### Steroids for Bronchopulmonary Dysplasia

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| Site | All CHB |
| Setting/Population | Inpatient NICU (Neonatal Intensive Care Unit) |
| Clinician | All NICU clinicians |

#### Guideline

* A consensus statement was reaffirmed in 2014 by the American Academy of Pediatrics regarding postnatal corticosteroids to treat or prevent bronchopulmonary dysplasia (BPD) in preterm infants recommending the following:
* High daily doses of dexamethasone (approximately 0.5 mg/kg per day) have been shown to reduce the incidence of BPD but have been associated with numerous short- and long-term adverse outcomes, including neurodevelopmental impairment, and at present there is no basis for postulating that high daily doses confer additional therapeutic benefit over lower-dose therapy. **Recommendation: in the absence of randomized trial results showing improved short- and long-term outcomes**, **therapy with high-dose dexamethasone cannot be recommended.**
* Low-dose dexamethasone therapy (<0.2 mg/kg per day) may facilitate extubation and may decrease the incidence of short- and long-term adverse effects observed with higher doses of dexamethasone. Additional randomized controlled trials (RCTs) sufficiently powered to evaluate the effects of low-dose dexamethasone therapy on rates of survival without BPD, as well as on other short- and long-term outcomes, are warranted. **Recommendation: there is insufficient evidence to make a recommendation regarding treatment with low-dose dexamethasone.**
* Low-dose hydrocortisone therapy (1 mg/kg per day) given for the first 2 weeks of life may increase rates of survival without BPD, particularly for infants delivered in a setting of prenatal inflammation, without adversely affecting neurodevelopmental outcomes. Clinicians should be aware of a possible increased risk of isolated intestinal perforation associated with early concomitant treatment with inhibitors of prostaglandin synthesis. Further RCTs powered to detect effects on neurodevelopmental outcomes, aimed at targeting patients who may derive most benefit and developing treatment strategies to reduce the incidence of isolated intestinal perforation, are warranted. **Recommendation: early hydrocortisone treatment may be beneficial in a specific population of patients; however, there is insufficient evidence to recommend its use for all infants at risk of BPD.**
* Higher doses of hydrocortisone (3–6 mg/kg per day) instituted after the first week of postnatal age have not been shown to improve rates of survival without BPD in any RCT. RCTs powered to assess the effect of this therapy on short- and long-term outcomes are needed. **Recommendation: existing data are insufficient to make a recommendation regarding treatment with high-dose hydrocortisone.**

##### Purpose

The purpose of this guideline is to provide a reference for the safe and effective use of steroids in the prevention and rescue management of BPD in the neonate.

#### Procedure

##### Background

Previous studies have shown that the systemic administration of dexamethasone decreases the incidence of BPD at 28 days PNA and 36 weeks PMA and allows for earlier extubation and fewer ventilator days. However current data do not show significant long-term benefits to the use of dexamethasone. Specifically survival does not improve after dexamethasone administration by the time of discharge, nor does it affect the length of hospitalization. In addition there are many short and long term adverse effects to the use of systemic corticosteroids, specifically dexamethasone. Short-term side effects include hyperglycemia (possibly requiring insulin therapy), hypertension, gastrointestinal bleeding and intestinal perforation (3 times higher than controls), poor weight gain, poor head growth, hypertrophic obstructive cardiomyopathy, and a trend toward higher incidence of periventricular leukomalacia. Current data looking at long-term outcomes also demonstrate an increased incidence of neurodevelopmental delay (relative risk 1.7 times higher than controls) and cerebral palsy (relative risk 2.9 times higher than controls).

Though more data is clearly needed, at this point we conclude that the risk: benefit ratio is not in favor of using systemic dexamethasone for the routine treatment of BPD. However, for life threatening RDS or BPD and before committing a baby to a tracheostomy or long term treatment in a NICU or rehabilitation hospital, both of which potentially carry a neurodevelopmental cost, a course of dexamethasone, methylprednisolone or hydrocortisone should be considered.

Alternative Corticosteroid Molecules to Dexamethasone Therapy:

Dexamethasone has a very long plasma half-life, compared with cortisol,and has been used for long treatment periods at multiple times the physiologic secretion of cortisol. Premature infants have immature detoxification processes, which can make the relative dose of higher-dose regimens of dexamethasone potentially more toxic, since dexamethasone contains sulfites, which are potentially toxicto the developing brain. A number of other steroids are widely used in diverseinflammatory and immune diseases in children, and adults suchas status asthmaticus, acute respiratory distress syndrome, nephrotic syndrome, and acute graft rejection multiplesclerosis.

Dexamethasone is 5 times more potentthan methylprednisolone in its genomic activity, but is only 1.2 timesas potent in its nongenomic activity. Thus, dexamethasone is likely to havea very different side effect profile than methylprednisolone orprednisolone. Hydrocortisone mayproduce different effects than dexamethasone and prednisone because of its mineralocorticoid properties.Animal experiments investigating the neurotoxicity of glucocorticoidsshowed that exposure to high-dose dexamethasone promoted neuronal apoptosis,and that adrenal insufficiency accentuated this effect. However, pretreatment with physiologic doses of corticosterone(the cortisol equivalent in the rat) was protective, because ofits affinity for the mineralocorticoid receptor in the brain.These differential effects may afford opportunities to obtain thebenefits we seek while minimizing side effects by selecting the glucocorticoid with the desired T1/2, glucocorticoid and mineralocorticoid potency and side effect profile.

Methylprednisolone has a shorter half-life and a lower anti-inflammatory activity than dexamethasone, a negligible mineralocorticoid effect, and no sulfiting agents. Methylprednisolone has been safely used in many clinical conditions. Recently, the benefits and medium-term side effects of methylprednisolone were evaluated for the first time among 90 preterm infants (<30 week's gestation) at risk for BPD. In this study, methylprednisolone was as effective as dexamethasone in weaning from mechanical ventilation, with fewer side effects; the incidence of periventricular leukomalacia was significantly lower among infants treated with methylprednisolone as compared with those treated with dexamethasone. This open study had an inadequate sample size to draw any conclusion concerning the lower incidence of side effects. However, consistent with these findings, in a study comparing prednisone to dexamethasone in childhood leukemia, prednisone was shown to be significantly less neurotoxic.

In another recent study looking at hydrocortisone in BPD, a randomized, placebo-controlled pilot study of 40 extremely low birth weight infants was performed. Low-dose hydrocortisone treatment (1 mg/kg/day) during the first 2 weeks of life increased survival without BPD and improved other measures of respiratory and systemic outcome, without apparent increase in adverse effects. Again, this pilot study was too small to draw conclusions about adverse effects.

Inhaled steroids have no efficacy or safety advantage over systemic steroids and are currently not recommended.

In summary, although there is insufficient evidence to assess long-term effects of any steroid preparations other than dexamethasone, the data is suggestive of improved side effect profiles with similar efficacy for both prednisone and hydrocortisone, allowing their use to be considered when steroid use is indicated.

##### Assessment

PREVENTION of BPD in HIGH RISK premature neonates

For infants less than 28 weeks gestational age and between 14-28 days of life, who are at high risk for development of bronchopulmonary dysplasia, the clinical team should consider use of low dose steroids for BPD prevention. Specifically in infants exposed to prenatal inflammation. Steroids used for prevention of BPD may help reduce inflammation, promote extubation, and reduce additional barotrauma. Goal is to attempt to intervene prior to formation of fibrosis. Long term outcomes have shown no adverse neurodevelopmental outcomes at 18-22 months in patients receiving hydrocortisone early for prevention of BPD (see appendix for evidence based guideline)

Definition of high risk neonates:

Intubated or risk on BPD calculator (<http://bit.ly/BPDcalc>) of > 60% of BPD. If patient was recently intubated consider excluding patient if respiratory failure is due to other causes (i.e. sepsis).

Avoid concurrent use with indomethacin medication given increased incidence of spontaneous intestinal perforation.

RESCUE Therapy for Severe BPD

The use of systemic steroids should be reserved for exceptional clinicalcircumstances (i.e. when an infant is on maximal ventilatory support at high risk for mortality), or when the child has **Severe BPD** and alternative treatment choices (tracheotomy, transfer to rehabilitation facility) are less acceptable than the potential side effect profile of steroids.

Definition of severe BPD:

1. Approaching EDC and unable to wean off of vent and therefore considering tracheotomy.
2. Past EDC and unable to wean off of NCO2 > 1L/min flow and therefore unable to discharge home.

If steroids are used we recommend the following:

1. Parentsshould be fully informedabout the known short- and long-termrisks and agree to treatment with corticosteroids. While a formal consent form is not required, a note documenting the discussion should be written in the patient’s chart.
2. Other medical management should already be optimized. Specifically, the patient should be fluid restricted, diuretics should have been tried, and sepsis or patent ductus arteriosus should have been treated.
3. If a patient does not show a response, the use of steroids should be discontinued after 72 hours.

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|  | **Benefits** | **Risks** | **Properties** |
| **Dexamethasone** | Most widely studied.Decreased rates of BPD and improvement in mortality. | ***Highest*** ***rates*** of hyperglycemia, hypertension, hypertrophic cardiomyopathy, poor weight gain and CP risk | No mineralocorticoidRelative potency: 25Biological ½ life: 32 hrs |
| **Methylprednisolone/ Prednisolone** | Improvement in weaning off oxygen in BPD patients | No data on long-term neurodevelopment outcomes | Negligible mineralocorticoid activityRelative potency: 5Biological ½ life: 18 hrs |
| **Hydrocortisone** | Decreased rates of BPD and improvement in mortality. | Increased risk of spontaneous intestinal perforation with concurrent indomethacin use | Has both glucocorticoid and mineralocorticoid activityRelative potency: 1Biological ½ life: 8 hrs |

##### Implementation

Prevention

If steroids are to be used as PREVENTION therapy for high risk neonates, we recommend hydrocortisone because it has most evidence based studies of efficacy and lower risk and higher benefit in high risk populations. See EBG/Appendix for additional details.

Hydrocortisone

Low dose Hydrocortisone for PREVENTION:

* Day 1-2: 1 mg/kg/dose q6 hours
* Day 3-5: 0.5 mg/kg/dose q6 hours
* Day 6-8: 0.5 mg/kg/dose q12 hours
* Day 9-10: 0.5 mg/kg/dose q24 hours

Rescue

If steroids are to be used, **we recommend methylprednisolone** because of its apparently superior risk: benefit ratio compared to other steroids. Either dexamethasone or hydrocortisone is also acceptable:

**Methylprednisolone**

Methylprednisolone for RESCUE

* Day 1-5: 2 mg/kg/dose q 24 hours
* Day 6-10: 1 mg/kg/dose q 24 hours
* Day 11-14: 1 mg/kg/dose q48 hours for two doses (skip day 11, **give dose on day 12**, skip day 13 and **give dose on day 14**).

For longer term use, consider continuing to decrease dose to 0.5 mg/kg every other day then let child outgrow dose.

**Dexamethasone**

The majority of the studies showing adverse results used relatively high dose, long duration therapy with dexamethasone started within the first week of life. Therefore, we recommend using the minimum dose of steroid that achieves a clinical response and starting after the first week of life. The following treatment guidelines are adapted from a multi-centered study of inhaled nitric oxide for the prevention of BPD study. They attempt to expose the infant to the lowest, shortest course of dexamethasone.

Dexamethasone for RESCUE (based on DART: Dexamethasone A Randomized Controlled Trial)

* Day1-3: 0.15 mg/kg/dose q 24hours
* Day 4-6: 0.1 mg/kg/dose q24 hours
* Day 7-8: 0.05 mg/kg/dose q24 hours
* Day 9-10: 0.02 mg/kg/dose q24 hours

If clinical team opts to use hydrocortisone for RESCUE, refer to prevention dosing above. If patient arrives from OSH on hydrocortisone taper, discuss with pharmacy if taper should continue as planned or be adjusted.

##### Evaluation

Evaluate effectiveness of the procedure and patient outcomes.

#### Documentation

Complete [patient care documentation](http://chbelibrary/C14/rnsg/rn_sg/Nursing%20Standards%20and%20Guidelines/04%20Patient%20Documentation/rn_sg_041_002_pt_doc_guidelines.doc) as described in the Standards and Guidelines.

#### Resources

[Hydrocortisone for BPD Prevention Weaning Tool](http://chbshare.chboston.org/elibrary/ptsvc/manuals/pcm/cccm/pcmnicu/nicupcm/NICU%20Hydrocortisone%20for%20BPD%20Prevention%20Weaning%20Tool.xlsx)

[Methylprednisolone/ Prednisolone for BPD Rescue Weaning Tool](http://chbshare.chboston.org/TS/ptsvc/nicu/NICU/methypred%20wean%208.14.17.xlsx)

[Dexamethasone for BPD Rescue Weaning Tool](http://chbshare.chboston.org/TS/ptsvc/nicu/NICU/Dexamethasone%20wean%20tool.xlsx)

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#### Document Attributes

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##### Appendix: Steroid Use for Prevention of BPD in High Risk Neonates

