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 (< 7 days) should not be used to prevent BPD given increased risk for neurodevelopmental impairment (primarily CP).
2. Late dexamethasone (>/= 7 days) should be reserved for treatment/prevention of BPD in mechanically ventilated patients at high risk (>65%) for BPD. (BPD Calculator)[7]
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 >/= one month interval between dexamethasone courses. ***(Dosing is the same for the second course)***.

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. The need for oxygen at 36 weeks postmenstrual age (PMA) was thought to be a better predictor of abnormal pulmonary outcomes in infancy for VLBW infants <32 weeks than the need for oxygen at 1 month of life. However, neither of these definitions characterized the wide spectrum of BPD severity. In 2019, Jensen *et al.* assessed 18 prespecified severity-graded definitions of BPD and found that the definition of BPD that best predicted childhood morbidity characterized disease severity according to the mode of respiratory support at 36 weeks PMA, regardless of supplemental oxygen used. This definition is shown below:[10]

GESTATIONAL AGE < 32 WEEKS	
Timing of Assessment	36 weeks PMA
OUTCOMES	
Grade 1	Nasal cannula at flow rate </= 2 L/min
Grade 2	Nasal cannula at flow rates >2 L/min or noninvasive positive airway pressure
Grade 3	Invasive mechanical ventilation

Note: Based on this definition, infants breathing in room air at 36 weeks PMA do not have BPD. Of note, these criteria correctly predicted death or serious respiratory morbidity in 81% of study infants.

II. COCHRANE DATABASE OF SYSTEMIC REVIEWS ON CORTICOSTEROIDS FOR BPD

Early Administration (< 7 days) 2021	
Mortality	No evidence of reduced mortality (at 28 days, at discharge, or at follow-up)
BPD	Decreased incidence of BPD at 28 days of life and at 36 weeks PMA
Death or BPD	Decreased incidence composite outcome of death or BPD at 28 days
Failure to extubate	Reduced rates of failure to extubate at 3, 7, 14, and 28 days of life
Gastrointestinal complications	Increased risk of GI perforation during primary hospitalization, but no evidence of an effect on the incidence of NEC
Cerebral Palsy at latest reported age	Increased risk of cerebral palsy. Studies treating with dexamethasone or hydrocortisone (RR 1.42 [1.06-1.91]). Studies treating with dexamethasone (RR 1.77 [1.21-2.58])
Death or cerebral palsy	Increased composite outcome in infants treated with dexamethasone (RR 1.18 [1.01-1.37])
Other	Increased risk of hypertrophic cardiomyopathy
	Increased risk of growth failure
	Increased risk of hyperglycemia
	Increased risk of hypertension
	No effect on risk of infection
	Reduced any ROP

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. No new studies were identified compared with the 2017 Cochrane Review.

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, longer-term follow-up into late childhood is vital for assessment of the effects of early systemic steroids on higher-order neurological function such as cognitive function, executive function, academic performance, behavior, mental health motor function and lung function.

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. In 2 studies, hydrocortisone was the corticosteroid. Twenty-three studies were included in this review.

Late Administration (>/= 7 days) 2021	
Mortality	Decreased mortality at latest reported age (RR 0.81 [0.66-0.99-0.85]); there was no effect on mortality in the subgroup treated with dexamethasone
BPD	Decreased incidence of BPD at 36 weeks PMA in the studies treating with dexamethasone (RR 0.76 [0.66-0.87])
Death or BPD	There was a decreased risk of the combined outcome (RR 0.75 [0.67-0.84])
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
Cerebral Palsy	No significant increase in risk of cerebral palsy (RR 1.17 [0.84-1.61])
Mortality or Cerebral Palsy	No significant increase in the composite outcome (RR 0.95 [0.77-1.16])
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
	Increased risk of hyperglycemia
	Increased risk of hypertension

Conclusions:

- Late systemic postnatal corticosteroids reduces the risks of mortality and BPD without evidence of increased risk of cerebral palsy.
- Studies are limited to investigate long-term neurodevelopmental outcomes. Longer-term follow-up into childhood is needed.
- **This review supports the use of late systemic corticosteroids for infants who are mechanically ventilated.**

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.[7]

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.*

References:

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