Newborn Critical Care Center (NCCC) Clinical Guidelines

Dexamethasone for Treatment or Prevention of Bronchopulmonary Dysplasia (BPD)

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 considered 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 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.

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 unfairly biased infants born more premature. Moreover, the need for oxygen at 36 week's 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 NICHD now has a standardized definition of BPD: [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 the 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. AAP POLICY STATEMENT ON USE OF CORTICOSTEROIDS AND BPD

The most recent (2010) American Academy of Pediatrics' statement on the postnatal use of corticosteroids to prevent or treat BPD in premature infants followed a systematic review of the literature.[1] Their conclusions and recommendations were as follows:

a. High daily doses of dexamethasone (approximately 0.5 mg/kg/d) have been shown to reduce BPD but have been associated with adverse outcomes, including neurodevelopmental impairment. In the absence of randomized trial results showing improved outcomes, therapy with high-dose dexamethasone cannot be recommended.

b. Low-dose dexamethasone (< 0.2 mg/kg/d) may facilitate extubation and may decrease the risk of adverse effects observed with higher doses. However, there is insufficient evidence to make a recommendation regarding treatment with low-dose dexamethasone.

c. Low-dose hydrocortisone therapy (1 mg/kg/d) given for the first 2 weeks of life may increase survival without BPD, particularly for infants delivered in a setting of prenatal inflammation, without adversely affecting neurodevelopmental outcomes. There might be increased risk of isolated intestinal perforation associated with early concomitant treatment with inhibitors of prostaglandin synthesis. There is insufficient evidence to recommend early hydrocortisone treatment for all infants at risk for BPD.

d. Higher doses of hydrocortisone (3-6 mg/kg/d) after the first week of life have not been shown to improve survival without BPD in any RCT. Existing data are insufficient to make a recommendation regarding treatment with high-dose hydrocortisone.

NOTE: There is an ongoing Neonatal Research Network (NRN) trial on use of hydrocortisone and prevention of BPD. Details can be found at www.clinicaltrials.gov.

III. COCHRANE DATABASE OF SYSTEMIC REVIEWS ON CORTICOSTEROIDS FOR BPD

Early Administration (< 8 days)

Regimens varied considerably; including courses as short as 1-2 days to courses of up to 4 weeks. Twenty-nine RTCs enrolling 3750 patients were included in this review.

Mortality	No evidence of reduced mortality (at 28 days, at discharge, or at follow-up)
BPD	Decreased incidence of BPD at 28 days and at 36 weeks PMA
Death or BPD	Decreased incidence 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

Follow-up studies were limited to 12 out of the 28 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]); there was a non-significant increase in the risk of the combined outcome of death or CP (RR 1.09 [0.95-1.25])
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 causes 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 in some cases; 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.
- **Hydrocortisone in the doses and regimens used in the reported RCTs has few beneficial or harmful effects and cannot be recommended for the prevention of chronic lung disease.**[2]

Late Administration (> 7 days)

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.

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 0.72 [0.63-0.82])
Failure to extubate	Reduction in extubation failure rates
Metabolic complications	Increased risk of hyperglycemia and hypertension
Gastrointestinal complications	No significant increase in NEC, GI bleeding, and GI perforation
Other complications	No 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

Follow-up studies showed:	
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]); there was a non-significant increase in the risk of the combined outcome of death or CP (RR 1.09 [0.95-1.25])
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 late corticosteroid therapy may not outweigh actual or potential adverse effects.
- **Although there continues to be concern about an increased incidence of adverse neurological outcomes in infants treated with postnatal steroids, this review of postnatal corticosteroid treatment for chronic lung disease initiated after seven days of age 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 in some cases; in some studies the surviving children have only been assessed before school age, when some important neurological outcomes cannot be determined with certainty, and no study was sufficiently powered to detect increased rates of important adverse long-term neurosensory outcomes.
- 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]

IV. 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, sepsis, and postnatal corticosteroids.

An **online estimator** for the prediction of BPD, sponsored by the NICHD, that 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]

V. 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*

References:

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8. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB, DART Study Investigators. Low-Dose Dexamethasone Facilitates Extubation Among Chronically Ventilator-Dependent Infants: Multicenter, International, Randomized, Controlled Trial. Pediatrics, 2006; 117:75-83.

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