



# PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

## Pharmacologic Strategies for the Prevention of Bronchopulmonary Dysplasia





**Clinical Practice Guideline:** Pharmacologic Strategies for the Prevention of Bronchopulmonary Dysplasia

**Points of emphasis/Primary changes in practice:**

1. Hydrocortisone therapy may be utilized for the prevention or attenuation of bronchopulmonary dysplasia (BPD) in neonates at  $\geq 14$  days of life with  $\geq 60\%$  risk for BPD as determined by the NICHD BPD Outcome Estimator.
2. While evidence does support at least a small, short-term benefit of Vitamin A administration for BPD prevention, there is not proven long term benefit and our group has chosen not to institute this preventive therapy given administration difficulties.
3. Caffeine therapy will be utilized for the indications in the CAP trial (prevention or treatment of apnea or to facilitate the removal of an endotracheal tube).
4. After 2-3 weeks of life, infants who are evolving towards a diagnosis of BPD may develop specific phenotypes (e.g., pulmonary fluid retention, air trapping, pulmonary hypertension) that might warrant use of diuretic, bronchodilator and/or iNO therapies. There are no definitive data to support the use of these therapies early as the phenotype is evolving to **prevent** BPD. Some data have supported the use of these therapies to lessen the impact of symptoms that develop and potentially to have at least short term effects on oxygen and ventilator requirements or work of breathing.

**Rationale for change:**

To recognize potential opportunities and optimize and standardize utilization of pharmacologic prevention strategies for infants at risk for bronchopulmonary dysplasia (BPD).

**Questions? Please contact: NICU Clinical Pharmacist**



<b>Clinical Guideline Name</b>	Pharmacologic Strategies for the Prevention of Bronchopulmonary Dysplasia
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**I. Purpose**

The purpose of this clinical practice guideline is to address a trajectory towards prolonged ventilator dependence in preterm neonates with respiratory failure. The scope of this guideline encompasses appropriateness of the following pharmacologic therapies as strategies to lower risk of BPD development:

- (i) Corticosteroids (hydrocortisone, dexamethasone, inhaled budesonide)
- (ii) Vitamin A
- (iii) Caffeine
- (iv) Diuretics (furosemide, chlorothiazide), bronchodilators (albuterol, ipratropium bromide) or iNO

**II. Scope**

Inclusion criteria:	Neonates ≤ 30 weeks gestation
Exclusion criteria:	Gestational age > 31 weeks*
	Known congenital abnormalities impacting cardiopulmonary development

\*although the evidence for steroid use is largely in infants < 30 weeks, clinical judgment may be used in applying these guidelines to neonates at older gestational ages.

**Note:** This CPG only addresses the pharmacologic aspects of BPD **prevention**, NOT ongoing symptomatic therapy. Non-pharmacologic management (provision of respiratory care, nutrition, developmental care, infection control, etc.) is also fundamental to the avoidance of BPD and should be optimized prior to and in conjunction with the utilization of pharmacologic interventions.



### Definitions

Chronic Lung Disease (CLD) is a non-specific, overarching term used to capture a number of chronic respiratory entities that have been described since the late 1960s (Old BPD, New BPD, CPIP, etc), regardless of gestational age at birth. Generally, these infants are requiring ongoing supplemental oxygen or mechanical respiratory support (including CPAP) when they have reached 36 weeks postmenstrual age (PMA). The term CLD of prematurity has also been used to describe infants born prior to 33 weeks gestation who remain on supplemental oxygen at 36 weeks PMA.

Evolving CLD is an unofficial term used to describe infants with pulmonary immaturity who continue to require substantial ventilatory and/or supplemental oxygen support after the first week of life and prior to the 36 weeks PMA time point when an official diagnosis of BPD can be made.

BPD is defined in this CPG as the receipt of any supplemental oxygen at 36 weeks PMA among infants born prior to 33 weeks of gestation. Use of mechanical ventilation or CPAP with room air might also be considered under this label, however, for consistency, we are applying the definition that requires persistent oxygen use.

### III. Corticosteroids

Dexamethasone reduces the incidence of BPD; however, a randomized clinical trial of high-dose, prolonged dexamethasone also demonstrated an increased risk of cerebral palsy (CP).<sup>1</sup> Meta-analyses of available trials demonstrate that the risk/benefit ratio of corticosteroid therapy is dependent on the baseline risk of BPD.<sup>2,3</sup> Infants who remain on mechanical ventilation at 36 weeks PMA are not only at risk of ongoing lung disease, but also are at substantial risk of quadriparetic CP.<sup>4</sup>

Because of the risk of CP, we do not recommend routine use of high-dose dexamethasone. There are no informative large clinical trials of low-dose dexamethasone or hydrocortisone.<sup>5</sup>

An increasing number of observational studies suggest that hydrocortisone might be an effective preventive treatment for BPD that is associated with far less risk of cerebral palsy than dexamethasone.<sup>6,7</sup> Because, at this point, no clinical trial data are available to definitively assess the potential benefits and risk of hydrocortisone with respect to BPD reduction and adverse neurodevelopmental outcome, the medication should be utilized with appropriate consideration of the risks and benefits of therapy.<sup>8</sup>

In the future, we will tailor our overall approach based on data from ongoing randomized, controlled trials.



To assess BPD risk, we will utilize a published, validated predictive model.<sup>9</sup> A threshold of 60% cumulative risk of moderate BPD, severe BPD, and death for infants on invasive mechanical ventilation at or beyond 14 days of age will be utilized as an indication that it is appropriate to consider hydrocortisone therapy (Appendix 1).<sup>2,3</sup>

#### [NICHD Neonatal Research Network Neonatal BPD Outcome Estimator](#)

The standard regimen of hydrocortisone chosen for several retrospective reports and utilized in an ongoing clinical trial (specified in Appendix 1) should be individualized based on clinical response to therapy. For example, an abbreviated time-course for tapers may be appropriate for patients who do not respond to therapy and those who very rapidly wean from mechanical ventilation.

Given the delicate balance of risk and benefit associated with this intervention and the experimental nature of hydrocortisone for this indication, the decision to treat with hydrocortisone should be made only among intubated infants, after optimizing all other management strategies, and with the goal of achieving extubation. We recommend careful review of the following issues prior to the initiation of hydrocortisone:

- Respiratory support has been optimized
- Nutrition has been optimized (given the potential negative impact of glucocorticoids on growth that may require additional nutritional supplementation)
- Initiation of caffeine has been considered, as described below

Input of another neonatology colleague might be worthwhile in assessing the above elements and should be sought at the primary neonatologist's discretion.

Since hydrocortisone for BPD prevention is lacking a clinical trial evidence base at this time, there should be open discussion of the potential risks and benefits with the baby's parents and their permission sought prior to initiation of treatment.

Infants receiving hydrocortisone should be monitored closely for complications of glucocorticoid therapy: hypertension, hyperglycemia, and poor weight gain.

Small trials completed prior to 2012 suggest that inhaled corticosteroids do not prevent BPD.<sup>10</sup> However, the Neonatal European Study of Inhaled Steroids suggest potential efficacy (10% decrease in the incidence of BPD).<sup>11</sup> Unfortunately, a trend towards increased mortality with inhaled corticosteroid use is of concern. Additionally, higher doses of inhaled corticosteroid were utilized in this trial compared to previous trials. Follow up at 18-22 months corrected age will be informative. Pending this follow up, inhaled corticosteroids (including fluticasone and budesonide) do not have a role for prevention of BPD.



#### IV. Vitamin A

Intramuscular vitamin A, given three times per week, reduces the incidence of BPD.<sup>12</sup> A study designed to look at short-term outcome (rate of BPD) showed a reduction of 7% in the rate of BPD; however, no benefit of Vitamin A was found on the rate of death or neurodevelopmental impairment at 18-22 months. Additionally, vitamin A has no impact on rehospitalization, diuretic or bronchodilator use at follow-up, any home oxygen use, or duration of home oxygen use.<sup>13</sup>

The withdrawal of vitamin A from the market in late 2010 did not have an appreciable impact on the incidence of BPD.<sup>14</sup> The main reason cited by most practitioners for choosing not to administer IM Vitamin A is discomfort and small benefit associated with the need for three injections per week.<sup>15</sup>

At this time, BWH will not resume the practice of routine vitamin A administration to neonates born at < 1000 grams.

#### V. Caffeine

Caffeine therapy at standard doses for the prevention or treatment of apnea or to facilitate the removal of an endotracheal tube reduces the incidence of BPD, reduces the incidence of cerebral palsy and cognitive delay at 18-21 months of age, and reduces in incidence of developmental coordination disorder at 5 years of age.<sup>16-19</sup>

Caffeine therapy should be utilized at standard doses for the prevention or treatment of apnea or to facilitate the removal of an endotracheal tube in infants born at < 1250 grams (Appendix 2).

Caffeine should not be initiated in fully ventilator-dependent infants with serious acute lung injury.<sup>20</sup>

Potential benefits of caffeine therapy include a mild diuretic effect, bronchodilation, and improved diaphragmatic contractility. However, the benefits of these properties in fully ventilator-dependent infants with serious acute lung injury have not been demonstrated. If caffeine is utilized in this setting, potential adverse effects must be considered and the baby should be watched closely for his/her response. Caffeine may increase agitation and ventilator asynchrony in infants requiring mechanical ventilation and may lower seizure threshold in infants with brain injury.

Caffeine should not be initiated at high doses (> 20 mg/kg loading dose and > 10 mg/kg/day).<sup>21</sup>



Additional boluses or increased maintenance doses may be utilized in select infants with persistent apnea despite standard doses and no signs of caffeine toxicity (Appendix 2, see DAG for literature review).<sup>22, 23</sup>

#### **IV. Diuretics, bronchodilators, and iNO**

There are no data suggesting that loop or thiazide diuretics or bronchodilators prevent BPD. Only one of eight large randomized clinical trials of iNO suggested a benefit of the treatment in BPD prevention. Therefore, we do not recommend the use of any of these agents for BPD prevention. One or more of these therapies might prove useful in treating symptoms that develop in infants with evolving chronic lung disease. Those potential uses will be addressed in a subsequent CPG addressing Treatment of Evolving and Established BPD.



## Appendix 1 – Abbreviated hydrocortisone drug administration guideline

### Hydrocortisone

1.25 mg/kg/dose IV/PO q6h x 7 days, then q8h x 5 days, then q12h x 5 days, then q24h x 5 days

\*Taper may be tailored based on individual patient situation. Please contact Clinical Pharmacist.

\*The bioavailability of oral hydrocortisone in neonates is unknown. Use 1:1 IV:PO conversion based on adult literature demonstrating 80-100% absorption.

Glucocorticoid for the treatment of pressor-resistant hypotension or facilitation of weaning from mechanical ventilation to prevent bronchopulmonary dysplasia

#### **Administration time and preparation:**

**Intravenous:** Infuse over 30 minutes

**Oral:** Compounded 2 mg/mL suspension. Refrigerate.

**Compatibility:** TPN, intralipid, calcium gluconate, dopamine, epinephrine, fentanyl, furosemide, heparin, insulin, morphine, pancuronium, potassium chloride, vecuronium

**Incompatibility:** Midazolam

**Monitoring:** Blood pressure continuously, blood glucose every 6-12 hours

**Adverse Effects:** Hypertension, hyperglycemia, potential for growth inhibition, potential for increased risk of rickets due to decreased calcium absorption in the gastrointestinal tract





## Appendix 2 – Abbreviated caffeine drug administration guideline

20 mg/kg IV, PO x 1, then 5-10 mg/kg/day

For persistent apnea, may bolus 20 mg/kg x 1, then increase maintenance dose by 5 mg/kg/day to maximum maintenance dose of 20 mg/kg/day

Maximum daily dose including bolus and maintenance doses: 40 mg/kg/day

Methylxanthine respiratory stimulant for the treatment of apnea of prematurity

### **Administration time and preparation:**

**Intravenous:** Infuse bolus over 30 minutes; Infuse maintenance dose over 15 minutes

**Oral:** Commercially-available 20 mg/mL solution. Do not refrigerate.

**Compatibility:** TPN, alprostadil, dobutamine, dopamine, epinephrine, fentanyl, heparin, morphine

**Incompatibility:** Furosemide

**Monitoring:** Apnea, heart rate

**Adverse effects:** Tachycardia, irritability; signs of toxicity include tachycardia, feeding intolerance, jitteriness, and seizures



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