Critically Analyze the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>STRONG</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
</tr>
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<tr>
<td>Low</td>
<td>Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence</td>
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<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
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PICO Question 1: In newly delivered extremely premature non-intubated neonates, does early administration of caffeine compared to routine administration of caffeine prevent intubation and/or CPAP failure?

Recommendation: Strong recommendation with low quality evidence that extremely premature infants with birthweight ≤ 1250 grams should receive a 20 mg/kg bolus dose of caffeine within the first 6 hours of life. (1)

There is a paucity of evidence on the effect of the timing of caffeine administration on CPAP failure. Katheria et al. (2014) compared the outcome of caffeine administration within the first two hours of life and at 12 hours of life in 21 non-intubated premature infants. The study found that patients in the early caffeine group had a lower incidence of intubation in the first 12 hours (27 vs. 70%, p=0.08); however there was not a statistical difference between the two groups. (1)

PICO Question 2: In premature neonates receiving respiratory support in the delivery room, does CPAP interface by facemask compared to nasal prongs reduce the rate of CPAP failure?

Recommendation: Strong recommendation with low quality evidence that nasal prongs should be used to deliver CPAP in premature neonates. (2,3, 4-9)

A search of the literature revealed indirect evidence on the use of face mask interface compared to single nasal tube for delivery room resuscitation including positive pressure ventilation and CPAP. (2,3) Most studies evaluating CPAP interface in neonates utilized nasal prongs and/or nasal masks. (4-9) A 2008 meta-analysis investigated different devices for administration of NCPAP. Nasal prongs were found to be effective for CPAP delivery with short binasal prongs having a decreased rate of extubation failure after seven days than single prongs [RR 0.59 (95% CI: 0.41-0.85), typical RD -0.21 (95% CI: -0.35 to -0.07), NNT 5 (95% CI: 3 – 14)]. (10)

PICO Question 3: In small for gestation age (SGA) premature neonates, does administration of indocin for intraventricular hemorrhage (IVH) and pulmonary hemorrhage prophylaxis increase the risk of adverse outcomes?

Recommendation: Weak recommendation with low quality evidence to consider the use of prophylactic indocin in small for gestation age premature infants for the prevention of IVH and pulmonary hemorrhage. (11-16)

A review of the literature found one randomized control trial and three observational studies that included SGA neonates in their research on the risk of adverse outcomes with prophylactic indomethacin administration. (11-13) The studies did not provide a stratified analysis of SGA infants; however this population had similar outcomes reported. Schmidt 2001 found no difference in the mortality and morbidity between the indomethacin and placebo groups and a protective effect on the incidence of PDA in addition to severe
periventricular and intraventricular hemorrhage. The study found no other outcomes altered by the prophylactic administration of indomethacin. (11) Sharma 2010 found that postnatal indomethacin increased the incidence of isolated intestinal perforation (0.9% vs. 3.8%, p=0.01) however there was a decrease in the incidence of NEC (14.6% vs. 10%, p=0.04) compared to infants with no exposure. (12)

Two randomized trials that included SGA infants in their population compared indomethacin to ibuprofen for treatment of PDA. Both studies found no significant difference in the number of infants with severe complications. (14-15) Kelleher 2014 included SGA patients in the study to determine if ELBW infants receiving indomethacin should concurrently receive enteral nutrition. The study found that the rate of spontaneous intestinal perforation was lower in patients administered indomethacin while receiving enteral feeds than patients with no indomethacin administration or enteral feedings (RR 0.58, 95% CI 0.37-0.90; p=0.0159). (16)

**PICO Question 4:** In infants 36 weeks gestational age or greater with BPD, does higher oxygen saturation targets compared to conventional oxygen saturation targets decrease adverse outcomes?

**Recommendation:** Strong recommendation with moderate quality evidence that infants 36 weeks gestational age or greater with BPD should have oxygen saturation targets of 90% to 95%. (17-18)

A review of the literature found two randomized control trials that compared higher oxygen saturation targets to conventional oxygen saturation targets in infants greater than 36 weeks gestation with BPD. (17-18) Askie (2003) randomly assigned infants to a standard-saturation group (targets 91-94%) and a high-saturation group (targets 95-98%). The study found that the proportion of infants was significantly lower in the standard-saturation group compared to the high-saturation group for home oxygen use (17% vs. 30%, p=0.004) and dependence on supplemental oxygen at 36 weeks (46% vs. 64%, p=0.001). There was no difference in mortality between the two groups. (17) A 2000 randomized control trial compared patients with oxygen saturation target ranges of 89 - 94% (conventional arm) and 96 - 99% (supplemental arm). At the 3-month examination, infants in the supplemental arm remained hospitalized (12.7 vs. 6.8%; p=0.012), on oxygen (46.8% vs. 37%, p=0.02), and on diuretics (35.8% vs. 24.4%, p=0.002) longer than the conventional arm. (18)

**PICO Question 5:** In neonates, does the use of low positioned umbilical venous catheters (UVCs) compared to catheters placed at the juncture of the IVC and right atrium increase the risk of adverse events?

**Recommendation:** Strong recommendation with low quality evidence that low-lying UVCs should be replaced with either a peripheral intravenous catheter or centrally located intravenous access. (19-21)

There is a paucity of evidence on the association of low positioned umbilical venous catheters (UVC) and adverse events in neonates. In a retrospective review of 1,081 infants with UVCs, Grizell (2014) found that out of the nine neonates diagnosed with severe liver injury all had UVC catheter tips below the preferred T9 vertebral level assessed by radiograph. (19) Morag (2006) completed a retrospective review of 133 infants diagnosed with portal vein thrombosis (PVT). The study reported that a total of 95 (73%) of infants had a UVC placed; with 48 (50%) in inappropriate position (low, 18; intrahepatic 30). There was no association between the diagnosis of PVT and the presence of a UVC; however poor outcome was associated with inappropriate UVC placement (p=0.018). (20) The Baylor Section of Neonatology Guidelines for Acute Care of the Neonate recommends replacement of a low-lying UVC as soon as possible. (21)

**PICO Question 6:** In preterm neonates, does the use of postnatal corticosteroids compared to standard of care decrease the risk of BPD?

**Recommendation(s):**

- **Weak recommendation with high quality evidence** that for neonates born at 23-24 weeks gestation that remain mechanically ventilated for ≥ 14 days with a FiO2 requirement of greater than 30%, clinicians may choose to consider administration of IV dexamethasone to decrease the risk of chronic lung disease. Parents should be fully informed about the short- and long-term adverse effects of dexamethasone and be in agreement to this treatment for their child. (22-25, 31)

- **Strong recommendation with high quality evidence** Systemic dexamethasone should not be routinely administered to neonates born at 25 weeks gestation or older to decrease the risk of BPD. (22-25,34)

- **Strong recommendation with high quality evidence** Systemic dexamethasone should not be administered within the first seven days of life to decrease the risk of BPD. (22-25, 31)

- **Strong recommendation with high quality evidence** Systemic dexamethasone to decrease the risk of BPD should be dosed twice daily as a 10-day tapering course (0.15 mg/kg/day for 3 days, 0.10 mg/kg/day for 3 days, 0.05 mg/kg/day for 2 days, and 0.02 mg/kg/day for 2 days) with a cumulative dose of 0.89 mg/kg. (22-25, 31)

Remarks: Administration of dexamethasone has been reported to decrease the risk of BPD in preterm infants while increasing the risk for adverse effects including neurodevelopmental impairment, hyperglycemia, glycosuria, hypertension and hypertrophic cardiomyopathy.
A review of the literature found six meta-analyses, one randomized controlled trial, and four observational studies on the timing of administration, dosage, and/or type of steroid to use in the neonatal population to decrease the risk of BPD. Doyle (2014) was a meta-analysis to examine the benefits of administering postnatal steroids in the first week of life to preterm infants at risk for BPD. The study found that treatment with steroids reduced the incidence of chronic lung disease at 36 weeks’ postmenstrual age (PMA) (RR 0.79; 95% CI 0.71-0.88); however the incidence of cerebral palsy (RR 1.45; 95% CI 1.06-1.25) was increased. The same author completed a second meta-analysis on the benefits/harms of the administration of late (> 7 days of life) corticosteroid treatment in neonates. The use of corticosteroids in this age group resulted in a decrease in chronic lung disease at 36 weeks’ PMA (RR 0.76; 95% CI 0.68-0.85) and a non-significant increase in cerebral palsy (RR 0.98; 95% CI 0.97-1.00). Onland (2009) was a systematic review to assess the effect of various cumulative doses of dexamethasone. The study found that the reduction in the relative risk of BPD was most evident with cumulative doses of dexamethasone at ≥ 4 mg/kg. Treatment at greater than 3 weeks of age did not show a significant association between the dose of dexamethasone and neurodevelopmental sequelae. In a meta-analysis comparing the effects of hydrocortisone and dexamethasone treatment in neonates < 8 days, dexamethasone was shown to exert most of the benefits with reducing CLD at 36 weeks’ (RR 0.70; 95% CI 0.61-0.81) and most of the harm with increased risk of cerebral palsy (RR 1.75; 95% CI 1.2-2.55) while hydrocortisone had little effect on either outcome (CLD at 36 weeks’ – RR 0.96; 95% CI 0.82-1.12; and cerebral palsy – RR 0.97; 95% CI 0.70-1.19). Doyle (2014) found that as the risk of BPD increases in a population of neonates, the risk of cerebral palsy with administration of corticosteroids decreases. The study reported that a risk of BPD below 33% resulted in significant risk of death or cerebral palsy with corticosteroid treatment while a risk of BPD greater than 60% resulted in significant treatment benefit.

Evidence Supports
- Extremely premature infants with birthweight ≤ 1250 grams should receive a 20 mg/kg bolus dose of caffeine within the first 6 hours of life. – Strong recommendation, low quality evidence.
- Nasal prongs should be used to deliver CPAP in premature neonates. – Strong recommendation, low quality evidence
- Consider the use of prophylactic indocin in small for gestation age premature infants for the prevention of IVH and pulmonary hemorrhage. – Weak recommendation, low quality evidence
- Infants 36 weeks gestational age or greater with BPD should have oxygen saturation targets of 90% to 95%. – Strong recommendation, moderate quality evidence.
- Low-lying UVCs should be replaced with either a peripheral intravenous catheter or centrally located intravenous access. – Strong recommendation, low quality evidence.
- For neonates born at 23-24 weeks gestation that remain mechanically ventilated for ≥ 14 days with a FiO₂ requirement of greater than 30%, clinicians may choose to consider administration of IV dexamethasone to decrease the risk of chronic lung disease. Parents should be fully informed about the short- and long-term adverse effects of dexamethasone and be in agreement to this treatment for their child. – Weak recommendation, high quality evidence.
- Systemic dexamethasone to decrease the risk of BPD should be dosed twice daily as a 10-day tapering course (0.15 mg/kg/day for 3 days, 0.10 mg/kg/day for 3 days, 0.05 mg/kg/day for 2 days, and 0.02 mg/kg/day for 2 days) with a cumulative dose of 0.89 mg/kg. – Strong recommendation, high quality evidence.

Evidence Against
- Systemic dexamethasone should not be routinely administered to neonates born at 25 weeks gestation or older to decrease the risk of BPD. – Strong recommendation, high quality evidence.
- Systemic dexamethasone should not be administered within the first seven days of life to decrease the risk of BPD. – Strong recommendation, high quality evidence.

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.
References


21. Guidelines for Acute Care of the Neonate, Care of Very Low Birth Weight Babies, BCM Section of Neonatology, 2015


Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children’s Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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Development Process
This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
   - Baylor Section of Neonatology Guidelines for Acute Care of the Neonate
3. Literature Review of Relevant Evidence
   - Searched: PubMed, Cochrane Library, CINAHL
4. Critically Analyze the Evidence
   - 7 meta-analyses, 4 randomized controlled trials, and 17 nonrandomized studies
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Respiratory Management of the Preemie evidence-based review manual within EBOC.

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Evaluating the Quality of the Evidence
Published clinical guidelines were evaluated for this review using the AGREE II criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence in support of or against specific interventions and identifies where evidence is lacking/inconclusive. The following categories describe how research findings provide support for treatment interventions. “Evidence Supports” provides evidence to support an intervention “Evidence Against” provides evidence against an intervention. “Evidence Lacking/Inconclusive” indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn from the evidence.

The GRADE criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

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Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of Respiratory Management of the Preemie in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process
Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.

Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.
<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>April 2016</td>
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