JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Dexamethasone for Bronchopulmonary Dysplasia Prevention Clinical Pathway

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All Children's Hospital

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This pathway is intended as a guide for physicians, physician assistants, nurse practitioners and other healthcare providers. It should be adapted to the care of specific patient based on the patient's individualized circumstances and the practitioner's professional judgment.

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Rationale

Initiation of non-invasive ventilator strategies in ELBW infants starting from birth prevents barotrauma and volutrauma and significantly decreases the incidence and severity of bronchopulmonary dysplasia. However, a subset of ELBW infants continue to require ventilator support thereby increasing the risk of bronchopulmonary dysplasia. Identifying those patients using the updated 2022 BPD (Bronchopulmonary Dysplasia) calculator developed by NICHD, will allow use of low dose dexamethasone to facilitate extubation. Consideration to use postnatal steroids in ELBW infants requires careful and diligent evaluation of the published data. Risk benefit
analysis is an important consideration when subjecting preterm infants to postnatal steroids. AAP (American Academy of Pediatrics) guidelines in 2002 stated “the routine use of systemic dexamethasone for
the prevention or treatment of CLD in infants with very low birth weight is not recommended.” The AAP revised its statement in 2010, concluding the data were still insufficient to recommend routine use of glucocorticoid therapy in ventilator-dependent neonates, but that “the clinician must use clinical judgment when attempting to balance the potential adverse effects of glucocorticoid treatment with those of BPD.” (Watterberg 2010)

Background / Published Data and Levels of Evidence

a. Overview

- Increasing evidence indicates that bronchopulmonary dysplasia (BPD) results at least in part from an imbalance between pro-inflammatory and anti-inflammatory mechanisms, with a persistent imbalance that favors pro-inflammatory mechanism (Bancalari, 2008).

- Corticosteroids are potent anti-inflammatory agents and there is a clear rationale for the use of an anti-inflammatory agent to treat BPD. Multiple pro-inflammatory mediators and inflammatory cells are seen in airway samples from infants progressing toward BPD. Postnatal corticosteroids decrease this inflammation. (Speer, 2003). Corticosteroids decrease edema as part of their anti-inflammatory effect, and this decrease may contribute to improve gas exchange and lung mechanics.

- Corticosteroids decrease BPD and decrease extubation failures independently of the age at which treatments are started. Corticosteroids did lead to earlier extubation (risk of extubation failure before day 28) RR 0.84 CI=0.72-0.98, 95% and reduced risk of BPD at 28 days RR 0.85 CI= 0.79-0.92, 95%- and 36-weeks CA RR 0.69, CI=0.60- 0.80, 95% (Bancalari, 2008).

- Postnatal corticosteroids usually are given to the sickest very low birth weight (VLBW) infants who are on ventilators and are progressing toward BPD. VLBW infants have multiple complications and neurodevelopmental problems independent of corticosteroid use. Infants who have BPD have more neurodevelopmental problems than matched infants who do not have BPD. (Laughon, et al., 2009)

- CLD is associated strongly with the risk of delayed mental and motor development. Infants with CLD who were receiving mechanical ventilation (MV) at 36 weeks adjusted age might have an increased risk of neurodevelopmental impairments. (odds ratio 1.66 CI 95% 1.01-2.74) (Hintz, et al., 2005)

- In infants with CLD, corticosteroids improve respiratory compliance, reduce the need for oxygen supplementation but there is no evidence of effect on duration of hospitalization. (Doyle, et al., 2014)

- Selective use of a low dose (what dose?) Corticosteroid (but which one?) for as short a duration as possible (undefined) in the infants at highest risk for BPD is the best treatment that can be offered now (Jobe, 2009).

- The probability of BPD or death in extremely preterm infants can be estimated with reasonable accuracy using a limited amount of readily available clinical information using the newly updated risk calculator developed by the NICHD. (Greenberg, 2022)

b. Early vs late treatment

- An updated Cochrane Database meta-analysis of studies published between 2016 and 2020 for the use of early (<7 days) and late (> 7 days) systemic corticosteroids was published in 2021 showing the following results.

- Early systemic corticosteroids had an overall increase gastrointestinal perforation (RR 1.84, 95% CI 1.36 to 2.49; 16 studies, 3040 infants; high-certainty evidence) and cerebral palsy (RR 1.43, 95% CI 1.07 to 1.92; 13 studies, 1973 infants; high-certainty evidence). It also showed increased risks of hypertrophic cardiomyopathy and growth failure. It also showed a reduction of any retinopathy of prematurity (typical RR 0.88, 95% CI 0.80 to 0.97; 9 studies, 1345 infants). No evidence of increased developmental delay, major neurosensory disability or other long-term outcomes of blindness, deafness, formal psychometric testing, abnormal electroencephalogram (EEG), behavior problems, or rehospitalization in infancy (Doyle 2021A)

- Overall, late systemic corticosteroids had little to no effect on cerebral palsy (RR 1.17, 95% CI 0.84 to 1.61; 17 studies, 1290 infants; high- certainty evidence) or the combined outcome of mortality or cerebral palsy (RR 0.90, 95% CI 0.76 to 1.06; 17 studies, 1290 infants; high-certainty evidence). Data did not show differences in gastrointestinal complications: necrotizing enterocolitis, gastrointestinal bleeding, or gastrointestinal perforation.

- Late systemic corticosteroids did show an increase in severe retinopathy of prematurity overall, but it did not translate into a significant increase in blindness overall on follow up among survivors. There was also an increase in hypertrophic cardiomyopathy, hyperglycemia, glycosuria, and of hypertension (Doyle 2021, B)

- Early administration of systemic dexamethasone (within the first 7 days), though effective in reducing the incidence of BPD, confers more harm than benefit. As noted above, early administration is associated with an increased risk of intestinal perforation, gastrointestinal hemorrhage, hypertrophic cardiomyopathy, and CP; thus, it should be avoided. Dexamethasone administration after the first week reduces the incidence of BPD while minimizing the harms.

- In a retrospective cohort study of preterm infants treated with dexamethasone (0.72 mg to 0.89 mg/kg over 7–10 days) for BPD prevention either moderately late [14–28 day of life (DOL) or delayed (29–42 DOL, n = 30) showed that those in the moderately late group had fewer intubation days, fewer days of supplemental O2 and fewer hospital days than those in the delayed group (Cuna 2019). Harmon et al. reported a retrospective cohort study that showed that severe BPD was significantly higher in those who received therapy between DOL 50–63 and older. The aOR for death or BPD is higher in those who received therapy between DOL 15–21 and DOL ≥ 64. The early group (<28 DOL) was less likely to be discharged on O2 (55 vs 68%, p <0.001), less likely to have moderate or severe BPD (84 vs 92%, p <0.001), and statistically shorter duration of ventilation and supplemental O2 (Harmon et al. 2020). In a recent systematic review and meta-analysis by Ramaswamy et al. concluded that moderate-dose dexamethasone courses (cumulative dose of 2–4 mg/kg) initiated at 8–14 days carried the greatest protection against BPD with an RR of 0.61 (0.45, 0.79). Importantly, this study notes that none of the regimens studied was associated with an increased risk of NDI (Ramaswamy et al. 2021). All together, these data support an optimal period to consider initiating dexamethasone in ventilator-dependent premature neonates to be between the second and third weeks after birth, and its use up to DOL 49 is less likely to result in greater risks of neurodevelopmental delay.

c. High vs low dose

- High dose postnatal dexamethasone treatment for BPD was associated with decreased brain volumes on MRI scan at 18 year of age, specifically total brain tissue, and cortical white matter, thalamus, and basal ganglia nuclei. (Cheong, et al., 2014). Several

previous randomized control trials (RCTs) of high-dose dexamethasone therapy have demonstrated adverse long-term effects on growth, including head circumference and on functional neurodevelopmental outcome.

- Meta-analysis of studies with small numbers of patients in 2000 and 2001demonstrated that postnatal corticosteroids may increase the rate of CP and decrease neuro-performance in survivors. (Jobe, 2009)
- The Dexamethasone: A Randomized Trial (DART study) assigned 70 ventilator dependent infants with average birth weight of less than 700 g to a 10-day tapered dose at a mean postnatal age of 23 days. Enrollment was stopped because infants could not be recruited. It has been demonstrated that administering a lower dose of dexamethasone facilitates extubation by 10 days (OR: 11.6; 95% CI: 3.2-42.7 p<0.001), reduces oxygen and ventilator requirements and shortens the duration of intubation but no difference on BPD. (Doyle, et al., 2006). The same group, Doyle LW and colleagues from DART Study, showed lower dose dexamethasone given after the first week of life did not affect 2-year outcomes adversely. (Doyle, et al., 2007)
- Another meta-analysis of placebo controlled RCT's of the effects of different dosing regimens on rates of BPD and long-term neurodevelopment showed a reduction in BPD only among RCTs that prescribed a cumulative dose of 4 mg/kg or greater. Rates of neurodevelopmental impairment were similar between the treatment and control groups, regardless of dexamethasone dose (Onland, et al., 2009). An update of the meta-analysis showed that compared with moderate-dose dexamethasone regimens, high-dose regimens were associated with a lower risk of BPD and lower risk of adverse neurodevelopmental outcomes (Onland, et al., 2017).
- To explore the minimum effective dose in ventilator-dependent infants born at <29 weeks, Cuna et al. compared two dexamethasone regimens: 27 patients received the DART regimen, and 32 patients received a reduced version of the DART regimen (0.72 mg/kg over 7 days). They reported similar successful extubation rates (defined as extubation within 14 days of starting therapy and remaining extubated for more than 72 hours) in both groups: 56% in 7-day group and 67% in 10-day group. The average time to successful extubation was also similar: 5 days in 7-day course and 6 days in 10-day course. This study suggests that relatively low doses of dexamethasone are effective in facilitating beneficial short-term outcomes including extubation. Long-term outcomes, however, were not assessed (Cuna et al., 2017)
- A significantly larger cumulative dexamethasone dosing regimen was reported from a prospective, single-center, randomized study in 59 infants ≤ 27 weeks of gestational age (GA) and ~14 days of postnatal age at randomization. Infants were randomized to either a 42-day course (cumulative dexamethasone dose of 7.98 mg/kg), or a 9-day course (cumulative dose of 2.63 mg/kg—allowing for repeat courses if necessary). Significantly, more children in the 42-day group were alive without neurodevelopmental impairment (NDI) compared to those in 9-day group (93% vs 66%, p <0.02) (Marr 2019)
- The network meta-analysis by Ramaswamy et. al that found similar surface under the cumulative ranking curve ratings for high-dose dexamethasone and higher evidence rating and greater neurodevelopmental safety data compared with moderate-dose dexamethasone.

d. Length

- The Dexamethasone: A Randomized Trial (DART study) assigned 70 ventilator dependent infants with average birth weight of less than 700 g to a 10-day tapered dose at a mean postnatal age of 23 days.
- Gross SJ, Anbar RD demonstrated in a small number of infants randomly assigned to dexamethasone/placebo for 42 vs 18 days starting at 2 weeks of age had better neurodevelopmental outcomes when compared to placebo. (Steven, et al., 2005) 5- 45)
- O'shea and colleagues reported an increased risk for CP at 1 year of age in infants randomly assigned to the 42-day course of dexamethasone, but their composite outcomes of death or major neurodevelopmental impairment were similar to controls at school age. This same cohort had higher expiratory flows than controls and no adverse effects on lung function at school age. (O'shea, et al., 1999)
- Overall intact survival with IQ >70 was significantly greater for children in 42-day course (75 vs 35%, $p < 0.005$) with an NNT of only 3. Successful extubation rates were earlier (median 23 vs 35 days of age, $p < 0.01$) and higher (50 vs 15% after 1 week, $p < 0.005$) in the 42-day group. Successful extubation continued to be significantly higher for infants in the 42-day group at weeks 2, 3, and 4 ($p < 0.005$ for all time points). The need for re-intubation was lower in 42-day group (7 vs 25%, $p < 0.001$), but there was no difference in BPD between the two groups (Marr 2019).

e. Expert Opinion

Dexamethasone

- Doyle and his group showed that postnatal corticosteroids decrease the risk of death or CP in population of infants who have a 50% or greater risk of BPD. Based on those results the authors favor corticosteroid treatment of ventilator-dependent infants who are 14 to 28 days of age and are progressing toward BPD. (Doyle, et al., 2017)
- Another review using the GRADE approach framework by Jensen EA, Foglia EE, and Schmidt BS recommended among those with approximately 60% or greater probability of developing BPD, the balance may favor the use of corticosteroids. Authors suggest dexamethasone should not be routinely used to prevent BPD in all infants but may be indicated in some based on individual BPD risk (weak recommendation based on the need to balance benefits and harms (Schmidt B, 2015) (Jensen, et al., 2015)
- Dexamethasone facilitates extubation in infants who are chronically dependent on a ventilator, the benefits of a brief course of therapy in such infants could outweigh the risks.
- Ultimately, the clinician must weigh the statistical and population-based evidence and decide if corticosteroids might help a particular infant and if the risks are acceptable (Jobe, 2009). A guidance as to whether to start systemic corticosteroids (CS) in6 ventilator-dependent infants could use prediction equations for the risk of BPD: https://neonatal.rti.org/index.cfm?fuseaction=BPD_Calculator2.start
- Dexamethasone may be a harmful drug to the immature brain and can produce weight loss, poor weight gain, reduced brain growth, and abnormal lung growth. Consideration

must be given to limiting its use to situations where it is essential to achieve weaning from the ventilator. Lower doses and shorter courses should be considered for these infants. (Doyle, et al., 2014) (Doyle, et al., 2006)

- Recent trials have used lower doses 0.2, 0.15, or 0.1 mg/kg with weaning schedules over 7 to 10 days with apparently good acute effects on lung function. (Doyle, et al., 2006). Lower doses and shorter courses should be considered for these infants, total dose of only 0.89 mg/kg over 10 days was able to demonstrate acute benefits of extubation and reduce respiratory support. (Doyle, et al., 2010). Treatment schedules of 0.2 mg/kg or less tapered over 7 to 10 days seem to avoid hyperglycemia and hypertension. Toxicity from corticosteroids is related to dose and treatment duration in patients of all ages, the use of lower-dose, shorter-duration treatments make intuitive sense.
- An initial dose of 0.1 to 0.2 mg/kg/d for 3 days may help achieve extubation. If achieved, the dose can be tapered over 3 to 6 days. If extubation is not possible after the initial 3 days of treatment, it should be stopped. This approach is not evidence based; its attempt is to maximize benefit and minimize the risk of postnatal corticosteroids. (Jobe, 2009)
- The updated 2021 Cochrane Database metanalysis of use of late systemic corticosteroids showed that within the subgroups by drug, dexamethasone probably reduces the combined outcome of mortality or BPD at 36 weeks PMA (RR 0.75, 95% CI 0.67 to 0.84; 12 studies, 553 infants; moderate-certainty evidence), but hydrocortisone does not (RR 0.98, 95% CI 0.88 to 1.09; 2 studies, 435 infants; high-certainty evidence) ($P < 0.001$ for subgroup interaction). (Doyle 2021)

Hydrocortisone

- Watterberg and colleagues randomly assigned ventilated infants with BW 500-999 g to a 15-day tapered course of hydrocortisone or placebo within 2 days of birth. The trial was stopped because of increased intestinal perforation in hydrocortisone-treated infants who also received indomethacin as prophylaxis for PDA. (Watterberg, et al., 2004)

Prednisolone

- Bandari et al, in a retrospective report compared oral prednisolone in 131 oxygen dependent infants not intubated at 38 weeks' gestation who had BPD and a matched group of 254. Among the infants who had PCO2 values lower than 49 mmHg, those treated with prednisolone were weaned from oxygen more readily than infants in the comparison group. (Bhandari, et al., 2008)

- In a recent retrospective, single-center, cohort study of 98 intubated preterm infants ≤34 6/7 weeks and >7 DOL, Nath et al. compared three steroid regimens: dexamethasone starting at 0.2 mg/kg/day, hydrocortisone (HC) starting at 4–8 µg/kg/day (equivalent to dexamethasone 0.15–0.3 mg/kg/day), and methylprednisolone (MP) 2.4 mg/kg/day (equivalent to dexamethasone 0.4–0.5 mg/kg/day) over an average 10-day course. In this study, the decrease in the respiratory severity scale (RSS) was different only between the dexamethasone group (58.6% decrease) and HC group (19.4% decrease, $p < 0.002$). The

rates of extubation at day 3 and at day 7 were higher for dexamethasone (44 and 59%), than for either HC (40 and 44%) or MP (23 and 41%). (Nath et al 2020)

- The Preterm Erythropoietin Neuroprotection (PENUT) randomized clinical trial, a multicenter cohort study of extremely preterm infants with multiple adjustments, found that using dexamethasone for more than 14 days during the initial NICU stay was associated with lower BSID-III motor and language scores at corrected age 2 years. For infants exposed to dexamethasone, each additional day of dexamethasone exposure was associated with significantly lower cognitive and motor scores but not language scores (Puia-Dumitrescu, 2022)

- In the editorial by Parikh asking about use of SCS in neonates in high settings of non-invasive mechanical ventilation before 7 days of life, Ramaswamy replied that The National Institute of Child Health and Development (NICHD) risk calculator (2011), developed by the Neonatal Research Network (NRN), might be used as a guide to calculate this risk. Mentioning the meta-analysis by Doyle et al, he responded that it can be inferred that if the risk of BPD exceeds 65%, then the clinician could use SCS (specifically systemic dexamethasone) to prevent BPD. He also brought up the hypothetical scenario that a preterm infant of 23 weeks' gestation, with a birth weight of 510 g, of male sex, White race/ethnicity, and treated with continuous positive airway pressure therapy of 7 cm H2O, FiO2 −60% on day 7 of life, the NICHD NRN calculator predicts a 41% risk of moderate to severe BPD in this infant. The same infant at day 14 and day 21 with similar NRS requirements would have a 63% risk of moderate to severe BPD. So even such an infant, who might be on relatively higher continuous positive airway pressure support, might not qualify for postnatal systemic dexamethasone.

Clinical Management

Text *Disclaimer: Neonates <23 weeks GA are not included in this guideline due to limited evidence on safety and benefits using systemic corticosteroids in this patient population. If DART is thought to be needed for neonates in this group, further discussion is encouraged.*

DART Protocol

A. Eligibility criteria:
    a. Birth weight: <1000 grams or Gestational age at birth 23-28 weeks
    b. Postnatal Age: at least 14 days of life
    c. At greater than 60% risk for moderate and severe bronchopulmonary dysplasia and death, with documentation in the chart using smart phrase (.achnicubpdrisk)
    d. Not treating active infection or having signs of infection (normal CBC and/or CRP suggested to be obtained prior to starting the course)

e. No hemodynamically significant PDA (link)
f. Documentation in the chart about parental discussion about the DART protocol initiation

B. Risk for BPD assessment: document using (.achnicubpdrisk)
    a. Use the updated 2022 BPD outcome calculator at 14 and 28 days of life: https://neonatal.rti.org/index.cfm?fuseaction=BPD_Calculator2.start

C. DART Protocol
→ Start dexamethasone (via enteral or parenteral routes)
    - 0.075 mg/kg/dose q 12 hours for three days (6 doses)
    - 0.05 mg/kg/dose q 12 hours for three days (6 doses)
    - 0.025 mg/kg/dose q 12 hours for two days (4 doses)
    - 0.025 mg/kg/dose q 24 hours for two days (2 doses)
    - (Total of 0.89 mg/kg over 10 days)

D. Goals of therapy:
    a. Extubation
    b. Timing of extubation: day 3 to 7 of initiation of DART protocol
    c. Long term maintenance of extubation

E. Response to treatment assessment:
    a. Positive response: able to wean ventilator settings (decreased FiO2 and decreased MAP), extubate and continue the course
    b. Poor or no response: inability to wean ventilator settings within 3 days of starting DART protocol
    c. If poor or no response to DART protocol: discontinue dexamethasone
    d. Repeated course(s) of dexamethasone are associated with impaired neurodevelopmental outcomes and poor growth and are strongly discouraged.
    e. If repeated DART protocol is being considered a multidisciplinary meeting is mandatory for discussion of the case.

Summary

Text Preterm infants < 28 weeks' gestation and less than 1000 grams are at increased risk for the development of bronchopulmonary dysplasia. Judicious use of postnatal steroids using the updated 2022 NICHD BPD calculator will allow early extubation and prevent long term neurodevelopment morbidities in patients with BPD. It is important to underscore that a ventilator weaning regimen must be adhered in patients placed on dexamethasone therapy so that decisions can be made to withdraw in those infants who do not respond within three days of initiation of therapy. Repeated courses of dexamethasone may be more detrimental specifically in vulnerable preterm population.

Algorithm / Pathway

Eligibility Criteria

BW: <1000 g and/or GA at birth 23- 28 weeks

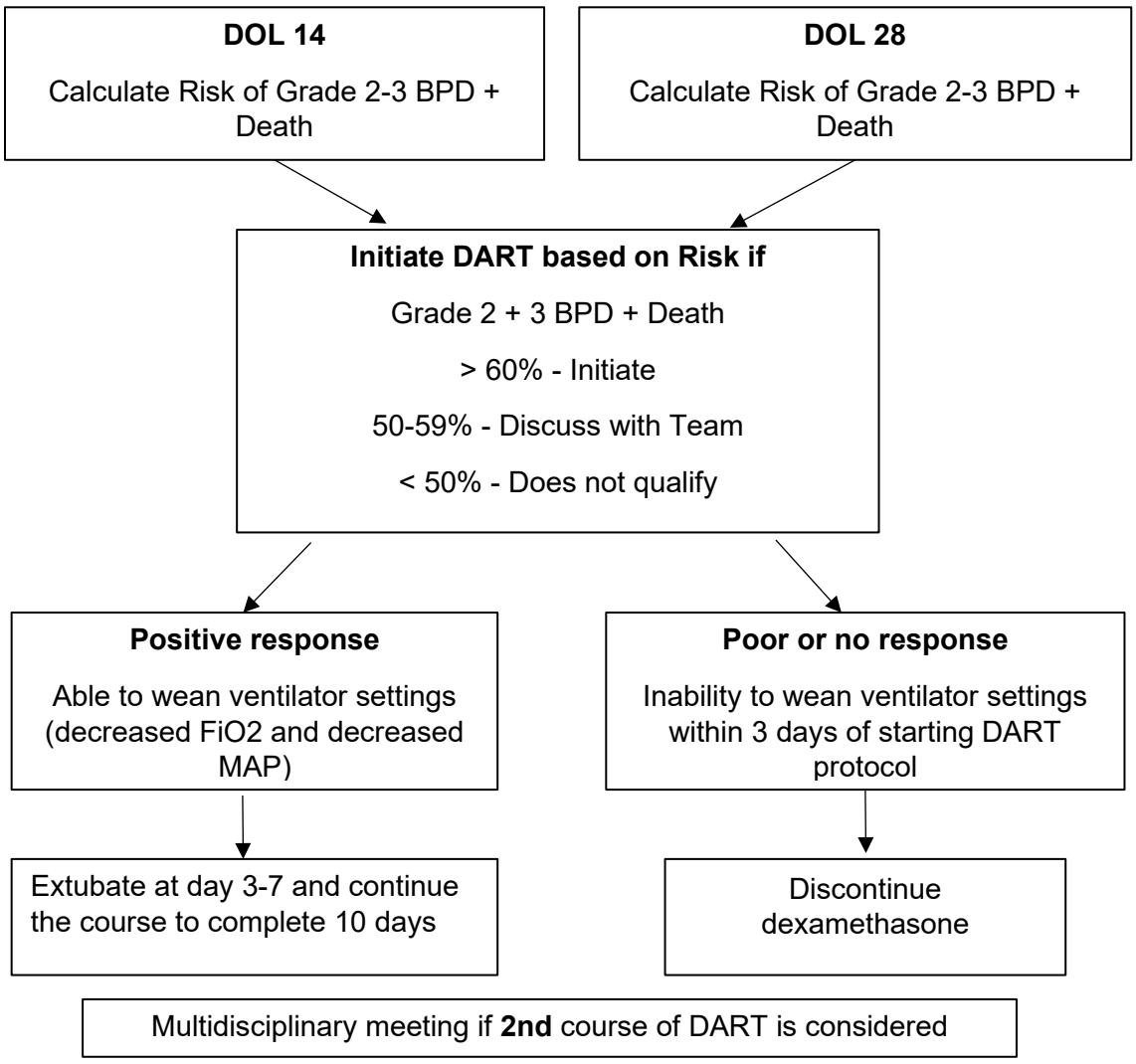
Postnatal Age: at least 14 days

At > 60% risk for BPD and Death (Sum of Moderate + Severe + Death)

Not treating active infection or having signs of infection (Normal CBC and/or CRP suggested to be obtained prior to starting the course)

No Hemodynamically Significant PDA

Documentation in the chart about parental discussion about the DART protocol initiation



Glossary

- DART- dexamethasone a randomized trial

- BPD- bronchopulmonary dysplasia

- MAP- mean airway pressure

- SCS- systemic corticosteroids

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Outcome Measures

Outcome Measures	Process Measures	Balancing Measures
% of patients with grade 2+3 BPD out off all of those at risk	% of neonates with BPD risk assessment completed at 14 and 28 DOL	% of pts with side effects from DART (hyperglycemia, infection, HTN, GI bleed, NEC, SIP, sepsis)
% of days of mechanical ventilation out of total days hospitalization at 36 wks CGA or discharge	% of neonates who received DART out of those neonates with >60% risk of mod + severe BPD + death at 14 DOL or 28 DOL	% of neonates who received DART that were not eligible based on updated CPG
% of neonatal death out of all of those at risk	% of neonates extubated within 3-7 days after start of DART course	% of neonates who received multiple courses of DART
		% of neonates with poor growth out of all of those who received DART

Clinical Pathway Team

Dexamethasone for Bronchopulmonary Dysplasia Prevention Clinical Pathway

Johns Hopkins All Children's Hospital

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