratory time for each phase of BPD.
2. Tidal volume for each phase of BPD (minimum to maximum).
3. PEEP cutoffs for each phase of BPD – initial settings.
4. Pressure support for each phase of BPD (minimum to maximum).

<table>
<thead>
<tr>
<th></th>
<th>Early Phase</th>
<th>Evolving Phase</th>
<th>Established Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti (seconds)</td>
<td>0.24-0.4</td>
<td>0.35-0.45</td>
<td>0.4-0.5</td>
</tr>
<tr>
<td>Tidal volume (ml/kg)</td>
<td>3-6</td>
<td>4-6</td>
<td>4-6</td>
</tr>
<tr>
<td>PEEP (cmH(_2)O)</td>
<td>4-6</td>
<td>4-6</td>
<td>5-7</td>
</tr>
<tr>
<td>PSV</td>
<td></td>
<td>6-10</td>
<td>6-18</td>
</tr>
</tbody>
</table>

### Monitoring of BPD patients

1. Pulse Oximetry.
2. Transcutaneous \(O_2\) and \(CO_2\) monitoring.
3. Arterial blood gas monitoring.
4. Invasive Blood pressure monitoring.
5. Pulmonary graphics (see chapter on graphics) generally not reliable.
6. Near infrared spectroscopy (NIRS; see chapter on neonatal monitoring).

### Early phase (up to 1 postnatal week)\(^{(7)}\)

1. Ensure antenatal steroid therapy and attempt to delay delivery for up to 48 hours for optimal effect, as long as there are no maternal/fetal contraindications to such an approach.
2. Set initial \(FiO_2\) at 0.3-0.4 for resuscitation.
3. Follow recommendations for initial target \(SpO_2\) in the first few minutes of life \((44)(45)\).
4. Attempt to stabilize infant on NCPAP of \(\sim6\) cm H\(_2\)O.
5. If infant exhibits increasing respiratory distress with \(FiO2 >0.3-0.4\) on NCPAP, give “early” surfactant i.e. within first 2 hours of life.
6. Administer loading dose of caffeine.
7. Once intubated, if possible, either use the INSURE technique or attempt to extubate to (S) NIPPV (settings as mentioned earlier).
8. If requiring long-term ventilation, use short inspiratory times (0.24–0.4 s), rapid rates (40–60 per min) and low PIP (14–20 cm H\(_2\)O), moderate PEEP (4–6 cm H\(_2\)O), and tidal volumes (3–6 mL/kg).
9. Wean PIP and rate, keeping the PEEP and Ti the same. The attempt should be to use the lowest MAP to maintain the blood gas targets, till the infant is ready to be extubated. For extubation settings, see chapter on (S) NIPPV.
10. Blood gas targets:
11. High-frequency ventilation for “rescue” if conventional ventilation fails; usually, if MAP >12 cmH\(_2\)O or there is evidence of air leak.

**Evolving phase (>1 postnatal week to 36 weeks’ PMA)**\(^{(7)}\)

1. Avoid endotracheal tube ventilation; maximize noninvasive ventilation [(S) NIPPV/nasal CPAP] for respiratory support.
2. Wean PIP and rate, keeping the PEEP and Ti the same. The attempt should be to use the lowest MAP to maintain the blood gas targets, till the infant is ready to be extubated. For extubation settings, see chapter on (S) NIPPV.
3. In the first few weeks of life, if the ventilator settings increase, it might due to a symptomatic PDA. Hence, if confirmed, manage with medical therapy. Consider at least 2 courses of medical therapy, before utilizing surgical ligation.
4. If the increase in ventilator settings are not secondary to a PDA, consider diuretic therapy in an attempt to temporary decrease ventilator settings and FiO\(_2\) requirements.
5. After postnatal week 3-4, consider a short-course of dexamethasone therapy to attempt to extubate the infant to (S) NIPPV. For extubation settings, see chapter on (S) NIPPV.

6. Blood Gas Targets:

<table>
<thead>
<tr>
<th>pH</th>
<th>7.25-7.35</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO(_2)</td>
<td>50-70 mm Hg</td>
</tr>
<tr>
<td>PaCO(_2)</td>
<td>50-60 mm Hg</td>
</tr>
</tbody>
</table>

**Established phase (>36 weeks’ PMA)**\(^{(7)}\)

1. If intubated, attempt to minimize ventilator settings; (may need more FiO2).
2. Maximize noninvasive ventilation [(S) NIPPV/nasal CPAP] for respiratory support.
3. Continue chronic diuretic therapy to attempt to minimize ventilator settings. The attempt should be to extubate and wean infant off O\(_2\), if possible, prior to discharge home.
4. Screen for pulmonary hypertension (PH); if present, consider inhaled nitric oxide (iNO) trial to decrease ventilator settings. Additional details provided in the PH section, under “Complications”.
5. Use of inhaled steroids and/or beta-agonists should be considered to decrease ventilator settings. The attempt should be to extubate and wean infant off O\(_2\), if possible, prior to discharge home.
6. A course of prednisolone might be helpful to wean O\(_2\). Dose of prednisolone: 2 mg/kg per day orally divided twice per day for 5 days, then 1 mg/kg per dose orally daily for 3 days, and then 1 mg/kg per dose every other day for 3 doses. \(^{(Add\ ref:\ PMID\ 18245407)}\)
7. Blood Gas Targets:
Management Of Severe BPD

**Table:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.25-7.35</td>
</tr>
<tr>
<td>PaO₂</td>
<td>50-70 mm Hg</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>50-65 mm Hg</td>
</tr>
</tbody>
</table>

**Figure 16:** This strategy for the two classical lung parenchymal abnormalities shows an algorithmic approach to each specific type of disease with bedside application.
Figure 17: The pictogram shows the key management control points in the bedside management of the two classical forms of the disease.
**Atelectasis**

If CXR shows uniform dense haziness, oxygenation is basic problem. Aim to keep MAP relatively higher. The addition of PSV reduces the work of breathing and facilitates uniform lung expansion in atelectatic areas, and facilitates weaning, but a close eye has to be kept on minute ventilation on lower settings and PIP and MAP on higher settings (Reference your PSV article Sinha donn archives of diseases of childhood fetal and neonatal edition 2009 new PMID please add) “*This is used most often as a means to prepare the child for extubation. The levels mentioned are titrated based on the weight of the infant and severity of lung disease.”

Initial settings:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>6-8 cm H2O</td>
</tr>
<tr>
<td>TV</td>
<td>5-6 ml/kg</td>
</tr>
<tr>
<td>Ti</td>
<td>0.45-0.55 s</td>
</tr>
<tr>
<td>PSV</td>
<td>6-18 cm H2O</td>
</tr>
</tbody>
</table>

Chest X-rays indicating the suggested optimal mean airway pressures to be used in the two types of diseases process described above.

SIMV mode:
- PIP 26 cmH2O
- PEEP 11 cmH2O
- Rate 40 / min
- PS 13 cmH2O
- Ti 0.45 s
- FiO2 0.95
Figure 18: The 2 CxRs shown above illustrates the difference in lung aeration after increasing the mean airway pressure – by increasing PIP and PEEP. PS was also increased.

SIMV: synchronized intermittent mandatory ventilation; PIP: peak inspiratory pressure; PEEP: positive end expiratory pressure; PS: pressure support; Ti: inspiratory time; FiO₂: fraction of inspired oxygen.

As noted in the CxRs below, increasing the PEEP by 1 cm H₂O was sufficient to improve aeration.
**Figure 19:** The 2 CxRs shown above illustrates the difference in lung aeration after increasing the PEEP by 1 cmH₂O.

SIMV: synchronized intermittent mandatory ventilation; PIP: peak inspiratory pressure; PEEP: positive end expiratory pressure; PS: pressure support; Ti: inspiratory time; FiO₂: fraction of inspired oxygen.

**Overdistension : Cystic variety**
Keep higher FiO₂ and keep MAP low

If CXR shows predominant cystic lesion, CO₂ retention tends to be the problem. Strategy: Focus on ventilation, tend to keep MAP lower, increase expiratory phase.

Initial settings:

<table>
<thead>
<tr>
<th>Setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEEP</strong></td>
<td>5-6 cm H₂O</td>
</tr>
<tr>
<td>TV</td>
<td>4-5 ml/kg</td>
</tr>
<tr>
<td>Ti</td>
<td>0.40-0.5 s</td>
</tr>
<tr>
<td>PSV</td>
<td>6-10 cm H₂O</td>
</tr>
</tbody>
</table>
This dangerous clinical state dictates perfect optimization of these basic parameters.

**Figure 20:**

![SIMV mode:](image)

- PIP 25 cmH₂O
- PEEP 5 cmH₂O
- Rate 45 / min
- Ti 0.32 s
- FiO₂ 0.65
- TV 3.5ml/kg

**Figure 21:**
**Figure 22:**

**SIMV mode:**
- PIP 22 cmH\(_2\)O
- PEEP 5 cmH\(_2\)O
- Rate 45 / min
- Ti 0.28 s
- FiO\(_2\) 0.45
- TV 3–3.5 ml/kg

**Figure 23:**

**SIMV mode:**
- PIP 20 cmH\(_2\)O
- PEEP 5 cmH\(_2\)O
- Rate 40 / min
- Ti 0.26 s
- FiO\(_2\) 0.4
- TV 3–3.5 ml/kg
Summary of Authors recommendations

1. Early phase  maximum priority on extubation within the first 72h of life.  To use volume-targeting or PSV is not an acute priority.

   After surfactant administration in the first few hours of life (if required), try to wean PIP, keeping PEEP~6 cmH2O, and decreasing...
FiO2, as long as the saturations are between 87-93% and blood gases are within the normal ranges (as specified in the tables). Once the ventilator settings and FiO2 have reached target values indicated, extubate to SNIPPV.

2. Evolving phase - This is a slower process. Weaning the ventilator pressures, (MAP) and simultaneously, increasing PS from 6 to 8 to 10 cms H20 (to achieve same MAP ? dr vineet ). It is important to keep TV within the target range. Diuretics are added and short-course steroids (the latter after 3-4 weeks of post natal life) given, if the weaning process is difficult. Once the vent settings and FiO2 have reached target values, extubate to SNIPPV.

3. Established phase The strategy is to be more of a “holding pattern”. The child is usually on chronic diuretics. PS increased gradually (6…8…10…12 cmH20) over days to weeks to see how the blood gases remain in the recommended range. PEEP increased to 7.( is MAP kept constant when titrating the PS and PEEP process ?
Keep TV within the target range. If not close to target settings for extubation, it maybe helpful to give a short course of steroids to attempt to extubate to SNIPPV.

**Surfactant Replacement Therapy**

Surfactant replacement therapy is clearly associated with decreased severity of RDS and its associated mortality. Although there is not substantial evidence that survivors have a decreased incidence of BPD, survival without BPD appears to be improved in some of the meta-analyses that have been undertaken. Use of synthetic surfactant (lucinactant) that contains the novel peptide sinapultide, a surfactant- associated protein B mimic revealed no statistically different differences in the outcomes of death and BPD, compared to animal-derived surfactants.

Newer minimally or less-invasive modes (using vascular catheters or feeding tubes) of surfactant delivery that do not require endotracheal intubations have been / are being tested in multi-center randomized clinical trials in order to assess their impact on BPD. Another attractive alternative, aerosol delivery, is awaiting testing for clinical efficacy.

**Nutrition**

1. **Fluid restriction:**

   Fluids restricted to maximum 130-140cc/kg/day. (Attempt to provide 110-120 Kcal/kg/day)

   Nutrition and fluid management are important parts of maintaining and repairing injury caused by BPD. Caloric content must be increased to meet the high energy needs required to increase metabolic rate and oxygen consumption. BPD energy requirements supersede standard infant caloric requirements by as much as 125%. Fluid management must be pristine to prevent right-sided heart failure, a common complication of severe BPD. Fluid restriction may be accomplished by adding diuretics, but electrolytes must be carefully monitored. Reducing lung fluid may improve lung function and decrease oxygen consumption and demand if cautiously implemented. Growth of BPD patients is dependent on adequate caloric intake and balance of protein, carbohydrates, fat, and key minerals such as calcium, phosphorous, and iron that are essential for growth and repair. Parenteral nutrition implemented during the early phase of BPD, ideally on the first day, is later followed by enteral nutrition consisting of high-calorie formulas,
composed of 10% protein, 50% fat, and 40% carbohydrate, on average. Carefully balancing the lipid to carbohydrate is essential to prevent increased CO$_2$ production and ventilator failure. (refer Chapter on Nutrition for details)

2 Fluid Restriction:
Multiple studies suggest that fluid overload contributes to an increased risk of BPD.\(^{(55)}\)

<table>
<thead>
<tr>
<th>Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>130-140 CC/KG/DAY</td>
</tr>
</tbody>
</table>

Vitamin A
Supplementation by Vitamin A demonstrated a significant decrease in BPD or death at 36 weeks PMA following treatment with vitamin A (55% vs. 62%).\(^{(56)}\) A meta-analysis of all published trials revealed that vitamin A supplementation was associated with a modest reduction in death or BPD at 36 weeks, which was of borderline statistical significance (RR 0.91, 95% confidence interval 0.82, 1.00, NNT 17).\(^{(57)}\)

<table>
<thead>
<tr>
<th>BPD prevention: 5000 IU thrice weekly IM FOR 4 WEEKS</th>
</tr>
</thead>
</table>

Omega 3 Fatty Acid And Bpd\(^{(58)}\)
The critical fatty acids Docosahexaenoic Acid (DHA) and Arachidonic Acid (AA) decline in preterm infants within the first postnatal week and are associated with neonatal morbidities, including BPD. DHA and AA are precursors to downstream metabolites that terminate the inflammatory response. Treatment with Resolvin D1 and/or Lipoxin A4 could potentially prevent lung injury of BPD. This is currently under evaluation.

Recommendations for Parenteral Nutritional Management of Hospitalized VLBW Infants

<table>
<thead>
<tr>
<th>Transitional Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids (ml/kg/day)</td>
</tr>
<tr>
<td>Period</td>
</tr>
<tr>
<td>Calories (Kcal/kg/day)</td>
</tr>
<tr>
<td>Carbohydrate (Glucose infusion rate) (mg/kg/min)</td>
</tr>
<tr>
<td>Protein (Amino acids) (gm/kg/day)</td>
</tr>
<tr>
<td>Lipids (gm/kg/day)</td>
</tr>
</tbody>
</table>
### Sodium (meq/kg/day)

<table>
<thead>
<tr>
<th></th>
<th>Minimal (first several days)</th>
<th>2(4 to 6 days of life)</th>
<th>3 (after day 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max fluid vol</td>
<td>140-150ml/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>3.5g/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enriched formula (30cal/oz, 1.0kcal/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patent Ductus Arteriosus guidelines**<sup>(59)</sup>

Those who developed a PDA or were at risk for right-heart failure were more likely to develop BPD. Fluid balance is interrupted by the presence of a patent ductus arteriosus, but can be controlled by applying positive expiratory pressure, invasively or noninvasively. Closure of the PDA is often accomplished by pharmacologic intervention with indomethacin or ibuprofen. However, Kabra et al demonstrated that infants receiving surgical closure in the early neonatal period had an increased risk of developing neurological impairment following the surgery, which later resulted in BPD.

Proposed staging system (adapted from McNamara and Hellman, unpublished clinical triaging system for ligation of a patent ductus arteriosus (PDA)) is being followed in most centres.

**Clinically significant PDA (csPDA)**

A "symptomatic PDA" or clinically significant (csPDA) is defined when clinical manifestations of pulmonary, cardiovascular, or systemic compromise occur as a result of significant left-to-right shunting.

Common signs and symptoms include:

- Murmur (systolic or continuous)
- Tachycardia
- Hyperdynamic precordium
- Wide pulse pressure > 25mmHg
- Increasing ventilatory requirements
- FiO₂ >0.4
- Pulmonary edema
- Acute pulmonary hemorrhage
- CXR – evidence of cardiomegaly and increased pulmonary vascularity

**Echocardiogram:**

All patients with a suspected PDA should have an echocardiogram to confirm the diagnosis, establish the size of the shunt and rule out ductal dependent congenital heart disease.

**Signs of an hemodynamically significant (HS)PDA on Echocardiogram include:**

1. Predominant left to right shunt through the ductus
2. Ductal diameter > 1.5mm
3. Enlarged left atrium (Left Atrial / Aortic root or LA/Ao ratio > 1.3)
4. Disturbed diastolic flow in the main pulmonary artery
5. Reverse end-diastolic flow in post ductal aorta

**Medical Management:**
1. Fluid restriction to ~120 ml/kg/day.
2. Consider diuretic therapy (Furosemide 2mg/kg/day).
3. Evaluate infant after 48-72h of above management. If infant fulfills the criteria (see below) for CSPDA and HSPDA, consider pharmacologic management.
4. Indications for pharmacological treatment include the following:
   - Presence of CSPDA and HSPDA defined by:
     - Presence of 2 or more clinical signs listed above, and
     - Presence of 2 or more echocardiographic findings noted above.

**DRUGS:** Non-steroidal anti-inflammatory agents: IV Indomethacin or IV Ibuprofen: While these are most effective if administered in the first 10-14 days of life, they may be used up to 4 weeks of life. A Cochrane database review showed no statistically significant difference in closure between ibuprofen and indomethacin. A decision to use one drug versus another should be based upon the infant's presentation and comorbidities.

Indication for ligation for PDA: After 2-3 complete courses of Indomethacin / ibuprofen. This can be attempted for up to 4 weeks of postnatal age, especially for ELBW infants.

(See chapter on cardiac issues: Section on PDA in neonate for more details)

**Inhaled Nitric Oxide Therapy**

Inhaled nitric oxide (iNO) may (60,61) or may not (62,63) be beneficial; hence, more studies are needed to better identify potential benefits to the target population likely to develop BPD. (64) The use of iNO does seem to be safe in this population, (65) although it does not seem to affect surfactant composition (66) or pulmonary function. (67) At present, routine use of iNO to decrease BPD in the preterm population is not recommended. (68)
Pharmacotherapy in BPD

Caffeine administration

Caffeine stimulates the respiratory center of a premature infant and prevents severe cases of apnea that might otherwise result in intubation and invasive mechanical ventilation. Minute ventilation, primarily by TV, is increased as a result of caffeine administration. In premature infants, caffeine has been shown to prevent BPD by reducing the need for additional respiratory support that may result in long-term sequelae. In a multicenter trial (n=35), infants < 1,250 g who received caffeine had lower BPD rates (35% compared to 44%) than infants who did not receive it. In addition, invasive ventilator days, need for CPAP, and supplemental oxygen were reduced by caffeine administration. There is evidence supporting the benefits of routine caffeine use in infants < 1,250 g without long-term effects on gastrointestinal, neurodevelopmental, or other complications.

Use of caffeine has been associated with decreased incidence of BPD and improved neurodevelopmental outcomes at 18-21 months corrected age. However, improved survival without disability in infants that received caffeine was not sustained up to 5 years of age. Early initiation (in the first 3 days of postnatal life) appears to be better. All 3 methylxanthines (noted in the table below) have been shown to help with the management of apnea of prematurity and/or improve the chances of successful extubation in preterm neonates.

A summary of the pharmacological management of BPD is shown in the table below:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Treatment of</th>
<th>Effect</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Hypoxemia</td>
<td>Improved Oxygenation</td>
<td>Longer hospital stay, home oxygen</td>
<td>Maintain saturations &gt;85% and &lt;95%</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Apnea of prematurity</td>
<td>Less apnea</td>
<td>Tachycardia, Feeding intolerance</td>
<td>Initiate early (first 3 postnatal days)</td>
</tr>
</tbody>
</table>
### Diuretics (loop, thiazides)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Cause</th>
<th>Side Effects</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Edema</td>
<td>Decreased pulmonary edema</td>
<td>Electrolyte imbalance, osteopenia, ototoxicity</td>
<td>Loop: use sparingly in early evolving BPD Thiazides: Consider for judicious chronic use</td>
</tr>
</tbody>
</table>

### Bronchodilators and Anticholinergics (albuterol, ipratropium)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Cause</th>
<th>Side Effects</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchospasm</td>
<td>Bronchodilation</td>
<td>Tachycardia, arrhythmias</td>
<td>Limit use in infants with bronchospasm and acute clinical response</td>
</tr>
</tbody>
</table>

### Steroids (early, moderately early, late, inhaled)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Cause</th>
<th>Side Effects</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Improved oxygenation, earlier extubation</td>
<td>Short term: hyperglycemia, gastrointestinal perforation Long term: increased risk for cerebral palsy</td>
<td>Last resort therapy for rapidly deteriorating pulmonary status</td>
</tr>
</tbody>
</table>

### Vitamin A

<table>
<thead>
<tr>
<th>Effect</th>
<th>Cause</th>
<th>Side Effects</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired lung Development</td>
<td>Small reduction in incidence of BPD</td>
<td>None reported</td>
<td>Used in some centers</td>
</tr>
</tbody>
</table>

### Bronchodilators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Preparation</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>Proventil, Ventolin</td>
<td>Inhalation solution MDI, 90 mcg/puff Oral</td>
<td>0.1-0.5 mg/kg every 2-6 hours 1-2 Puff every 4-6 hours 0.1-0.3 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>Xopenex</td>
<td>Inhalation solution MDI 45 mcg/puff</td>
<td>0.31 mg every 8 hours 1-2 Puffs every 4-6 hours</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Brethaire</td>
<td>Inhalation solution MDI 0.2 mg/puff Oral</td>
<td>0.1-0.3 mg/kg every 2-6 hours 1-2 puffs every 4-6 hours 0.05-0.15 mg/kg every 8-12 hours</td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>Alupent</td>
<td>Inhalation solution MDI 0.65 mg/puff</td>
<td>0.25-0.5 mg/kg every 2-4 hours 1-2 puff every 4-6 hours</td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>Maxair</td>
<td>MDI 200 mcg/puff</td>
<td>1-2 puff every 4-6 hours Children over 12 years old</td>
</tr>
</tbody>
</table>
The author’s and most centres prefer the use of albuterol, atropine and ipratropium in clinical management.

**Diuretics** \(^{75,76,77,78,79,80,81,82}\)

**Indication for diuretic therapy dose and duration:**
Indications for initial diuretic therapy (usually, furosemide) include increasing ventilator support settings and FiO\(_2\) requirements (>0.6), associated with pulmonary edema on the chest X-ray. This is usually seen at the end of first week of postnatal life in an intubated infant. The dose of furosemide is 2 mg/kg/dose IV given 1-2 times a day. We use this intermittently for the next 2-3 weeks, and/or till the infant reaches full feeds and then we replace with chronic diuretic therapy using spironolactone (2-4 mg/kg/day) and chlorothiazide (20-40 mg/kg/day). Monitoring of electrolyte levels is required, with frequent supplementation with NaCl and/or KCl to maintain their levels within normal values.

**Systemic Corticosteroid Administration** \(^{83}\)
The use of Dexamethasone may be considered in infants who are:
1. Requiring mechanical ventilation between 7 and 21 days of age,
2. In supplemental oxygen, and
3. At high risk of developing BPD.
4. The recommended course for use in National Women's Health is the course used in the DART trial.

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 to 3</td>
<td>0.075 mg/kg/dose</td>
<td>12-hourly</td>
</tr>
<tr>
<td>Days 4 to 6</td>
<td>0.050 mg/kg/dose</td>
<td>12-hourly</td>
</tr>
<tr>
<td>Days 7 and 8</td>
<td>0.025 mg/kg/dose</td>
<td>12-hourly</td>
</tr>
<tr>
<td>Days 9 and 10</td>
<td>0.01 mg/kg/dose</td>
<td>12-hourly</td>
</tr>
</tbody>
</table>

1. Some individuals may receive subsequent doses of 0.01 mg/kg/day every 2-3 days if there is significant deterioration after the tapering of the dose on day 10.
2. Repeat courses may be indicated in selected infants with severe BPD.
Hydrocortisone (84-88)

Hydrocortisone has been proposed as an alternative to dexamethasone because it is a less potent glucocorticoid and may mitigate against adrenal insufficiency experienced by some preterm infants and, thus, decrease the incidence of BPD. Overall, although hydrocortisone may be a promising alternative to dexamethasone for treating babies with BPD or prolonged ventilator dependence, there is no evidence at this time to show that it is effective or safe.

Inhaled corticosteroids (88-95)

Inhaled corticosteroids have less systemic absorption than systemic corticosteroids and their use has been suggested as a strategy to minimize the short- and long-term adverse effects of systemic corticosteroids. There is currently little evidence to support the routine use of inhaled corticosteroids for the prevention or treatment of BPD (Level 1 evidence). Inhaled corticosteroids do not appear to offer significant benefits over systemic corticosteroids for the treatment of infants who remain ventilator-dependent (Level 1 evidence).

Complications

1 Secondary to the disease:

1.1 Pulmonary hypertension (PH):

Pulmonary hypertension (PH): It has been recently recognized that PH occurs in some preterm infants as a complication of their BPD. It has been reported to be more common in infants who are extremely low (ELBW), have a history of oligohydramnios, and severe BPD and/or need for prolonged PPV. In established BPD, the incidence has been reported to be 25-40%. Diagnosis is usually made by echocardiography, but cardiac catheterization is considered the “gold standard.”

If evidence of PH documented in an intubated and ventilated patient, iNO given as a pilot trial at 20ppm to see if there is a response. If improvement noted (decreasing FiO2), keep on iNO for 1-2 weeks, and re-echo to see if there is any objective improvement in PH parameters. If present, add sildenafil (start with 0.5 mg/kg/dose q 6-8 hours, titrate dose up by 0.5mg/kg/dose every 24 hours, as tolerated, to reach a maximum dose of 3 mg/kg/dose q6 in 2 weeks), in an attempt to wean off iNO, for chronic therapy. The main side effect is systemic hypotension; usually, transient. Other pulmonary vasodilators that can be utilized include prostacyclins and bosentan. BPD infants with PH are at higher risk for increased morbidity and mortality compared to BPD infants without PH. Infants with BPD-associated PH may be at increased risk for pulmonary vascular problems as they grow older.

1.2 Airway Abnormalities:

a. Tracheomalacia: usually managed with higher levels of PEEP and/or tracheostomy and/or aortopexy, based on severity
b. Bronchomalacia: usually managed with higher levels of PEEP and/or tracheostomy, based on severity
c. “BPD spells”: 
**Figure 26:** This pictogram gives the pathological basis for treatment of hypoxic spells.
BPD spells:
- Due to trachea-/broncho-malacia, infants may have increased airway compliance. This may cause impaired clearance of secretions and tracheal collapse resulting in limitation of expiratory flow.\(^{(103,104)}\) These infants clinically present with significant airway obstruction and severe cyanosis.\(^{(103)}\) The spells are managed with sedation and/or muscle relaxants with increasing PEEP, depending upon severity. Morphine (0.05 -0.1 mg/kg) or fentanyl (1-3 microgram/kg) can be used for the short-term. Side effects include respiratory depression. For chronic sedation, suggest lorazepam (0.05-0.1 mg/kg/dose q 4-6 hourly) or midazolam (0.05-0.1 mg/kg/dose q 2-4 hourly). For paralysis, consider using pancuronium bromide 0.1 mg/kg/dose; repeat as needed. Pulmonary graphics may have some role in the management of the same.
- The strategy for managing “BPD spells” is sedation (morphine) and/or muscle relaxation. They do not respond well to ventilator changes of increasing PIP/PEEP or bronchodilators.
  - Sub-glottic stenosis: May require surgical intervention.
  - Airway granulomas: May require surgical intervention.
  - Pseudopolyps: May require surgical intervention.
- Pneumonia: choice of antibiotic: Prefer local treatment (nebulized antibiotics – see below). If treating systemically: first line Ampicillin + Gentamicin second line: As per sensitivity pattern in the local NICU.

It is Difficult to diagnose “pneumonia” in neonates due to lack of universally accepted definition. What one can diagnose is Bacterial Tracheitis. Clinically presents with respiratory deterioration in an intubated infant, associated with increased and thick secretions. Tracheal aspirate culture usually has evidence of “many” (>2+) inflammatory cells with culture suggesting growth of particular species. May be treated with Gentamicin or Tobramycin nebs, twice a day, for 5-7 days. Repeat tracheal aspirate cell counts/culture can be sent to confirm improvement.

2 Secondary to therapy:
   a. Electrolyte abnormalities due to diuretic use: Hyponatremia, hypokalemia, and hypocalcemia and osteopenia (secondary to calciuria). This is most commonly seen with furosemide.
   b. Adverse neurodevelopmental outcomes associated with early (<96 hours of PN life) of systemic steroid use.
   c. Use of Beta-agonists may increase large airway instability in infants with tracheomalacia and bronchomalacia.

Bronchoscopy Indications in an infant with established BPD:
1. Airway evaluation in infants in whom repeated extubation attempts have been unsuccessful.
2. Persistent atelectasis.
3. Isolated or localized hyperinflation.
4. Anatomic evaluation of airway if congenital and/or acquired anomalies are suspected.

Tracheostomy Indications:
Limited data for indications for tracheostomies in patients with BPD. Most are done for “severe BPD” indicated for chronic respiratory failure in infants unable to wean off ventilator support.
Pulmonary Outcomes:
It is important to keep in mind the limitations of most of these studies, which included preterm infants born before extensive use of antenatal steroids and surfactant.

Morbidity:
Infants with BPD have higher rates of re-hospitalizations (up to 50%) in the first year of life. Respiratory symptoms in patients with BPD persist beyond the first 2 years of life into the preschool years, adolescence, and early adulthood. It is unclear whether BPD severity or prematurity per se influences the persistence and severity of symptoms.

Radiologic Findings:
Chest radiograph and computed tomography (CT) scan abnormalities persist into adolescence and adulthood, with CT being more sensitive. A more severe clinical course correlates with greater radiologic and pulmonary function abnormalities. A CT scan scoring system may help with BPD prognosis.

Pulmonary Function:
Patients with BPD continue to have significant impairment and deterioration in lung function into late adolescence. Most studies have shown no reduction in exercise capacity in children with BPD when compared with healthy term infants or preterm infants without lung disease. From recent studies of large cohorts of premature infants, significant decrease in exercise capacity was reported despite normal mean lung function or mild small airway obstruction and gas trapping, which suggests that impaired exercise tolerance was perhaps secondary to poor fitness that may be improved with an exercise training program. Lung abnormalities that may persist into adulthood include airway obstruction, airway hyperreactivity, and emphysema.

Neurodevelopmental Outcomes:
Although preterm infants have an increased risk of neurodevelopmental impairment, BPD is an additional risk factor. This is probably a result of multiple contributing factors including frequent episodes of hypoxia, poor growth, and, potentially, postnatal steroids. Infants of <1500g BW with BPD have greater fine and gross motor skill impairment as well as cognitive function and language delay compared with those without BPD. Children with severe BPD have worse outcomes and require more interventions at 8 years of age than do children with mild or moderate BPD. BPD does not seem to be associated with a specific neuropsychological but, rather, a global impairment. The spectrum of neurodevelopmental impairment seems to correlate well with BPD disease severity.
### Summary of Treatment

<table>
<thead>
<tr>
<th>Therapeutic Intervention</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early phase (up to 1 postnatal week)</td>
<td></td>
</tr>
<tr>
<td>Oxygen supplementation</td>
<td>A wide variation in the acceptable oxygen-saturation levels exists across centers but it is generally &lt;95% (suggested: 87-93%)</td>
</tr>
<tr>
<td>Ventilatory strategy</td>
<td>Avoid intubation; if intubated, give ‘early’ surfactant Use short inspiratory times (0.24–0.4 s), rapid rates (40–60 per min) and low PIP (14–20 cm H₂O), moderate PEEP (4–6 cm H₂O), and tidal volumes (3–6 mL/kg) Extubate early to (S)NIPPV/nasal CPAP Blood gas targets: pH 7.25–7.35 PaO₂: 40–60 mm Hg; PaCO₂: 45–55 mm Hg High-frequency ventilation for ‘rescue’ if conventional ventilation fails</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Improves successful extubation rate Decreases BPD</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>If considering use, dose is 5000 IU administered intramuscularly 3 times per week for 4 weeks; 1 additional infant survived without BPD for every 14–15 infants who received vitamin A</td>
</tr>
<tr>
<td>Fluids</td>
<td>Restrictive fluid intake may decrease BPD</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Provide increased energy intake</td>
</tr>
<tr>
<td><strong>Evolving phase (up to 1 postnatal week)</strong></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>--</td>
</tr>
<tr>
<td><strong>Oxygen supplementation</strong></td>
<td>Same as for early phase</td>
</tr>
<tr>
<td><strong>Ventilatory strategy</strong></td>
<td>Avoid endotracheal tube ventilation; maximize noninvasive ventilation [(S)NIPPV/nasal CPAP] for respiratory support</td>
</tr>
<tr>
<td><strong>Methylxanthines</strong></td>
<td>Blood gas targets: pH 7.25–7.35; PaO₂: 50–70 mm Hg; PaCO₂: 50–60 mm Hg</td>
</tr>
<tr>
<td><strong>Vitamin A</strong></td>
<td>Same as for early phase</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>Same as for early phase; if using, continue for 4 postnatal weeks</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>Dexamethasone is effective in weaning off mechanical ventilation when used “moderately early” and “delayed” Increased incidence of neurologic sequelae with early use (&lt;96 h)</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td>Furosemide: may use daily or every other day with transient improvement in lung function Spironolactone and thiazides: chronic therapy improves lung function, decreases oxygen requirements</td>
</tr>
<tr>
<td></td>
<td>Same as for early phase</td>
</tr>
<tr>
<td>Established phase (36 weeks’ PMA)</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td><strong>Oxygen supplementation</strong></td>
<td>For prevention of pulmonary hypertension and cor pulmonale; a wide variation in the acceptable oxygen saturation levels exists across centers, but it is generally ~95%</td>
</tr>
<tr>
<td><strong>Ventilatory strategy</strong></td>
<td>Blood gas targets: pH 7.25–7.35; PaO₂: 50–70 mm Hg; PaCO₂: 50–65 mm Hg</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>Oral prednisolone may be helpful in weaning oxygen</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>Chronic therapy as for evolving phase</td>
</tr>
<tr>
<td><strong>Beta agonist</strong></td>
<td>Transient relief: increased compliance and reduced pulmonary resistance; no significant effect on incidence or severity of BPD</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td>Used in combination with beta agonists in infants with bronchospasm; Increased compliance and decreased respiratory system resistance</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td>Same as for early phase</td>
</tr>
<tr>
<td><strong>Immunization</strong></td>
<td>Prophylaxis against RSV and influenza decreases incidence of rehospitalization and morbidity</td>
</tr>
</tbody>
</table>

### Home therapy (127)

### Oxygen Saturation Target Range

The target range for SpO₂ (functional) levels is 90-95%. (128,129)

- If SpO₂ samples are 90-95% more than 50% of the time, do not alter oxygen flow.
- If SpO₂ samples are > 95% more than 50% of the time, then decrease flow.
- If SpO₂ samples are < 90% more than 50% of the time, then increase flow.
Criteria for discharge on oxygen

Infants who remain oxygen dependent at time of discharge who are otherwise well may be eligible for discharge on the home oxygen therapy. Babies who are discharged on oxygen usually fit the following criteria:

1) At least 36 weeks post conceptual age \(^{(130,131)}\)
2) No acute medical problem
3) No apnea
4) Immunized \(^{(132)}\)
5) Consistently gaining weight \(^{(128,129,133)}\)
6) Without aggressive retinopathy of prematurity stabilized or in regression without continuous SpO\(_2\) monitoring for at least one week prior to the expected date of discharge stable on O\(_2\) flow rate of 0.5L/minute
7) With satisfactory intermittent SpO\(_2\) downloads 2-3 times / week.