

## Chronic Lung Disease in Newborns

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**Abstract**

Chronic lung disease or bronchopulmonary dysplasia (BPD) occurs in preterm infants who require respiratory support in the first few days of birth. Apart from prematurity, oxygen therapy and assisted ventilation, factors like intrauterine/postnatal infections, patent ductus arteriosus, and genetic polymorphisms also contribute to its pathogenesis. The severe form of BPD with extensive inflammatory changes is rarely seen nowadays; instead, a milder form characterized by decreased alveolar septation due to arrest in lung development is more common. A multitude of strategies, mainly pharmacological and ventilatory have been employed for its prevention and treatment. Unfortunately, most of them have not been proved to be beneficial. A comprehensive protocol for the management of BPD based on the current evidence is discussed here.

**Key words:** *Bronchopulmonary Dysplasia, Prematurity, Prevention, Treatment*

## Introduction

Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) occurs in preterm infants who require mechanical ventilation and/or oxygen therapy for a primary lung disorder. Though the incidence of CLD has largely remained unchanged over the years, the improved survival of more immature infants has led to increased numbers of infants with this disorder.<sup>1</sup> These infants are more likely to have persistent respiratory symptoms requiring frequent hospital admissions especially in the first two years after birth.

## Definition and Incidence

The lack of uniformity in the diagnostic criteria for CLD partly explains the wide variation in the reported incidence among different centers.<sup>2</sup> The initial diagnostic criteria mandated continuing oxygen dependency during the first 28 days of life with compatible clinical and radiographic findings to label an infant as having BPD.<sup>3</sup> The fact that many infants would have intervals in the first few weeks during which they do not require any supplemental oxygen signified the major drawback of this definition. Later, it was proposed to use the need for supplemental oxygen at 36 weeks postmenstrual age (PMA) as the diagnostic criterion especially in preterm very low birth weight (VLBW) infants.<sup>4</sup> The later definition, used widely in clinical trials even now, has the limitation of spuriously labeling more mature infants (e.g. those born at 34-35 weeks) as having CLD.

To address the inconsistencies in the diagnostic criteria, the US National Institute of Health (NIH) organized a consensus conference in 2000 which suggested a new definition by incorporating many elements of previous definitions of BPD. The suggestion was to use oxygen need for  $\geq 28$  days and at 36 weeks PMA to identify different severity of BPD (*Table 1*).<sup>5</sup>

Recently, Ehrenkranz et al validated the consensus definition in a cohort of preterm (<32 weeks) extremely low birth weight (ELBW) infants and reported an incidence of 77% by the new criteria.<sup>6</sup> Few reports are available from the centers in India; one study from Chandigarh found the incidence of CLD (defined as need for oxygen at or beyond 28 days of life) to be 50% and 9% in ELBW and VLBW infants respectively.<sup>7</sup>

## Pathogenesis

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CLD has a multifactorial etiology; the major risk factors include prematurity, oxygen therapy, mechanical ventilation, infection, patent ductus arteriosus (PDA), and genetic predisposition.<sup>8</sup> By far the most important factor in the pathogenesis of CLD is prematurity. Exposure of immature lungs to high O<sub>2</sub> concentrations and positive pressure ventilation results in oxidative stress and ventilator induced lung injury (barotrauma/volutruma). The resulting injury and inflammation lead to abnormal reparative processes in the lung. This is compounded by inflammation resulting from infections (intra-uterine/postnatal infection) that occur commonly in these infants. PDA contributes further to this process by inducing pulmonary edema and vascular endothelial injury. Recently, genetic polymorphisms are also thought to play a role in the causation of BPD.<sup>9</sup>

### **Pathology: 'Old' vs. 'New' BPD**

The severe form of BPD ('old' BPD) seen in infants who received aggressive ventilation and were exposed to high inspired oxygen concentration from birth is rare nowadays. This form was characterized by severe morphological changes including emphysema, atelectasis and fibrosis, and marked epithelial metaplasia and smooth muscle hypertrophy in the airways and in the pulmonary vasculature.<sup>10</sup>

In contrast, the milder forms of BPD ('new' BPD) seen today occurs in infants who had only mild respiratory failure requiring shorter duration of ventilation and/or oxygen therapy immediately after birth. Pathologically, this form is characterized by a striking decrease in alveolar septation and impaired vascular development, changes more compatible with an arrest in lung development than with mechanical injury.<sup>11</sup>

### **Clinical and Radiological features**

Respiratory signs in infants with CLD include fast but shallow breathing, retractions, and paradoxical breathing. Rales and coarse rhonchi are usually heard on auscultation.

Radiographic features of 'old' and 'new' BPD are quite different, not surprising given the vastly different pathologic findings. 'Old' BPD, as originally described by Northway, had four distinct stages: stage 1, consistent with hyaline membrane disease; stage 2, opaque lung fields with air bronchograms due to areas of atelectasis alternating with emphysema; stage 3, small radiolucent fields; and stage 4, hyperinflated lungs with generalized cystic areas and dense fibrotic strands.<sup>10</sup> In contrast, infants with new BPD show only haziness reflecting diffuse loss of

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lung volume or increased lung fluid. Occasionally they have dense areas of segmental or lobar atelectasis or pneumonic infiltrates, but they do not show severe over inflation.

## **Management**

Given the multitude of factors that contribute to the pathogenesis of bronchopulmonary dysplasia, it is not surprising that there is no 'magic bullet' for its prevention and/or treatment. Indeed, the best bet for prevention of BPD would be to prevent preterm births itself, an implausible option as of now.

## **Prevention**

Prevention requires a multidisciplinary approach starting right from the antenatal period.

### ***Antenatal period:***

Use of antenatal steroids in mothers at risk for delivering a premature infant reduces the incidence of neonatal deaths and RDS but *does not* reduce the incidence of CLD. This could arguably be due to increased survival of very immature infants who are at high risk of BPD or because of the inability to detect a real protective effect.<sup>12</sup> Antenatal thyrotropin-releasing hormone (TRH) has not been effective in prevention of BPD.<sup>13</sup>

### ***After birth:***

#### **A. Ventilatory strategies**

Given that no '*ideal*' pharmacological agents are available for prevention of BPD, attention has now shifted to '*optimal*' ventilatory strategies that would prevent/reduce lung injury and permit adequate lung development.

- i) *Continuous positive airway pressure (CPAP)*: Early initiation of nasal CPAP has been shown to reduce the need for intubation and mechanical ventilation. Since one of the major risk factors for BPD is the need for mechanical ventilation, use of early CPAP should logically reduce its incidence. Numerous studies, mostly non-randomized, have reported the benefits of early CPAP in minimizing the need for mechanical ventilation and the incidence of chronic lung disease.<sup>14</sup> Surprisingly few randomized controlled trials are available till date in this regard. Recently, a multi-centric study on CPAP versus intubation and ventilation in infants born at 25-28 weeks' gestation found significant reduction in the need for oxygen at 28 days

of life but *not* at 36 weeks PMA.<sup>15</sup> Similarly, extubation to CPAP following early surfactant administration ('INTubateSURfactantExtubate') has been shown to reduce the need for mechanical ventilation but it is still uncertain if BPD is reduced by this approach. Clearly, more evidence is needed in this regard before coming to any meaningful conclusion.

- ii) *Nasal intermittent positive pressure ventilation (NIPPV)*: NIPPV is a method of augmenting NCPAP by delivering ventilator breaths via the nasal prongs. It is thought to improve the tidal and minute volumes and decrease the inspiratory effort required by neonates as compared to nCPAP. This should reduce the need for reintubation thus avoiding ventilator induced lung injury (VILI). The Cochrane review that included three RCTs found a trend towards reduction in rates of chronic lung disease (typical RR 0.73; 95% CI: 0.49, 1.07).<sup>16</sup> However, more trials are required to document the safety and effectiveness of this relatively new modality.
- iii) *Patient-triggered ventilation (PTV)*: Patient triggered modes (SIMV, assist-control, and pressure support ventilation) improve the infant-ventilator asynchrony; this should theoretically reduce the risk of VILI. The Cochrane review concluded that though PTV is associated with shorter duration of ventilation, it does not reduce the incidence of BPD.<sup>17</sup>
- iv) *High-frequency ventilation (HFV)*: Animal studies indicate that HFV could lead to less lung injury when compared to conventional ventilation. However, randomized controlled trials comparing elective use of HFV with conventional ventilation in preterm infants have yielded conflicting results. A recent meta-analysis that included 17 RCTs of conventional versus high frequency ventilation found no significant difference in the incidence of BPD. Therefore, elective use of HFV cannot be recommended for preterm infants with RDS at present.<sup>18</sup>
- v) *Volume targeted ventilation*: The observation that volutrauma and not barotrauma is the primary determinant of VILI has enthused neonatologists to use volume controlled/targeted modes of ventilation in place of conventional pressure controlled modes. Only a few randomized trials are available in this regard till date. The Cochrane review that included four RCTs found significant reduction in the duration of ventilation and pneumothorax rates but only a borderline reduction in the incidence of BPD (typical RR 0.34; 95% CI: 0.11, 1.05).<sup>19</sup> The trials did not report the combined outcome of BPD and death as well as long term respiratory/neurodevelopmental outcomes. More studies are needed to address the question of whether volume controlled ventilation would result in better long term respiratory outcomes.

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- vi) *Permissive hypercapnia*: Retrospective studies have suggested that hypocapnia that occurs during assisted ventilation is an independent risk factor for BPD. Subsequently, 'minimal ventilation' using smaller tidal volumes / less peak inflation pressures while accepting mild hypercapnia (PaCO<sub>2</sub> 45-55 mm Hg) was studied in preterm infants. One such study in preterm ELBW infants (target PaCO<sub>2</sub> >52 mm Hg in study group) reported less need for mechanical ventilation but no reduction in the need for supplemental oxygen at 36 weeks PMA.<sup>20</sup> Clearly, more studies are needed to prove the intended benefits of this promising strategy.
- vii) *Permissive hypoxemia*: Exposure to high oxygen concentration has long been recognized as an important factor in the pathogenesis of BPD. Preterm infants are more vulnerable to the harmful effects of free oxygen radicals. Surprisingly, there are few data to suggest either the optimal oxygen level required or the optimum target range for oxygen saturations (SpO<sub>2</sub>) in these infants. Observational studies suggest that in comparison with the more liberal oxygen therapy, the restrictive approach of accepting lower oxygen saturation values is associated with decreased incidences of CLD and ROP. Two RCTs have been conducted to see whether it is better to aim for high oxygen saturation in infants who are more than a few weeks old: BOOST-trial and STOP-ROP trial.<sup>21, 22</sup> Both these studies indicate that maintaining higher oxygen saturation (>95%) is associated with increased need for oxygen at 36 weeks PMA and greater use of postnatal steroids and diuretics in premature infants (when compared to maintaining lower oxygen saturation of 89-94%). Still, the uncertainty about 'optimal' oxygenation has led to wide variation of policies on oxygen-monitoring and therapy in neonatal nurseries. In response to the growing demand to resolve this uncertainty, an international collaborative effort has been mounted to conduct large multicentre RCTs, the results of which may help determine the optimal oxygen saturation targets in very premature infants.

## B. Fluids and Nutrition

- i. *Fluid restriction*: Anecdotal data indicate that relative fluid restriction reduces incidence of BPD in preterm infants. However, the systematic review of studies on fluid restriction has not found any significant reduction.<sup>23</sup> Moreover what represents fluid restriction in VLBW infants is not definitely known. Hence, no definite recommendation can be made regarding fluid restriction as a strategy for reducing the incidence of BPD.

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- ii. *Nutrition:* Nutrition plays an important role in lung development and maturation. Aggressive parenteral nutrition and early enteral feeding may help decrease the incidence of BPD in VLBW infants.<sup>24</sup> Ideally, nutritional management should begin from day one of life to minimize the respiratory morbidities. The initial management should meet the estimated fluid, protein, and energy needs. Since enteral feeding is often delayed in these infants due to gastrointestinal immaturity, parenteral nutrition with proteins and lipids should be initiated as soon as possible after birth. It should be continued until daily oral intake reaches at least 130 mL/kg. Only expressed breast milk is to be used for enteral feeding. Fortifying breast milk with human milk fortifier (HMF) will make up for deficiencies of protein and minerals like calcium and phosphorus. If fluids need to be restricted, addition of fat such as medium chain triglyceride (MCT) oil or glucose polymers will help in achieving the adequate growth.

The role of specific nutrients (e.g. inositol, vitamin E, selenium, glutamine etc. except for vitamin A) however, remains speculative till now.

#### C. Pharmacological strategies

- i) *Exogenous surfactant:* Prophylactic surfactant therapy in infants born before 30 weeks of gestation has not been shown to reduce the incidence of BPD. However, surfactant treatment for established RDS (*rescue therapy*) in infants born at or after 30 weeks gestation is associated with significant reduction in the incidence of BPD.<sup>25</sup> The apparent lack of effect in the first group could probably be due to the increased survival of more immature infants (similar to antenatal steroids).
- ii) *Vitamin A:* Vitamin A is essential for maintaining the integrity of respiratory tract epithelial cells. Very preterm infants are relatively deficient in vitamin A which has been shown to be associated with CLD. A large RCT of 807 infants with a birth weight of less than 1000 g has shown that a large dose of intramuscular vitamin A (5000 units three times a week for 4 weeks from birth) decreases the risk of CLD (OR 0.89; 95%CI 0.8-0.99).<sup>26</sup> A meta-analysis of seven RCTs has also confirmed this finding.<sup>27</sup> We use intramuscular vitamin A (in the above said dose) for ELBW infants with respiratory distress requiring supplemental oxygen or mechanical ventilation at 24 hours of age.
- iii) *Methylxanthines:* Xanthines such as caffeine and aminophylline have been routinely used for prevention/treatment of apnea and for facilitation of extubation in premature infants. Recently, a large RCT that used caffeine for these indications in infants with birth weights of

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500-1250g has shown a significant decrease in the incidence of BPD. The authors attributed this rather unexpected finding to reduced duration of mechanical ventilation in the caffeine treated group.<sup>28</sup> However, caffeine is not available in India and one should be careful before extrapolating the beneficial effects to aminophylline. We use aminophylline after extubation and for treatment of apnea of prematurity in preterm VLBW infants.

- iv) *Indomethacin / Ibuprofen therapy for PDA*: Patent ductus arteriosus is one of the major risk factors for BPD. Hence, prevention or treatment of PDA should ideally reduce its risk. However, prophylactic use of indomethacin in very low birth weight infants has failed to show any reduction in the incidence of BPD despite a significant reduction in the incidence of PDA.<sup>29</sup> Similar results are obtained with ibuprofen, another drug used for closure of PDA.<sup>30</sup> In contrast, treatment of symptomatic PDA could possibly reduce the incidence of BPD.<sup>31</sup>
- v) *Postnatal steroids*: Given that inflammation plays a central role in the pathogenesis of BPD, steroids were thought to be a natural choice for its management. However, this therapy has turned out to be the most controversial area of care following reports of adverse neurodevelopmental outcomes. Conventionally, steroid therapy is categorized into 3 broad groups based on the timing of initiation: early (during the first 96 hrs after birth), moderately early (between postnatal days 7 and 14), and delayed (after 3 weeks of age). Meta-analyses of RCTs of the first two regimes have shown a significant reduction in the incidence of BPD at 36 weeks PMA.<sup>32, 33</sup> However, there are important concerns regarding both short-term (hypertension, gastrointestinal perforation, poor somatic growth) as well as long-term adverse effects (neurodevelopmental outcomes including cerebral palsy). One systematic review in this regard found that infants who received steroids were twice as likely to develop cerebral palsy as the control infants.<sup>34</sup> In view of these findings, routine *early* use of high-dose steroids is not recommended at present. Considering the fact that no other treatment options have proved to be consistently beneficial in preventing BPD, some centers still recommend moderate early use of steroids at lower doses and for shorter durations in ventilator-dependent infants. We use steroids occasionally in ELBW infants who continue to be on mechanical ventilation even after 10-14 days of life (3-day course using low dose dexamethasone).<sup>35</sup>
- Inhaled steroids* thought to reduce the adverse effects associated with systemic administration have not been shown to be beneficial either for prevention or for treatment.<sup>36</sup>

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- vi) *iNO*: Animal studies have shown that iNO therapy, in addition to causing pulmonary vasodilatation also reduces lung inflammation and promotes lung growth. Unfortunately, most clinical studies in preterm infants with severe respiratory failure have not demonstrated any reduction in the risk of death or CLD with iNO.<sup>37</sup> Recently, two large RCTs conducted in this regard indicate that iNO therapy might be beneficial in a select group of preterm infants.<sup>38, 39</sup> However, one should remember that the appropriate dose, timing, duration, and more importantly, the subgroup of infants who are likely to benefit with this mode of therapy have not yet been clearly defined. Moreover, the prohibitive cost of iNO therapy precludes its use on a routine basis.
- vii) *Diuretic therapy*: Diuretics help by increasing the reabsorption of fluid from the lungs. Though studies have shown beneficial effects in lung physiology, no such effects were observed in mortality or the incidence of BPD. Coupled with the potential risks involved with long term therapy, chronic use of furosemide or any other diuretics cannot be recommended now. However, diuretics can be used sparingly if there are clinical/radiographic features of pulmonary edema in an infant with evolving or established BPD.<sup>40</sup> We use furosemide 0.5-1 mg/kg/day in infants with features suggestive of excess lung fluid; we stop after 24-48 hours if no improvement is noted in the clinical condition.
- viii) *Mast cell stabilizers*: Cromolyn sodium has been shown to decrease neutrophil migration and activation thus minimizing inflammation in the lungs. Two trials that have studied the possible role of cromolyn for prevention and treatment of BPD have not shown any benefit.<sup>41</sup>
- ix) *Bronchodilators*: They have not been found to be useful for prevention of BPD.<sup>42</sup>
- x) *Emerging therapies*: Preterm infants are susceptible to oxidant injury because they are deficient in antioxidant enzymes. Hence, antioxidants such as superoxide dismutase (SOD) promise to be an exciting strategy for prevention of BPD. A randomized trial that enrolled around 300 infants proved the safe nature of the drug CuZnSOD, but did not find any difference in the primary outcome of BPD at 36 weeks PMA. Interestingly, SOD treated infants had fewer episodes of respiratory illness at 1 year of age suggesting that the drug could prevent long-term lung injury caused by reactive oxygen species.<sup>43</sup> Further studies are needed to define its exact role in the management of BPD. Other antioxidants/free radical scavengers like vitamins C and E, allopurinol, N-acetyl-Cysteine have not been proved to be useful till now.

The options available for prevention and their current status are summarized in *Table 2*.

### Treatment of evolving/established BPD

There are extremely limited data from clinical trials on which to base optimal ventilatory management in established BPD. The major goal is to maintain adequate gas exchange with as minimal support as possible. CPAP and NIPPV should be attempted as much as possible. For infants on ventilator, the settings should be titrated keeping in mind the rapidly changing pulmonary mechanics (increasing airway resistance as well as improving compliance). Often, slow rates with long  $T_i$  are needed as the disease progresses. Some neonates with marked variability in compliance and resistance may benefit from volume targeted ventilation. Similarly, PTV may be useful in infants who 'fight the ventilator'.<sup>44</sup> Accepting relatively high  $\text{PaCO}_2$  (45-55 mm Hg provided  $\text{pH} > 7.25$ ) and slightly low saturations (88-93%) would help in minimizing the ventilator settings and thus help in early extubation (*Table 3*).

The role of drugs in evolving/established BPD is minimal except in select group of infants (*Table 3*). Most of the drugs used in this regard have already been discussed under prevention of BPD. Diuretics and bronchodilators can be used if the clinical condition warrants but should be stopped if no response occurs within 24-48 hours of initiation of therapy. This is especially important in case of diuretic therapy. Steroids initiated after 3 weeks of life (*late regime*) does not reduce the need for oxygen at 36 weeks PMA but definitely reduces the need for home oxygen therapy. However, it is associated with increased incidence of growth failure and hypertension.<sup>45</sup> One should weigh the risk-benefit ratio before initiating steroids for an infant with established BPD. Infants with 'BPD spells' (sudden episodes of deterioration due to marked expiratory airflow limitation) may require sedation and muscle relaxation to reduce agitation.

Infants developing BPD require 20 to 40% more calories than their age-matched healthy controls. Their caloric requirement varies from 120 to 150 Kcal/kg/day. This can be achieved by fortifying breast milk with human milk fortifier (HMF) or infant formula. For infants who require more calories, fat supplementation (e.g. MCT oil) is preferable to adding carbohydrates because of the less pronounced effects on  $\text{CO}_2$  levels (*Table 3*).<sup>24</sup>

Figure 1 summarizes the steps of prevention and treatment of BPD (starting from the antenatal period until the time of discharge) in a preterm VLBW infant.

**Table 1: Definition of BPD <sup>5</sup>**

	Gestational age	
	< 32 weeks	> 32 weeks
<b>Time point of assessment</b>	36 weeks PMA or discharge*	> 28 days but < 56 days postnatal age or discharge*
<b>Treatment with oxygen</b>	> 21% for at least 28 days	> 21% for at least 28 days
<b>BPD</b>		
<b>Mild</b>	Breathing room air at 36 weeks PMA or discharge*	Breathing room air at 56 days postnatal age or discharge*
<b>Moderate</b>	Need* for <30% oxygen at 36 weeks PMA or discharge*	Need* for <30% oxygen at 56 days postnatal age or discharge*
<b>Severe</b>	Need for $\geq$ 30% oxygen and/or positive pressure (IMV/CPAP) at 36 weeks PMA or discharge*	Need for $\geq$ 30% oxygen and/or positive pressure (IMV/CPAP) at 56 days postnatal age or discharge*

\*- whichever comes first

(PMA, Postmenstrual age; BPD, bronchopulmonary dysplasia; IMV, Intermittent mandatory ventilation; CPAP, continuous positive airway pressure)

**Table 2: BPD - Preventive strategies and their current status**

Strategies	Proven benefit	Promising (needs more studies)	Probably beneficial (effects ±)	No benefit
<b>Ventilatory</b>	-	NIPPV Volume targeted ventilation Permissive hypercapnia Permissive hypoxemia	Early CPAP Patient triggered modes	High frequency ventilation
<b>Fluids and nutrition</b>	-	Aggressive early enteral and parenteral nutrition	Fluid restriction	
<b>Pharmacological</b>	Vitamin A Postnatal steroids (but harmful as well)	Superoxide dismutase	Antenatal steroids Exogenous surfactant Methylxanthines iNO therapy Diuretics	Antenatal TRH Prophylactic indomethacin / ibuprofen Inhaled steroids Bronchodilators Mast cell stabilizers

(NIPPV, Nasal intermittent positive pressure ventilation; CPAP, continuous positive airway pressure; iNO, Inhaled nitric oxide; TRH, Thyrotropin releasing hormone)

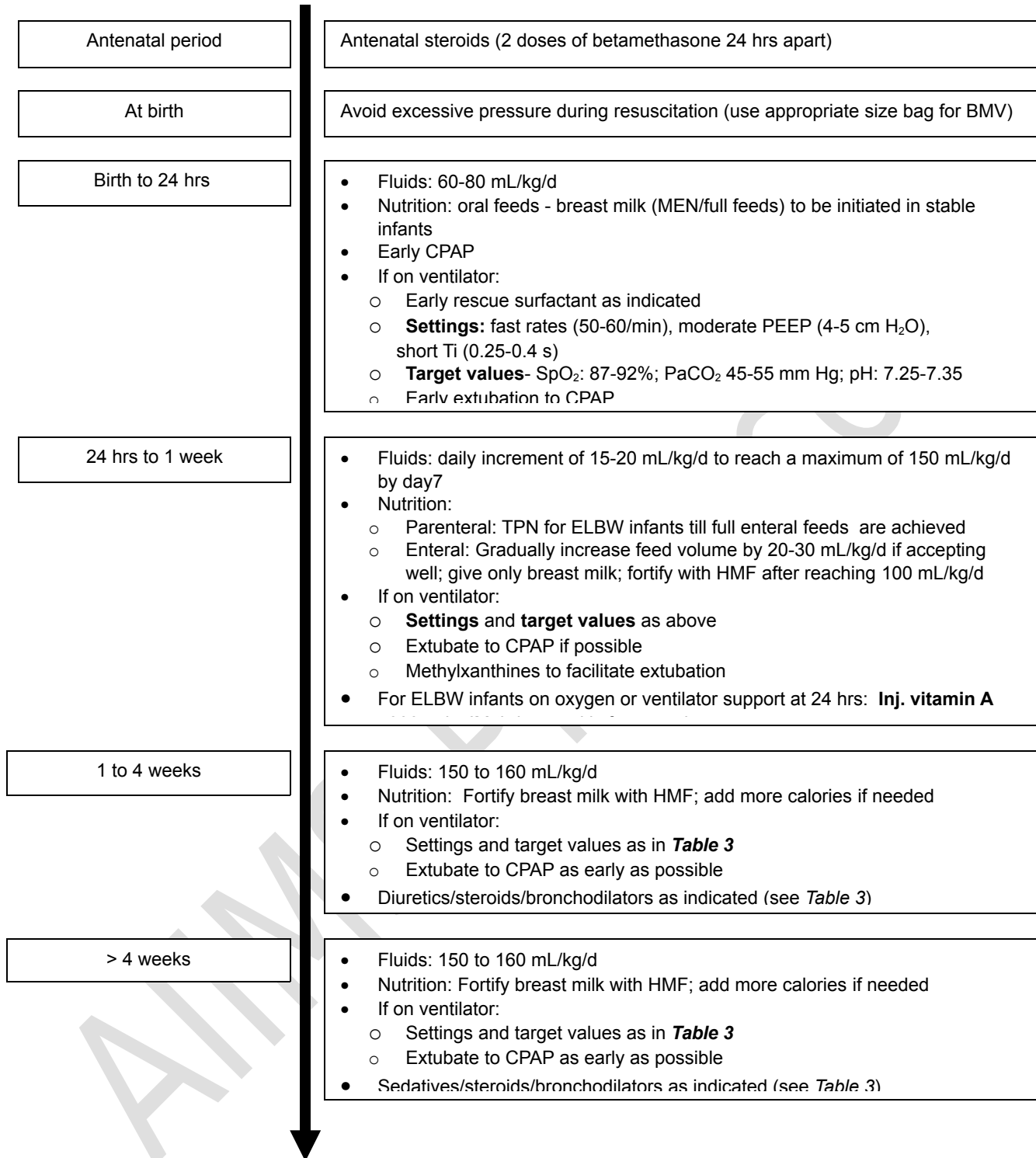
**Table 3: Management of evolving or established BPD #**

	<b>Evolving BPD (2-4 weeks age)</b>	<b>Established BPD (&gt;4 weeks age)</b>
<b>Ventilatory strategies</b>	<ul style="list-style-type: none"> <li>• Minimizing ventilatory support (e.g. using nCPAP whenever possible)</li> <li>• Tolerating slightly higher PaCO<sub>2</sub> (45-55 mm Hg provided pH &gt;7.25)</li> <li>• Target SpO<sub>2</sub>: 88-93%</li> <li>• If on IMV:                             <ul style="list-style-type: none"> <li>○ Use PTV if possible</li> <li>○ Slow rates (25-40/min)</li> <li>○ Moderate PEEP (4-5 cm H<sub>2</sub>O)</li> <li>○ Moderate Ti (0.35-0.45 sec)</li> <li>○ Low tidal volume (3-6 mL/kg)</li> <li>○ Early extubation to CPAP</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Minimizing ventilatory support</li> <li>• Tolerating higher PaCO<sub>2</sub> (55-60 mm Hg provided pH &gt;7.25)</li> <li>• Target SpO<sub>2</sub>: 89-94%</li> <li>• If on IMV:                             <ul style="list-style-type: none"> <li>○ Use PTV if possible</li> <li>○ Slow rates (20-40/min)</li> <li>○ Moderate PEEP (4-8 cm H<sub>2</sub>O)</li> <li>○ Longer Ti (0.4-0.7 sec)</li> <li>○ Larger tidal volume (5-8 mL/kg)</li> </ul> </li> </ul>
<b>Pharmacological strategies</b>	<ul style="list-style-type: none"> <li>• Methylxanthines to facilitate extubation</li> <li>• Steroids:* Consider in ELBW infants on ventilator support even after 10-14 days of age</li> <li>• Specific management:                             <ul style="list-style-type: none"> <li>○ Diuretics for features of pulmonary edema</li> <li>○ Bronchodilators for bronchospasm</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Steroids:* Individualize based on the clinical condition</li> <li>• Specific management:                             <ul style="list-style-type: none"> <li>○ Bronchodilators for bronchospasm</li> <li>○ Sedation and muscle relaxation for 'BPD spells'</li> </ul> </li> </ul>
<b>Others</b>	<ul style="list-style-type: none"> <li>• Nutrition:                             <ul style="list-style-type: none"> <li>○ Increase daily calorie intake to 120 to 150 Kcal/kg/d</li> <li>○ Give expressed breast milk fortified with HMF</li> <li>○ Use fat supplementation (e.g. MCT oil) for providing additional calories</li> <li>○ Give multivitamin supplements to meet RDA</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Same as for evolving BPD</li> </ul>

# Modified from Reference 44

\* Could result in potentially harmful effects including adverse neurodevelopmental outcomes; counsel parents before initiation of therapy

(nCPAP, nasal continuous positive airway pressure ;IMV, intermittent mandatory ventilation; PTV, patient triggered ventilation; PEEP, positive end expiratory pressure; Ti, Inspiratory time; HMF, human milk fortifier; MCT, medium chain triglycerides; RDA, recommended dietary allowance)



**Figure1: Flow-chart for management of BPD**

(BMV, bag and mask ventilation; CPAP, continuous positive airway pressure; PEEP, positive end expiratory pressure; MEN, Minimal enteral nutrition; ELBW, extremely low birth weight infants; TPN, total parenteral nutrition; HMF, human milk fortifier; PTV, patient triggered ventilation; Ti, Inspiratory time)

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