Newborn Critical Care Center (NCCC) Clinical Guidelines

Postnatal Systemic Steroid Use for Treatment or Prevention of Bronchopulmonary Dysplasia (BPD)

CLINICAL GUIDELINE SUMMARY

1. Early dexamethasone (< 8 days) should not be used to prevent BPD given increased risk for neurodevelopmental impairment (primarily CP).
2. Late dexamethasone (>/= 8 days) should be reserved for treatment/prevention of BPD in mechanically ventilated patients at high risk (>65%) for BPD. (BPD Estimator)
3. The DART study dosing regimen should be used for the treatment course (see last page or Neofax for dosing schedule).
4. A second treatment course of dexamethasone may be administered with a recommended interval of one month between courses. ***(Dosing is the same for the second course)***. A third course or daily long-term dexamethasone is not recommended.

GUIDELINE BACKGROUND AND SUMMARY OF EVIDENCE:

I. BPD: DEFINITION AND CLASSIFICATION OF SEVERITY

Historically BPD was defined as an oxygen or respiratory requirement at 28 days of age. As survival improved for infants at lower gestational ages, it was recognized that this definition is unfairly biased against infants born more premature. Moreover, the need for oxygen at 36 weeks postmenstrual age (PMA) was a better predictor of abnormal pulmonary outcomes in infancy for VLBW infants <32 weeks than the need for oxygen at 1 month of life. The definition and classification of BPD continues to be a subject of debate, but the following NICHD definition is widely used: [7]

GESTATIONAL AGE < 32 WEEKS	
Timing of Assessment	36 weeks PMA or discharge home (whichever comes first)
OUTCOMES	
Mild BPD	Therapy with oxygen >21% for at least 28 days, but not at 36 weeks PMA or time of discharge
Moderate BPD	Therapy with oxygen >21% for at least 28 days PLUS need for <30% oxygen at 36 weeks PMA or time of discharge
Severe BPD	Therapy with oxygen >21% for at least 28 days PLUS the need for ≥30% oxygen and/or positive pressure (PPV or nasal CPAP) at 36 weeks PMA or time of discharge

Note: If an infant is receiving supplemental oxygen or respiratory support at 36 weeks PMA for disease processes not related to lung disease (e.g. mechanical ventilation for apnea), they are not necessarily diagnosed with BPD. Oxygen requirement for an acute event after 36 weeks PMA does not change their diagnosis of BPD, as the respiratory support algorithm is to be reflective of their chronic support needs.

II. COCHRANE DATABASE OF SYSTEMIC REVIEWS ON CORTICOSTEROIDS FOR BPD

Early Administration (< 8 days) 2017	
Mortality	No evidence of reduced mortality (at 28 days, at discharge, or at follow-up)
BPD	Decreased incidence of BPD, defined as needing oxygen supplementation at 28 days or at 36 weeks PMA
Death or BPD	Decreased incidence composite outcome of death or BPD at 28 days (RR 0.92 [0.88-0.96]) and death or BPD at 36 weeks PMA (RR 0.89 [0.84-0.95])
Failure to extubate	Reduction in extubation failure rates
Metabolic complications	Increased risk of hyperglycemia and hypertension
Gastrointestinal complications	Increased risk of GI bleeding and GI perforation; no evidence of increased incidence of NEC
Other complications	Based on one study, early corticosteroids increased the risk of hypertrophic cardiomyopathy and growth failure
	Early corticosteroids reduced the risk of PDA
	No effect on the incidence of air leaks, severe IVH, pulmonary hemorrhage, PVL, or infection
	Reduced incidence of any ROP, severe ROP, and severe ROP in survivors

Regimens varied considerably in the studies included in this Cochrane review; including courses as short as 1-2 days to courses of up to 4 weeks. 32 RCTs enrolling 4395 patients were included in this review.

Follow-up studies were limited to 13 out of the 32 studies identified for this meta-analysis:	
Developmental delay	One study showed an increased risk of developmental delay (RR 1.68 [1.08-2.61]), although the criteria for diagnosis were not explicit.
Cerebral palsy (CP)	Risk for CP was increased with early corticosteroids (RR 1.45 [1.06-1.98]); but there was little difference in the risk of the combined outcome of death or CP (RR 1.03 [0.91-1.16])
Major neurosensory disability	No significant effects were found on major neurosensory disability or the combined outcome of death or major neurosensory disability
Abnormal neurological exam	There was an increased risk of an abnormal neurological exam (RR 1.81 [1.33-2.47]) and the combined outcome of death or abnormal neurologic exam (RR 1.23 [1.06-1.42])
Other Outcomes	No significant differences in other long-term outcomes, such as: blindness, deafness, formal psychometric testing, abnormal EEG, behavior problems, or rehospitalization

Conclusions:

- The benefits of early postnatal corticosteroid treatment (≤ 7 days), particularly dexamethasone, may not outweigh the adverse effects of this treatment.
- **Although early corticosteroid treatment facilitates extubation and reduces the risk of chronic lung disease and patent ductus arteriosus, it is associated with short-term adverse effects including gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy and growth failure.**
- **Long-term follow-up studies report an increased risk of abnormal neurological examination and cerebral palsy.** However, the methodological quality of the studies determining long-term outcomes is limited; the surviving children have been assessed predominantly before school age, and no study has been sufficiently powered to detect important adverse long-term neurosensory outcomes.
- There is a compelling need for the long-term follow-up and reporting of late outcomes, especially neurological and developmental outcomes, among surviving infants who participated in all randomized trials of early postnatal corticosteroid treatment.

Late Administration (> 7 days) 2017	
Mortality	Decreased mortality at 28 days (RR 0.49 [0.28-0.85]); there was no effect on mortality before discharge, or on mortality at the latest reported age
BPD	Decreased incidence of BPD at 28 days (RR 0.87 [0.81-0.94]) and at 36 weeks' PMA (RR 0.72 [0.61-0.85])
Death or BPD	There was a decreased risk of the combined outcome at 28 days (RR 0.84 [0.78-0.89]) and at 36 weeks' PMA (RR 0.77 [0.70-0.86])
Failure to extubate	Reduction in extubation failure rates
Metabolic complications	Increased risk of hyperglycemia, glycosuria, and hypertension
Gastrointestinal complications	No significant increase in NEC, GI bleeding, or GI perforation
Other complications	No significant effect on infection rates, pneumothorax, or severe IVH
	There was an increased risk of hypertrophic cardiomyopathy
	There was an increased risk of ROP overall, but not in survivors

The dose of dexamethasone used was an initial dose of 0.5 - 1.0 mg/kg/d with duration of therapy between 3 days and 6 weeks. Twenty-one RCTs enrolling 1424 patients were included in this review.

Follow-up studies showed:	
Bayley Testing	No significant difference in rates of children with low cut-off scores for the Mental Development Index or the Psychomotor Developmental Index on Bayley scales
Cerebral palsy (CP)	Cerebral palsy at latest reported age was not significantly increased overall (RR 1.16 [0.82-1.64])
Major neurosensory disability	No significant effects were found on major neurosensory disability including hearing or deafness
Abnormal neurological exam	There was an increased risk of an abnormal neurological exam (RR 1.81 [1.05-3.11]) but the clinical importance of this finding is unclear as there were no important increases in CP or major neurosensory disability
Other Outcomes	No significant differences in other long-term outcomes, such as IQ, respiratory heatlh/function, blood pressure, or growth

Conclusions:

- **Although there continues to be concern about an increased incidence of adverse neurological outcomes in infants treated with postnatal steroids, this Cochrane review suggests that late therapy may reduce neonatal mortality without significantly increasing the risk of adverse long-term neurodevelopmental outcomes**. However, the methodological quality of the studies determining the long-term outcome is limited.
- Given the evidence of both benefits and harms of treatment, and the limitations of the evidence at present, **it appears prudent to reserve the use of late corticosteroids for infants who cannot be weaned from mechanical ventilation and to minimize the dose and duration of any course of treatment**." [3]

III. PREDICTION OF BPD AND THRESHOLD FOR CORTICOSTEROID THERAPY

Many factors have been associated with an increased risk for the development of BPD, including: **birth weight**, **gestational age**, male **sex**, **race**, oxygen therapy at 24 hours, mechanical ventilation at 48 hours, duration of assisted ventilation, PDA, NEC, and sepsis.

An **online estimator** for the prediction of BPD, sponsored by the NICHD, which includes the above bolded demographics and the current respiratory support needs can be found here. [8]

Threshold for corticosteroid therapy:

- Results from a meta-analysis by Doyle et al showed that dexamethasone use in patients with a greater than 65% risk of BPD were at lower risk for death or CP. [5]

- Patients with a low risk (less than 35%) for BPD were at an increased risk of death or CP.
- Wilson-Costello et al found that patients with a low BPD risk had higher rates of neurodevelopmental impairment when treated with dexamethasone (OR 2.9 [1.8-4.8]); patients with higher BPD risk (> 50%) experienced less harm (OR 1.9 [1.4-1.6]). [6]

IV. DEXAMETHASONE DOSING: A RANDOMIZED TRIAL (DART STUDY)

Eligible Infants: Very preterm (gestational age: < 28 weeks) or ELBW (birth weight: < 1,000g) infants who were ventilator dependent after the first 1 week of life (> 168 hours of age) and for whom clinicians considered corticosteroids a treatment option. Seventy infants were recruited from 11 centers. Study results showed shorter duration of intubation and improvement in ventilator and oxygen requirements. There was no significant difference in mortality or rates of chronic lung disease in the study sample recruited. [4]

DART DOSING REGIMEN	
Twice daily doses of 10 day course (total dose = 0.89 mg/kg)	
Day 1 - 3	0.15 mg/kg/d for 3 days
Day 4 - 6	0.1 mg/kg/d for 3 days
Day 7 - 8	0.05 mg/kg/d for 2 days
Day 9 - 10	0.02 mg/kg/d for 2 days

** Dose is the same if a second course is administered. Recommended duration between courses is one month*

V. USE OF EARLY HYDROCORTISONE FOR PREVENTION OF BPD

Over the last 10 years, there has been increasing interest in the routine use of early low-dose systemic hydrocortisone to counteract the state of relative adrenal insufficiency (AI) that is experienced by extremely preterm infants and thereby reduce the risk of certain neonatal morbidities, including BPD. To date, there have been 5 randomized control trials specifically designed to test the efficacy of prophylaxis of early AI with hydrocortisone to improve survival without BPD. A recent systematic review and individual patient data meta-analysis of these 5 trials concluded the following[9]:

- Preterm infants treated with early systemic hydrocortisone had significantly higher chance of survival without BPD compared to those infants treated with placebo (53 versus 46%, NNT = 13)
- Early hydrocortisone use was associated with higher incidence of spontaneous GI perforation, but this risk was observed only when hydrocortisone was given concurrently with indomethacin, and appeared to be avoidable if ibuprofen was used for PDA treatment
- Early hydrocortisone use was associated with higher incidence of late onset sepsis, *particularly in infants exposed to chorioamnionitis*, but there were no adverse effects observed in terms of mortality or 2-year neurodevelopmental outcomes

- Early hydrocortisone did not appear to have any adverse effect on neurodevelopment when assessed at 2 years, and seemed to have a small, not statistically significant, beneficial effect in reducing the risk of neurodevelopmental impairment

Although the data from these trials is promising, the prophylactic use of hydrocortisone for BPD prevention is not widespread and is not currently the standard of care.

References:

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