St. Luke's Neonatology

Small Baby Guidelines for Infants <28 weeks Gestational Age

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Goals:

- Optimize clinical outcomes
- Educate and empower staff
- Educate and empower families
- Respect our patients as individuals
- Standardize care delivery
- Provide compassionate, consistent, interdisciplinary care

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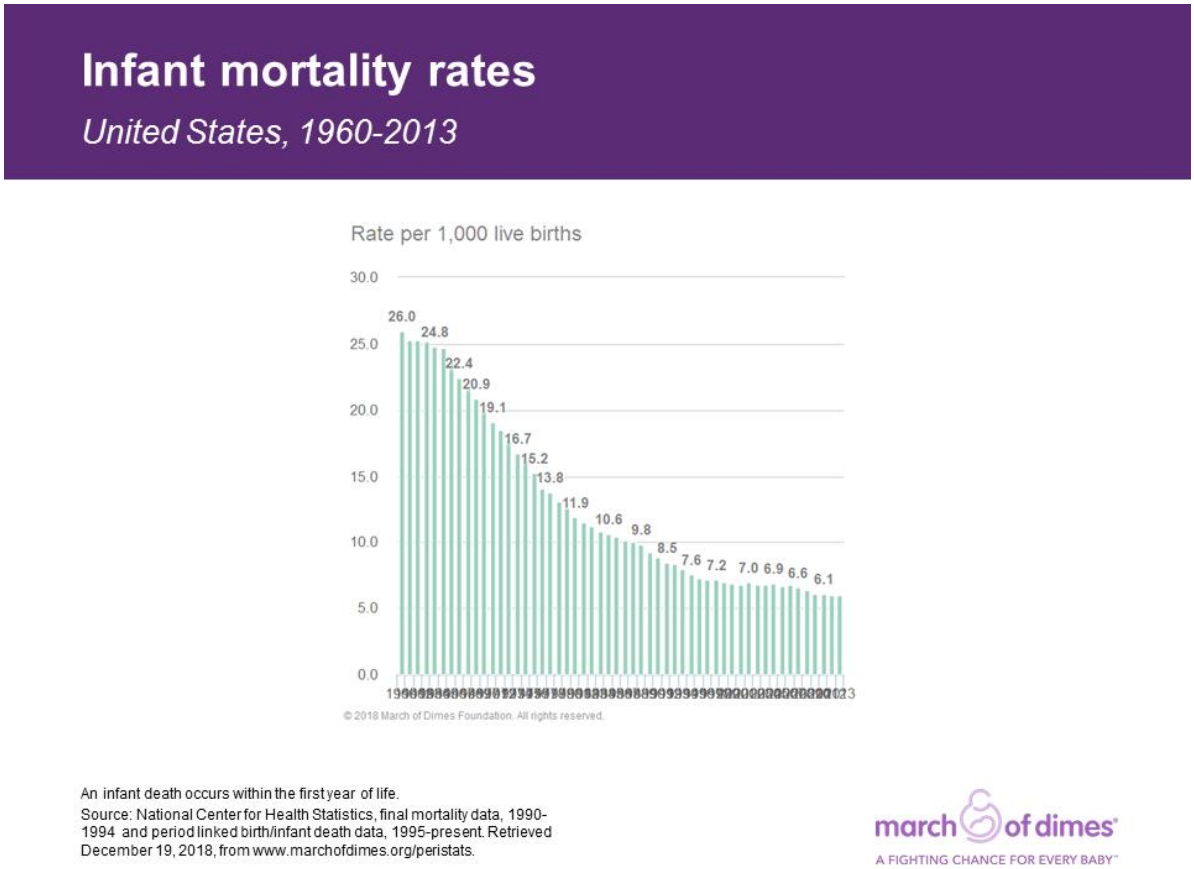
Background

Over the last 40+ years that Neonatology has been recognized as a Pediatric subspecialty, tremendous progress has been made in improving the outcomes of premature and critically ill newborns. The infant mortality rate (IMR) in 1960 was 26/1000 live births. By 1975, it had decreased to 16/1000 live births, with 70% of these deaths in the neonatal period. In 1976, the landmark document "Toward Improving the Outcome of Pregnancy" was published with authorship from 4 major contributors: American Academy of Pediatrics, American College of Obstetrics and Gynecology, American Medical Association, and the March of Dimes. This led to the development of regionalization of high-risk pregnancy and newborn care into regional centers of excellence and dramatically improved both infant and neonatal mortality rates (NMR) (1986 IMR 10.4/1000 live births, NMR 6.7/1000 live births).

Over the intervening 30 years, advances in pharmacotherapy, ventilatory equipment and practices, resuscitation skills, and understanding of the physiologic challenges of transition from fetal to extrauterine life well prior to physiologic maturity have led to not only further improvement in NMR, but also survival at progressively lower gestational ages. In the U.S., as of 2013 data, IMR has declined to 6/1000 live births. Per the World Health Organization, NMR in the U.S. stands at 3.7/1000 live births as of 2016. The limits of viability have been pushed such that infants at 23-24 weeks now routinely survive, with some centers reporting survival as low as 21 weeks gestation age.



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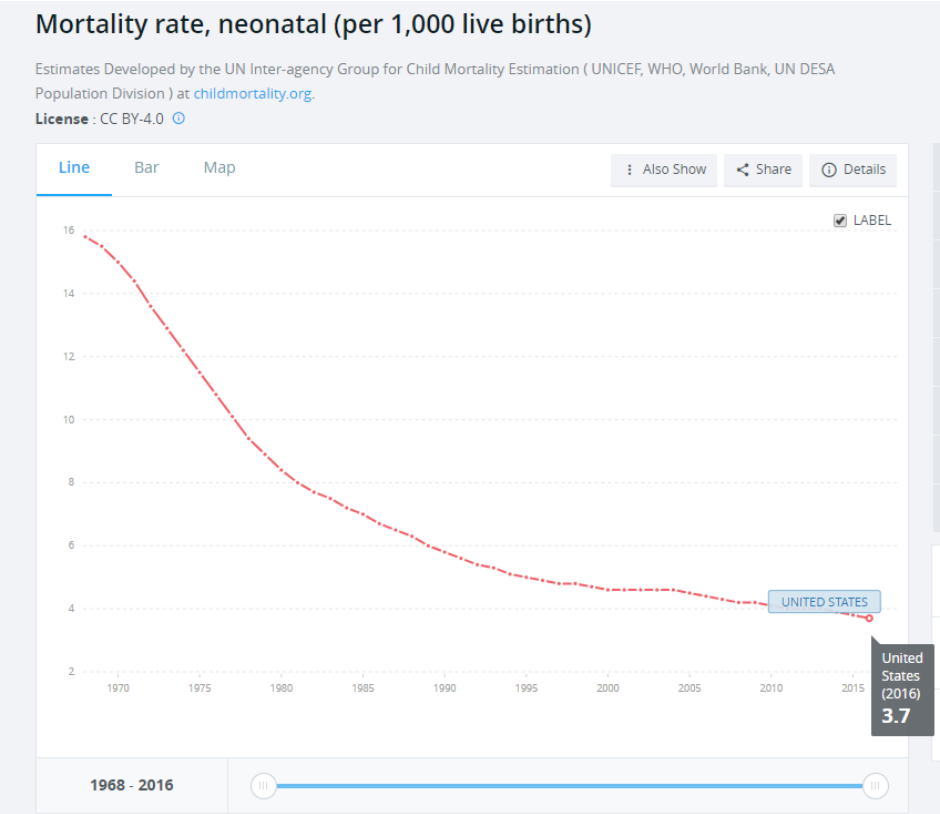


In 1975, an infant born at 1 kg had >95% MORTALITY. In 2005, an infant born at 1 kg had >95% SURVIVAL.

Despite the impressive advances in survival at lower and lower gestational age thresholds, this survival continues to carry with it a substantial burden of morbidity which can impact not only the quality of life of the child, but also the integrity of the family dynamic. Not to be forgotten also is the tremendous financial burden that prematurity imposes on individual families and on the healthcare system as a whole.

In 2001, there were 1.45 million bankruptcy filings in the U.S. Himmelstein et al surveyed 1771 personal bankruptcies and interviewed 931 individuals and/or families. 46.2% identified medical expenses as the primary cause of their bankruptcy filing, with the number one cited factor being the high out of pocket cost ($11,854 on average). Of note, 75.7% had insurance. The second most cited factor was sounded by parents of premature infants or chronically ill children. They noted not only the high out of pocket costs, but also the lost wages from time taken off work and the high cost of home care (Himmelstein 2005).

Nationally, the costs of healthcare continue to escalate. A now decade-old report from the Institutes of Medicine estimated the annual cost of prematurity at $26.2 billion (2005 US Dollars) (Waitzman 2006). Of this total, $16.9b was direct medical care, $5.7b was lost productivity, $1.1b was for special education, $0.9b was for early intervention programs, and $1.9b was related to increased maternal delivery costs. While these figures are eye-popping, it is

important to note that total U.S. healthcare expenditure in 2016 was estimated at over $3.3 trillion dollars, 17.1% of the entire U.S. gross domestic product (www.cms.gov 2018). Thus, prematurity and related costs are <1% of total U.S. healthcare expenditure. Considering that the vast majority of healthcare dollars are spent in the last 6 months of life, and the life expectancy of the vast majority of NICU graduates is near normal (~75+ years), this makes the return on investment of treating even the extremes of prematurity unquestionable.

Lastly, since 2011, St. Luke's Neonatology has embraced a large and growing body of evidence throughout multiple high-risk industries which has demonstrated clearly that standardization of work leads to greater reliability and decreased errors. From the airline industry, to nuclear energy, to the U.S. military, and now to healthcare, there is very clear evidence that creating 'standard operating procedures' improves efficiency, safety, work satisfaction, and outcomes. All healthcare providers know that there are often multiple approaches to treating clinical conditions, and many demonstrate equivalency in these approaches. But employing multiple approaches in the same unit or sometimes even on the same patient can actually worsen outcomes, and certainly frustrates staff and family members. Hence, one of our primary objectives within the annual St. Luke's Neonatology Retreat efforts, and in particular for these Small Baby Guidelines, is to assimilate the peer reviewed literature, expert opinion, and collective experience of our well-trained individual group members and staff to create one consistent care approach for our most vulnerable patient population. Our goal is to create clinical pathways, algorithms, and electronic ordersets that simplify the process of following the standard approach. All providers recognize that there will be unique circumstances where rational deviation from a pathway may occur. But we believe that the 80/20 rule will likely apply, with roughly 80% of our care able to be delivered in a standardized manner, allowing the clinician to focus more closely on the 20% who do not follow the norm.

This Guideline is structured with first a discussion regarding the St. Luke's Neonatology position on our standard for resuscitation at the limits of viability, followed by an organ-systems-based approach to the multiple aspects of care for these tiny patients. Each chapter attempts to delineate the best approach to care in the first 24 hours of age, the first week of age, the first month of age, and then chronic care considerations. While these guidelines are intended to apply to infants who are 27 6/7 weeks and less, it is understood that the same guidelines and care may also be relevant to infants greater than this age, and also may apply somewhat less to larger infants even within this scope.

Periviability

The challenges at the limits of viability are substantial. In 2015, as part of the annual St. Luke's Neonatology Retreat, the neonatal and maternal-fetal medicine teams performed a deep analysis and literature review of our local statistics as well as national and international evidence regarding the survival and outcomes of extremely premature infants (22-25 weeks GA). Survival data at 22-23 weeks was noted to be significantly skewed due to increased incidence of non-resuscitation based on both parental wishes and provider recommendations. Not surprisingly, centers that did offer resuscitation were noted to have improved survival. Over time, these same centers are noting a slow decrease in the nonetheless significant morbidities associated with extreme prematurity.

The outcome of the periviability discussion led to the following recommendations and guidelines that were adopted by St. Luke's Neonatology in September of 2015. For the purposes of these Guidelines, gestational age determination is based on maternal dates, and either a first trimester ultrasound, a second trimester ultrasound, or by clinical exam if ultrasound is not available. In general, the preferred method of dating a pregnancy is maternal dating in combination with a first trimester ultrasound. Due to decreasing accuracy with second trimester ultrasound and clinical exam, some latitude should be expected when discussing specific timing of interventions to account for these limitations.

Family Counseling:

1. Counseling and representation of statistics should be provided on a standard written checklist form (see below) for parents to reference during and after the session.
2. Parents should be offered time to think about the information provided and further discussions with providers should be made readily available.
3. When possible, counseling should be done in conjunction with the OB provider and when not, communication with the OB provider regarding results of the conversation should occur. Details of the discussion and any parental decisions made should be clearly documented in the maternal medical record.
4. Counseling should be individualized and tailored to the family's education level, cultural background, and other factors needed for comprehension, including using interpreters where appropriate.

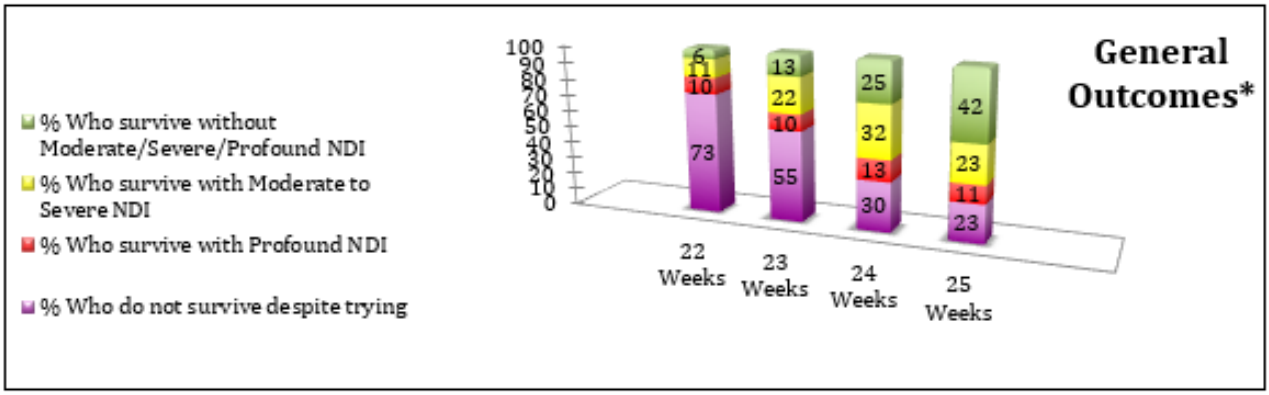
Neonatology Counseling for 22-25 Week EGA Pregnancies:

St Luke's Children's Hospital

Scott Snyder, MD
Charlene Crichton, MD
Amy T. Kirk, MD
Scott A. Knight, MD
Jennifer Merchant, MD
Erik Meyers, MD
Yukiko Miura, MD
Declan O'Riordan, MD
Nathan Thornton, MD
Tim Ulrich, MD
James W. VanLooy, MD

Neonatology Counseling For 22-25 Week Estimated Gestation Pregnancies*

v.12-15-20



Est. Gestational Age _____, Est. Fetal Wt_____, Sex: M__F__, Singleton Y / N , Steroids Y / N

Based on the above information, for infants whom resuscitation with mechanical ventilation is attempted, we estimate:#

_____ % Average Survival of Infants receiving active treatment
____-____ % Hospital range of Survival of Infants receiving active treatment
_____ % Do not survive even with active treatment

OUTCOMES AT 18-26 MONTHS CORRECTED AGE AMOUNG INFANTS WHO SURVIVE

____-____ % Profound Neurodevelopmental Impairment
____-____ % Moderate to Severe Neurodevelopmental Impairment
____-____ % Moderate -Severe Cerebral Palsy (Static Spastic Paralysis)
____-____ % Cognitive Developmental Delay

Profound Neurodevelopmental Impairment (NDI) - *Severe Cerebral palsy (minimal coordination and control of muscles; unable to walk independently, require wheelchair and other equipment to move around. Can have painful muscle spasms and often require medication and/or surgeries to help with this. Unable to feed themselves and most require feeding tube for nutrition. Many children have poor control of their head and body. They develop spine curvature and hip problems that may require surgery). These children are often hospitalized with respiratory problems, infections, seizures, or pain management concerns. Blindness and deafness … Thinking and problem solving are markedly below similar aged children; these children are not able to verbally communicate without assistive technology. Their abilities are often similar to infants and do not progress significantly beyond that level despite interventions. They are never independent at any age.*

Moderate to Severe Neurodevelopmental Impairment (NDI) - *Moderate to severe cerebral palsy (tight muscles and or poor muscle control that makes activities of daily life more difficult; delay in sitting, crawling and walking and may require assistive devices and or braces. Poor control of arms and hands in fine movement such as dressing, toileting, eating, drinking, some children require feeding tubes short or long-term). These children have higher likelihood of hospitalizations after discharge form the NICU and may have significant respiratory problems for months to years. Vision problems require glasses and sometimes surgery to help eyes work together; the vision may not be corrected fully despite these treatments. Hearing loss that improves but may not be normal with hearing aids. Thinking and problem solving is below that of similar aged children and many children struggle with verbal communication, require special education services; some children may not be independent as adults.*

Survival without Moderate-Severe or Profound Neurodevelopmental Impairment (NDI) - *Minor disabilities such as correctable hearing and vision defects, minor motor function problems (mild weakness), minor pulmonary deficiencies, increased rate of attention deficit and other learning issues.*

*The **general outcomes** are based on a composite of SLHS data and a Meta-analysis of 65 studies published from 2000-2017. (Hilde Tinderholt Myrhaug, et al Pediatrics 143:2 Feb 2019).

#These estimates are based on standardized assessments of outcomes at 18 to 22 months of infants born at Neonatal Research Network centers between 1998 and 2003. Infants were 22 to 25 weeks, between 401 and 1,000 grams at birth. Infants not born at a Network center and infants with a major congenital anomaly were excluded. These estimates are based only on the 3,702 infants who received intensive care. The rate of a given outcome, had intensive care been attempted for all infants, is likely to be slightly less. These data are not intended to be predictive of individual outcomes. Instead, the data provide a range of possible outcomes based on specific characteristics. Please note that these data provide only possible outcomes, and that the estimates apply only at birth.

Prenatal obstetrical care:

1. The preponderance of data recommends that at >23 $^{6/7}$ weeks gestation, prenatal steroids, magnesium sulfate for neuroprotection prophylaxis, as well as GBS prophylaxis and/or antibiotics for premature prolonged ROM should be given if risk of preterm delivery is significant.
2. Data does not recommend use of steroids, magnesium sulfate or GBS prophylaxis at gestations < 23$^{0/7}$ weeks. However if thorough discussion of the risks has taken place with the family, and if the family is insistent on resuscitation if delivery occurs between 22$^{0/7}$ - 23$^{0/7}$ weeks, then St. Luke's Neonatology believes that steroids should be given at 21$^{5/7}$ weeks to optimize chances of survival and to potentially decrease morbidity.
3. When possible, patients presenting to outside facilities in labor at the limits of viability should be transported and managed by perinatal specialists. Decisions regarding transport are complex and must include multifactorial considerations that balance the risks and benefits to the family as well as the fetal patient. Strong evidence supports improved survival and outcomes when delivery of the periviable infant occurs at a tertiary center equipped to handle such infants. In all cases where transport of these patients is not possible, consultation with a perinatologist should be recommended by the consulting neonatologist, if not already obtained by the obstetrical provider.
4. The obstetrical provider should provide information and recommendations regarding available obstetric interventions and the relative risks and benefits. St. Luke's Neonatology believes that in all cases of potential preterm delivery at <28 weeks, consultation with Neonatology and Maternal Fetal Medicine should be obtained. Current data do not consistently support routine cesarean section at the limits of viability, and cesarean sections at < 24 weeks GA have a higher rate of complications in subsequent pregnancies. Fetal monitoring and C/S for fetal distress should be considered if the fetus is considered viable and will be resuscitated at > 22$^{6/7}$ weeks.

Neonatal Recommendations:

1. While some countries report better survival and outcomes for 22 and 23-week infants, given the differences in follow up testing and perinatal and neonatal practices, it seems most relevant to use National Institute of Child Health and Human Development (NICHD) estimations where clinical practices most closely represent ours.
2. Whenever possible, counseling of parents should use the multifactorial NICHD calculator rather than solely gestational age in order to provide the most accurate estimates of both survival and outcome measures. Multifactorial analysis allows for reducing the effect of inaccurate gestation dates. Like most NICUs, St. Luke's does not presently have the numbers or the long term follow up to adjust these models to our data. Our survival data reasonably matches or exceeds NICHD data at 23- and 24-weeks' gestation over the last 10 years.

3. In general, given the continued poor combined survival and neurodevelopmental outcome data (<10%) for <$23^{0/7}$ week gestation infants, we continue to recommend that resuscitation be withheld in this gestational category.
4. In general, given the survival and neurodevelopmental outcome data for infants born at $23^{0/7}$-$23^{6/7}$ weeks gestation, we recommend that data be presented to families and the decision to resuscitate be strongly influenced by their opinion. However, in the absence of strong opinion, we recommend resuscitation in concordance with the 2015 AAP Committee on Fetus and Newborn statement (Cummings 2015).
5. In general, given the survival and neurodevelopmental outcome data for infants born at $24^{0/7}$-$24^{6/7}$ weeks gestation, we recommend that data be presented to families and the decision to resuscitate be influenced by their opinion while strongly advocating for resuscitation.
6. Given the survival and neurodevelopmental outcome data for infants born at or beyond $25^{0/7}$ weeks gestation, we recommend in concordance with legal precedence, that resuscitation not be withheld despite parent wishes. Exceptions should be made for unique circumstances related to either maternal or neonatal comorbidities that are likely to negatively influence survival or favorable outcomes.

Summary of Intervention Recommendations:

- 22 weeks – Strongly discourage resuscitation. If family insistent, emphasize statistics and proceed with resuscitation and minimize heroics, recognizing that chest compressions and epinephrine are likely not indicated in this age group.
- 23 weeks – Neutrally offer resuscitation based on family wishes and outcome statistics. Support family decision for nonintervention. Recognize that chest compressions and epinephrine may not be indicated in this age group.
- 24 weeks – Advocate for resuscitation but support family decision for nonintervention.
- 25 Weeks – Advocate resuscitation in all cases unless negative comorbities.

Gestation	NICHD survival w active resus	SLN survival 2008-17 (incl nonresus)	NICHD % w/out severe impairment	NICHD % w/out mod-sev impairment
22 weeks	**23%**	**11%**	**15%**	**9%**
23 weeks	**33%**	**41%**	**25%**	**16%**
24 weeks	**57%**	**71%**	**46%**	**31%**
25 weeks	**72%**	**81%**	**61%**	**45%**

Fluids, Electrolytes, and Nutrition

Extremely small babies present the healthcare team with very challenging nutritional support needs. Excellence in meeting these needs allows for the best obtainable outcomes for these tiny infants. An extensive literature and evidenced based clinical care review has been performed and we have broken down our nutritional goals and guidelines into several phases of nutritional care: early fluid and electrolyte management, transitional, stabilization, and growth phases. Finally, babies progress to the oral feeding stage of meeting their nutrition needs.

Fluid and electrolyte management in the Extremely Low Birth Weight (ELBW) infant is critical to survival. The amount of fluid present in the plasma, interstitial fluid, and cellular fluid changes throughout the fetal and neonatal period. One of the many factors influencing fluid requirements is insensible water loss by mechanisms such as evaporation and transepidermal water loss. ELBW infants are especially susceptible to this due to their large body surface area and immature skin, often resulting in an initial hypernatremia and the associated complications. Some ELBW infants also experience hyperkalemia, hyperglycemia, and/or hyper/hyponatremia, resulting in various other complications. A standardized approach to initial fluid management that considers the infant's age, size, skin and insensible fluid losses is necessary. It is also notable that the goals for fluid and nutrition intake change during the transition phase, stabilization phase, and growth phase. Careful management of the metabolic and fluid changes is essential to meeting the long-term nutritional intake and growth demands of these infants. All other organ systems, and especially the brain and neurodevelopment, are absolutely dependent on optimal nutrition and growth, making this one of the most important aspects of small baby care.

Additionally, recent nutrition guidelines recommend early aggressive amino acid (AA) intake for the ELBW population to maintain nitrogen balance & prevent catabolism. There is evidence to support that fluid and electrolyte balance may be further impacted by providing early aggressive AA in PN solutions that do not contain adequate substrate for nutrient metabolism. Of note, Starter Parenteral Nutrition (SPN) solutions should not be infused at greater than 100ml/kg/day to avoid excessive AA administration.

The parenteral supply of AA and energy maintains the cell in an anabolic state, promoting uptake of both phosphorous and potassium, resulting in hypophosphatemia and hypokalemia. Phosphorous is required for amino acid and glucose metabolism pathways and will be released into circulation from the bone if necessary for cellular requirements. At the same time, calcium will be mobilized from the bone, resulting in hypercalcemia. The resulting phenomenon of hypophosphatemia, hypokalemia and hypercalcemia is described as neonatal Placental Incompletely Restored Feeding Syndrome, also referred to simply as Refeeding Syndrome (RFS). As such, an approach that allows for providing potassium, phosphorous and calcium in a ratio to support cellular metabolism while providing necessary protein intake has been outlined in our guideline. RFS is discussed in more detail below. Please note that separate TPN guidelines are included below for infants without or with RFS.

Fluid Electrolyte and Nutrition Guidelines (<28 wks or <1000 grams):

Initial management: 0-24 hrs

- Admission:
  - Place central lines, UAC and double lumen UVC.
  - Via UAC: infuse (0.45%) Na Acetate w/ 1-unit heparin/ml @ 0.8 ml/hr (goal rate is 0.5ml/hr to minimize non-nutritional fluid admin, decrease rate as soon as tolerated, ideally by DOL 1.
  - Admission labs:
    - ABG and glucose. CBC at 6 hrs of age.
    - CBC on admit if PIH, IUGR, TTT, blood loss or hypotension.
- Labs:
  - POCT Chem 8 at 12-hrs of age; establish trend with POCT lytes.
  - BMP, gas with Ical at 24 hrs of age; if IUGR: add Phos by 24-48 hrs.
  - Avoid heel sticks if possible.
- Fluid / Nutrition Goal:
  - Initial Total Fluid: 100-120 ml/kg including UAC fluids @ 0.5 ml/hr (goal rate to minimize non-nutritional fluid admin, transient increases may be required, see above).
  - SPN D5% AA3.5% @ 90-100 ml/kg provides GIR: 3.1-3.5, 3.1-3.5 g pro/kg, 28-31 kcals/kg.
  - SPN D10% AA3.5% @ 80-100 ml/kg provides GIR: 5.5-6.9, 2.8-3.5 g pro/kg, 38-48 kcals/kg. *Start with SPN D10% first, then change to D5% if needed for hyperglycemia.*
  - *Goal to start custom PN & IL before end of first 24-hrs (to allow Calcium, Phos, K).*
  - *Start oral care with colostrum as soon as available. Start trophic feeds (EBM or DHM) by 6-hrs @ 10 ml/kg/d (divided q6h); maintain until ready to initiate FAT.*

Transition Phase: 25 hrs – 5 days
(May last 3-5 days or slightly longer)

- If BW < 750 grams, greater insens losses; start TF @ 100-120 ml/kg or more; up to 140-160 ml/kg.
- If BW 750 – 1000 grams, start TF @ 100 ml/kg; may require up to 140-160 ml/kg during this phase.
- Total Fluid – advance fluids cautiously - only 10-20 ml/kg/day (or restrict) based on GA, BW, % wt loss/insensible losses/diuresis/UOP, Na level, feeds.
- Fluid: Increase (or restrict) free water in response to Na Goal of 135-145 mEq/L.

  *if < 135, consider decreasing the fluid intake.

  *if > 145, consider increasing the fluid intake.
  - Aim to maintain Na < 155 mEq/L (Bhatia J 2006).

        - Be aware of extraneous Na-intake (drips*) (No need for additional Na for the first 2-3 days of life except to provide Phos and Acetate).*
        - Use Humidity per guidelines. See Thermoregulatory/Integumentary chapter.
- Calcium/Phos: Provide Phosphorous to support AA and Dextrose metabolism.
    - Phos: 1-1.6 mMol/kg (use 0.5-1 mEq/kg each of Na & K).
        - K-Phos can be added to custom PN, once UOP established.
        - If able to provide Phos of 1-1.6 mMol/kg, Calcium will be max of: 1.6-2.5 mEq/kg.
        - Refer to **Table 1** for Ca:Phos 0.8:1 molar ratio dosing.
- Acid-Base Balance**:** Adjust Acetate (OAC) within PN to maintain serum CO2 within goal of 18-24.
    - *1 mEq OAC is converted to 1 mEq bicarbonate in the liver. Na or K must be ordered to provide Acetate within PN. Be aware of UAC fluids with Acetate as well as competing need for Phos in initial PN. Avoid iatrogenic alkalosis with timely acetate weaning.*
- GIR: Minimum of 5mg/kg/min. Advance 0.5-1 mg/kg/min per day if glucose is $\leq$ 150; (goal BG: 80-120).
    - If hyperglycemia develops manage per ELBW Hyperglycemia Mgmt and ELBW Insulin Drip Guidelines. Tolerate glucoses 150-250.
    - Avoid hypoglycemia.
- Amino Acids: Advance to 3.5-4 grams pro/kg (only restrict if Cr > 1.5).
- Lipids/TG monitoring: Safe to start lipids DOL 0-1.
    - If less than 1000 gm, SGA/IUGR, given post-natal steroids, presumed sepsis:
        - Follow triglyceride levels, checking after reaching 1, 2 and 3 gm/kg/day for infants <750gm. If 751-1000gm, check level at 2 gm/kg/day and additionally only if abnormal or borderline elevated.
        - Goal of < 250. Hold advance or decrease IL 0.5-1 g/kg if TG level ≥ 250-400.
        - If TG level is > 400, aim to provide 0.5 gm/kg/day to meet EFA goals; do not omit longer than 24-hrs.
- Carnitine: provide 10 mg/kg/day while providing lipids to an infant who is NPO, on trophic feeds, or if persistently elevated TG levels.
    - *While controversial, the benefits of carnitine supplementation may include improved fatty acid oxidation, improved lipid tolerance, positive nitrogen balance, and weight gain. The estimated requirement of carnitine is 2-10mg/kg/day. (Salguero 2018).*
- Vitamins/Minerals:
    - Use "protocol" dosing to provide standard Peds MVI dose of 2 ml/kg/day & SLHS-custom Trace Elements which includes a total of 400 mcg/kg/day Zinc. Refer to NICU TPN Guide for dosing Trace Elements for different conditions.

- Labs:
  - POCT Chem 8 q 6-24 hours for the first 3 days of life then at least q am while nutritional adjustments are being made.
  - Check Phos at 5 days of age; if IUGR check Phos at 24hrs. If hyperglycemia, may trend Phos more regularly.
- Feeds: Begin trophic feeds (or FAT) if not hypotensive or on pressors. Use mother's milk or donor milk whenever possible. See further discussion of feedings below.
- Enemas: Avoid use of glycerin enemas if possible. (If ordered, administer with use of feeding tube, not syringe, to decrease risk of trauma.)

Stabilization Phase: DOL 5-14
(ECF contraction/diuresis complete/Regain to BW)

- Start to require Na & K in greater amounts:
  - Na: 2-3 mEq/kg typical but may need significantly more
  - K: 1.5-2 mEq/kg (more if SGA/low Phos/refeeding syndrome)
  - Ca:Phos:
    - Continue invert (0.8:1 ratio) – ***see Table 1***
      - May advance total amounts if Phos value AND i-Ca support Ca increase (see table 1 for 0.8:1 molar ratio).
- Nutrition Goal: 90-110 kcal/kg, 3.5-4 g pro/kg by DOL 7.
- Ca:Phos - recheck Phos by DOL 7:
    - *Needs to be > 1 wk old, not IUGR & trend of 2 Phos values > 5, to allow advance to 1:1 – 1.2:1 molar* ***(refer to Table 2).***

Growth Phase: DOL 10-14/beyond

- Aim to match intrauterine growth rate *and prevent EUGR - wt gain goal ≥ 18-22 g/kg/day.*
- Hyponatremia (now more likely reflects insufficient Na intake vs. fluid changes).
  - Na: 3-5 mEq/kg (up to 7 mEq/kg).
- Other Lytes:
  - K: 2-4 mEq/kg
  - Ca:Phos – if infant remains on PN > DOL 10-14 without fortified feeds, need to address if can go to 1:1 molar ratio & goal of Ca 3-3.8 mEq/kg & Phos 1.6-1.8 mMol/kg (see Table 2).
    - Note: if PHOS > 5 (x2 labs), infant is only on 22 kcal/oz feeds, can decrease Ca within PN, but will still require Phos intake of 1-1.6 mMol/kg, until on 24 kcal/oz fortified feeds. *Consult RD for assistance.*
- EN continues to advance; PN starts to decrease.
- Nutrition Goal (EN+PN): >110-125 kcal/kg, 3.5-4.5 g pro/kg. TF ≥ 150-160ml/kg/day.
- Nutrition Goal (FULL EN): >130-150 kcal/kg, 4-4.5 g pro/kg. Need 165 ml/kg (24 kcal/oz) or 145-150 ml/kg (27 kcal/oz).
- Oral Feedings per Breast and Bottle Feeding Algorithm (BBFA) starting at 32wks PMA.

TPN Guidelines (<28 wks or <1000 gm):

DOL	Total Fluid (ml/kg)	SPN/custom	GIR	AA Only (g/kg)	Lipids (g/kg)	Electrolytes*	Labs for following day (AM draw)
first 24-hrs	100-120 ml/kg *includes SPN or UAC fluids *start EBM or DHM by 6-hrs.	SPN @ 80-100 ml/kg **UAC or other for difference*	4-5	2.8-3.5	n/a, or if fluid available start at 0.5	n/a in SPN +/- Ca 1-2 mEq/kg	BMP, iCal; *if IUGR/SGA: add Phos*
1	100-120 ml/kg *Continue trophic feeds or start FAT*	CUSTOM	Adv by 0.5-1 **Hold adv if Phos < 4 and/or BG > 150*	3-3.5	0.5 gm/k/d Adv by 0.5gm/kg/d	Ca:Phos ratio (0.8:1 molar) Phos: 1-1.6 mMol/kg K: 1 mEq/kg (prefer *K, if +UOP)* Na: 0-1 mEq/kg	POCT Chem 8
2	120-140 ml/kg *trophic feeds*	CUSTOM	Same as above	3.5-4	1	Same	BMP, Mg, TG, iCal
3	120-140 ml/kg *trophic feeds*	CUSTOM	Same as above	3.5-4	1.5	Same or Liberalize Na/K	POCT Chem 8
4	140-150 ml/kg	CUSTOM	Same as above	4	2	Ca:Phos 0.8:1 Liberalize Na/K if indicated	BMP, Phos, TG if on 2gm IL
5	150-160 ml/kg	CUSTOM	Max of 10-12 if BGs < 150	4	2.5	Ca:Phos 0.8:1 Liberalize Na/K if indicated	POCT Chem 8
6	150-160 ml/kg	CUSTOM	Max of 10-12 if BGs < 150	4	3	Ca:Phos 0.8:1 Liberalize Na/K if indicated	POCT Chem 8, TG if on 3gm IL
7	150-165 ml/kg	CUSTOM	GIR↓ as feeds ↑	3.8-4	3	Ca:Phos 1:1 molar if Phos > 5; otherwise 0.8:1	POCT Chem 8, Phos
8	150-165 ml/kg	CUSTOM	GIR↓ as feeds ↑	2.8-3	↓ lipids** as feeds ↑	Same	POCT Chem 8
9	150-170 ml/kg	CUSTOM	GIR↓ as feeds ↑	1.5-1.8	↓ lipids** as feeds ↑	Same	POCT Chem 8 or BMP PRN
10	150-170 ml/kg	SPN D10% @ 20-30 ml/kg	GIR 2.5-4 as nearly full feeds	0.8-1.5	OFF	Consider custom PN if high Na/OAC requirement or enteral Na	Order BMP & Phos, for 5-7 days OFF PN

**** If IUGR/SGA: add Phos within 24-48 hrs; add Magnesium if IUGR/SGA and NO maternal Magnesium.***

*****As feeds increase, total fat intake as combo of IL + feeds acceptable up to 5.5 g/kg/day short-term.***

Monitoring I-Calcium: (SLHS lab normal: 1-1.2)

- Low: < 0.9-1
- Normal: 1-1.2
- Elevated: iCa 1.45-1.6 mMol/L
    - Hypercalcemic neonates don't show symptoms; concern for peripheral or CNS calcification due to impaired ability for excretion.

Intervention:

- Start Phos infusion within 24 hours of life to prevent altered mineral homeostasis, i.e. hypercalcemia; provide 0.8:1 molar ratio Ca:Phos within PN – first week or iCa >/= 1.4-1.7.
- If severe (iCa > 1.7-1.8 mMol/L), STOP all PN Ca, recheck in 12-24 hrs.

Due to high AA intake & placental incompletely restored feeding syndrome, Phos is necessary for energy metabolism. Dose Phos intake based on Na/K salts available. If adequate UOP, select K-ion as preferred Phos source. Dose Calcium based on Phos ordered. Use these tables to find the amount of Calcium to provide within PN.

Table 1: 0.8:1 Ca:Phos molar ratio

*No changes for first 1-2 weeks; once Phos > 5 (x 2), may adjust to "normal" ratio – refer to next table.

Provide Calcium intake of:	If PN Phos intake is:
Ca (mEq/kg)	**Phos (mMol/kg)**
1.6	1
1.7	1.1
1.9	1.2
2.1	1.3
2.2	1.4
2.4	1.5
2.5	1.6
2.9	1.8
3.2	2

Table 2: 1:1 – 1.2:1 Ca:Phos molar ratio

For use AFTER week 1, AND once Ca/Phos normalize → Phos > 5 (x 2 values); i-Ca 1-1.2.

*This is the typical ratio goal to meet needs for preterm bone mineralization, once infant is in growth phase. Also ok for use with prolonged PN, restart of PN after period of EN only, while in growth phase.

Provide Calcium intake of:	If PN Phos intake is:
Ca (mEq/kg)	**Phos (mMol/kg)**
2-2.4	1
2.2-2.6	1.1
2.4-2.8	1.2
2.6-3.1	1.3
2.8-3.3	1.4
3-3.6	1.5
3.2-3.8 (goal)	1.6
3.6-3.8 (goal)	1.8

Refeeding Syndrome (RFS) Nutrition and Lab Considerations:

RFS is characterized by metabolic disturbances (hypophosphatemia, hypokalemia, and hypomagnesemia) after resuming nutrition in severely malnourished patients. Infants with IUGR or who are SGA are at highest risk, even if AGA at birth. This includes infants of mothers with placental insufficiency and/or PIH. The more severe the IUGR, the greater the risk of electrolyte abnormalities. *Early, aggressive parenteral nutrition sets the stage for ALL ELBW & VLBW infants to show metabolic disturbances consistent with or similar to RFS.*

Clinical Consequences of Hypophosphatemia:

- Respiratory failure (diaphragm weakness) – VLBW neonates with hypophosphatemia were significantly more likely to require mechanical ventilation for ≥ 3 days.
- Hemolysis, leukocyte dysfunction, thrombocytopenia, decreased O2 delivery.
- Neuromuscular dysfunction with weakness and paresthesia
- Ileus/delayed gut motility – delayed advancement of enteral feedings

Clinical Symptoms of Hypokalemia:

- Arrhythmia/cardiac arrest –not reported or observed in neonatal population
- Neuromuscular dysfunction with weakness and paresthesia
- Ileus/delayed gut motility – delayed advancement of enteral feedings

Clinical Symptoms of Hypomagnesemia:

- Weakness, tremors, seizures, delayed gut motility
- May induce hypokalemia by impairing Na/K ATPase
- May induce hypocalcemia by impairment of parathyroid function
- Arrhythmia possible

Clinical Consequences of Hyperglycemia:

- Hyperosmotic state\dehydration from excessive UOP
- Possible increased infectious risk from impaired neutrophil function

Management Guidelines for Abnormally Low Electrolyte Values:*

	Indication	Standard NICU Replacement Dose
Hyponatremia	<120 mmol/L	Consider replacement with D5NS or 3% sodium chloride (**MUST** calculate Na deficit, consider Gomella Hyponatremia chapter for reference. Use extreme caution if using 3% NaCl for correction. Correction should occur SLOWLY, at a rate of approximately 1mmol/L per hour.)
Hypokalemia	<3 mmol/L	KCl 1mEq/kg/dose IV
Hypocalcemia	Ionized Ca <0.9 mmol/L	Calcium Gluconate 200mg/kg/dose
Hypophosphatemia	<3 mg/dl	NaPhos 0.3 mmol/kg/dose
Hypomagnesemia	<1 mg/dl	Magnesium sulfate 50mg/kg/dose

Management Guidelines for Abnormally Elevated Electrolyte Values:*

	Management Guidelines
Hypernatremia	• Increase TPN if glucose/protein concentrations allow • Add additional fluid source as needed • Do not increase UAC fluids to greater than 1ml/hr • Consider NG/OG sterile water infusion if hypernatremia is persistent or severe

Hyperkalemia	• If K >7mg/dl, repeat lab value to confirm and consider intervention
	• If intervention needed the following may be used:
	  ○ Albuterol nebs or MDIs
	  ○ IV Calcium Gluconate
	  ○ IV Furosemide
	  ○ IV Bicarbonate
	  ○ IV or SQ Insulin (ensure adequate glucose infusion)

Hypercalcemia	• If asymptomatic but total Calcium >12mg/dl, check ionized Calcium and Phosphorus • If ionized Calcium >1.5 mmol/L, consider intervention • If intervention needed, consider 20ml/kg Normal Saline bolus followed by IV or PO furosemide

Hypermagnesemia	• Obtain Mg level at 24hrs if mother received magnesium therapy prenatally
	  ○ If level >3mg/dl, hold Magnesium out of TPN for 72 hrs then add back in as standard panel value
	  ○ If level <3mg/dl, use standard panel in TPN starting on DOL 2

*Source: Adapted from MUSC, original author unknown

TPN Guidelines in Known/Suspected Refeeding Syndrome (<28wks or <1000 gm):

DOL	Total Fluids (ml/k/d)	SPN/ custom	GIR	AA Only (g/kg)	Lipids (g/kg)	Electrolytes	Special considerations	Labs for following day (AM draw)	Phosphorus Initially serum levels are likely normal *despite intracellular depletion.*
first 24 hrs	100-120 ml/kg	SPN 80-100 ml/kg	4-5	2.8-3.5 Only restrict AA if no phos in PN	NA	Consider Ca 1-2mEq/kg/d	Advance kcal only ≤5-10 kcal/kg/day. Must give phos to adv GIR or kcals Risk for hypoglycemia in 1st 24-48h then hyperglycemia	BMP, Phos, Mg	Abn <4 Severely low <2.5 Replace with NaPhos for <3 Add to PN for Phos 3-4
1	100-120 ml/kg *Continue trophic feeds or start FAT*	CUSTOM	Adv by 0.5-1 *Hold adv If Phos <3 and/or BG > 150*	3-3.5	0.5gm/k/d Adv by 0.5gm/k/d	Provide Phos and K in PN. Mg if no maternal MgSO4 Ca:Phos ratio (0.8:1 molar) Phos: 1-1.6 mMol/kg K: 1 mEq/kg (prefer K, if +UOP) Restrict Na (0-1)	Hypokalemia 1st sign of RFS give KCl bolus if <2.5mg/dl Hypomagnesemia <1.5mg/dl Low magnesium may prevent adequate repletion of K & Phos	POCT Chem 8	Phos <3.5, daily monitoring while nutrition advances until Phos >4.5, then repeat in 2-3 days or once on "full-nutrition/feeds" to ensure Phos >5.
2	120-140 ml/kg *Trophic feeds*	CUSTOM	Same as above	3-3.5	1	Same	Hyperinsulinemia causing Na and fluid retention	POCT Chem 8	
3	120-140 ml/kg *Trophic feeds*	CUSTOM	Same as above	3-3.5	1.5	Same or liberalize Na/K	*Reminder: adv total kcals by only 5-10 kcal/kg/day if showing RFS. *Or hold kcal adv if Phos < 3.5.	POCT Chem 8, Phos, Mg	
4	140-150 ml/kg	CUSTOM	Same as above	3-4	2	Ca:Phos 0.8:1 Liberalize Na/K		POCT Chem 8	
5	150-160 ml/kg	CUSTOM	Same as above	3-4	2.5	Ca:Phos 0.8:1 Liberalize Na/K			
6	150-160 ml/kg	CUSTOM	Same as above	4	3	Ca:Phos 0.8:1 Liberalize Na/K		POCT Chem 8 Phos, Mg	Repeat in 2-3 days or when on full feeds. Goal >5
7	150-165 ml/kg	CUSTOM	GIR↓ as feeds ↑	3.8-4	3	Ca:Phos 1:1 if phos > 5 Otherwise 0.8:1		BMP	
8	150-165 ml/kg	CUSTOM	GIR↓ as feeds ↑	2.8-3	↓ lipids** as feeds ↑	Same		BMP/POCT Chem 8 PRN	
9	150-170 ml/kg	CUSTOM	GIR↓ as feeds ↑	1.5-1.8	↓ lipids** as feeds ↑	Same		BMP/POCT Chem 8 PRN	
10	150-170 ml/kg	SPN D10%	2.5-4 as nearly full feeds	0.8-1.5	D/C	Consider custom PN if high Na/OAC reqmt or oral Na		BMP, Phos 5-7 days off PN	

**As feeds increase, total fat intake as combo of IL + feeds acceptable up to 5.5 g/kg/day short-term

Glucose Management:

Infants at the extremes of prematurity are prone to perturbations in glucose homeostasis. Prior to initiation of IVF, these infants are at high risk for hypoglycemia due to almost nonexistent glycogen stores. This is particularly exacerbated in infants who are SGA or septic. There continues to be some debate regarding the ability of both term and preterm infants to tolerate brief periods of hypoglycemia, as well as what truly defines hypoglycemia in infants. With the infeasibility of ever completing a large, well-controlled RCT to inform this dilemma, the position of St. Luke's Neonatology is that for this patient population who is at high risk for multifactorial neuronal injury, all infants with blood glucose <50 will be aggressively treated.

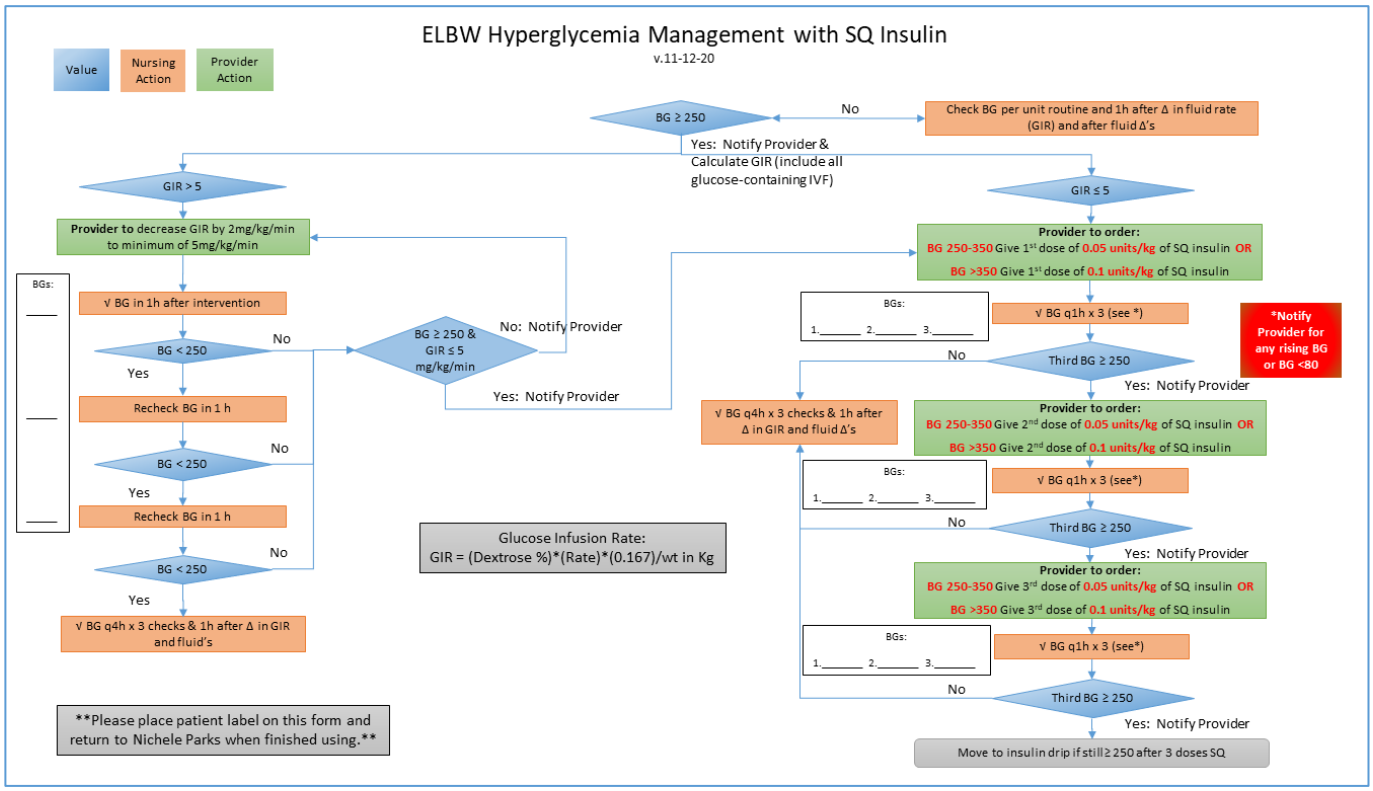
Once on IVF, this population is also prone to hyperglycemia, even despite judicious management of the glucose infusion rate (GIR), due to physiologic and biochemical mechanisms that can lead to excess glucose production, insulin resistance, and glucose intolerance (Hemachandra 1999). Based on this challenging aspect of fluid and nutrition management, we have established the following guidelines for the management of persistent hyperglycemia including initiation and maintenance of insulin infusion and monitoring of blood glucose levels. We identified three primary goals to this approach:

1. Decrease the frequency of hyperglycemia (defined as serum glucose concentrations of greater than 250 mg/dL)
2. Increase the frequency of appropriate treatment of hyperglycemia (as defined by the new guidelines)
3. Decrease the number of days when caloric intake is below the estimated basal energy expenditure (BEE), which we define as 50 kcal/kg/day.

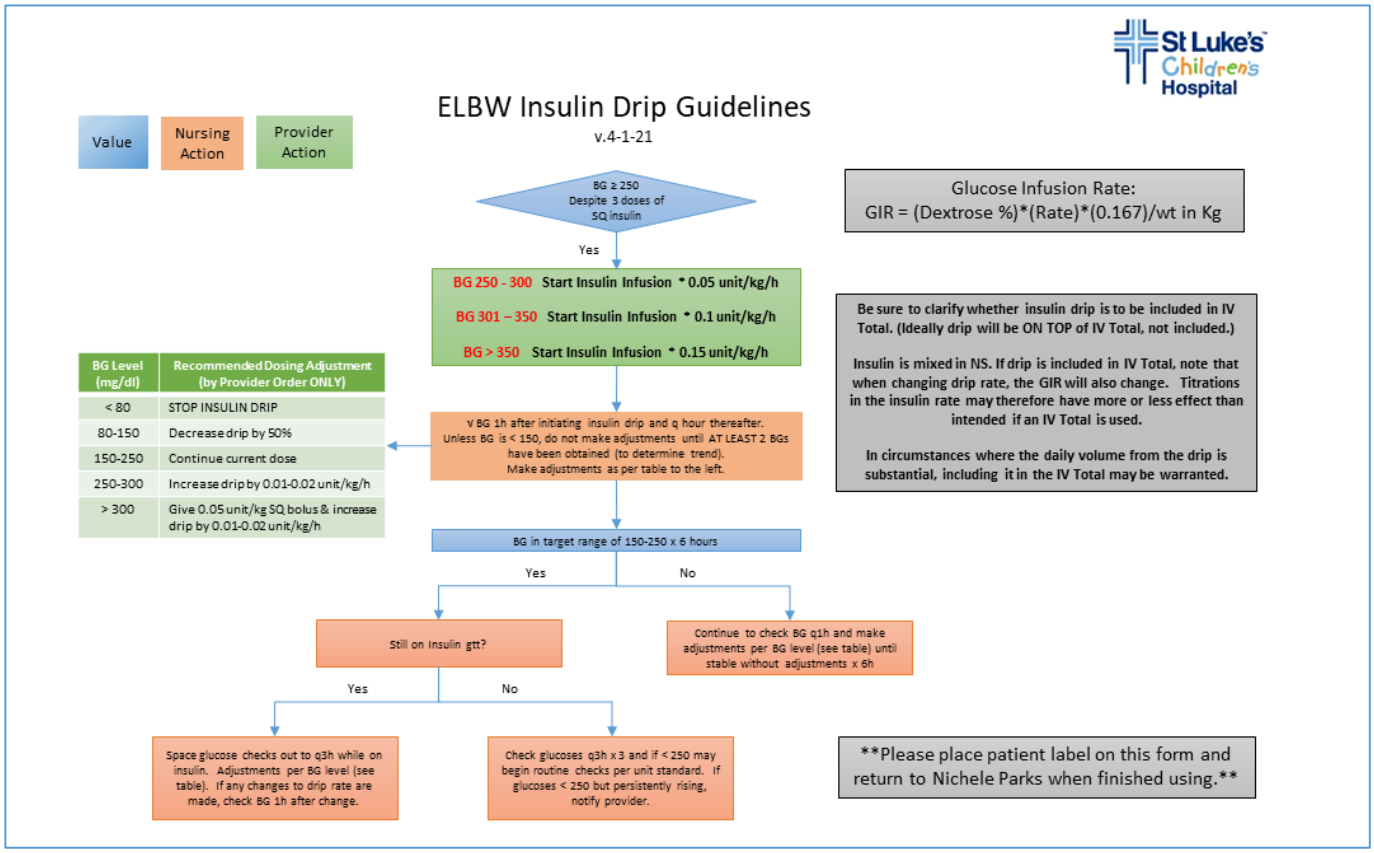
Providers should consider starting insulin treatment when blood glucose levels are ≥250 mg/dl. Consideration should be given to checking urine for glucose. ELBW infants may have a lower renal threshold for glucose and are at an increased risk of osmotic diuresis related to hyperglycemia. Checking for glycosuria at a lower glucose level may be prudent in these infants. If adjustments in GIR can be made, it should be decreased to no lower than is needed to maintain total calories of 50 kcal/kg/day, inclusive of protein (feeds+AA+glucose+lipids). A GIR of 5 mg/kg/min and IL of 2 gm/kg/d (including protein) will meet the estimated BEE of ~50-55 kcal/kg/d.

Insulin should be considered if the infant has persistent hyperglycemia despite not yet advancing the GIR to 5 mg/kg/min, or if there is persistent hyperglycemia despite reduction in GIR to 5 mg/kg/min. The following algorithms summarize the approach to both intermittent insulin dosing and the administration of insulin drips.

ELBW Hyperglycemia Management with Subcutaneous Insulin:



ELBW Insulin Drip Guidelines:



Feedings:

Current evidence is overwhelmingly in favor of utilizing human milk for enteral nutrition in all infants. Particularly important for the ELBW population, human milk confers a host of nutritional, immunologic, microbiological, infectious, and neurodevelopmental benefits. Whenever possible, prioritization should always be to utilize maternal expressed breast milk (EBM). Particularly important, maternal colostrum provides substantial immune benefits when delivered, even prior to establishment of intestinal feedings. Swabbing the cheeks with colostrum is believed to promote oral immune therapy and a "top down" colonization of the gastrointestinal tract with beneficial and commensurate bacterial flora, which may subsequently prevent or reduce colonization with potentially pathogenic microorganisms commonly found in the hospital setting. Evidence also suggests that lactobacillus, one of the most common bacteria normally found in breastmilk, aids in neonatal tolerance of feedings due to lactase enzyme production. Establishment of a healthy, normal microbiome is also believed to have lifelong impacts on overall health.

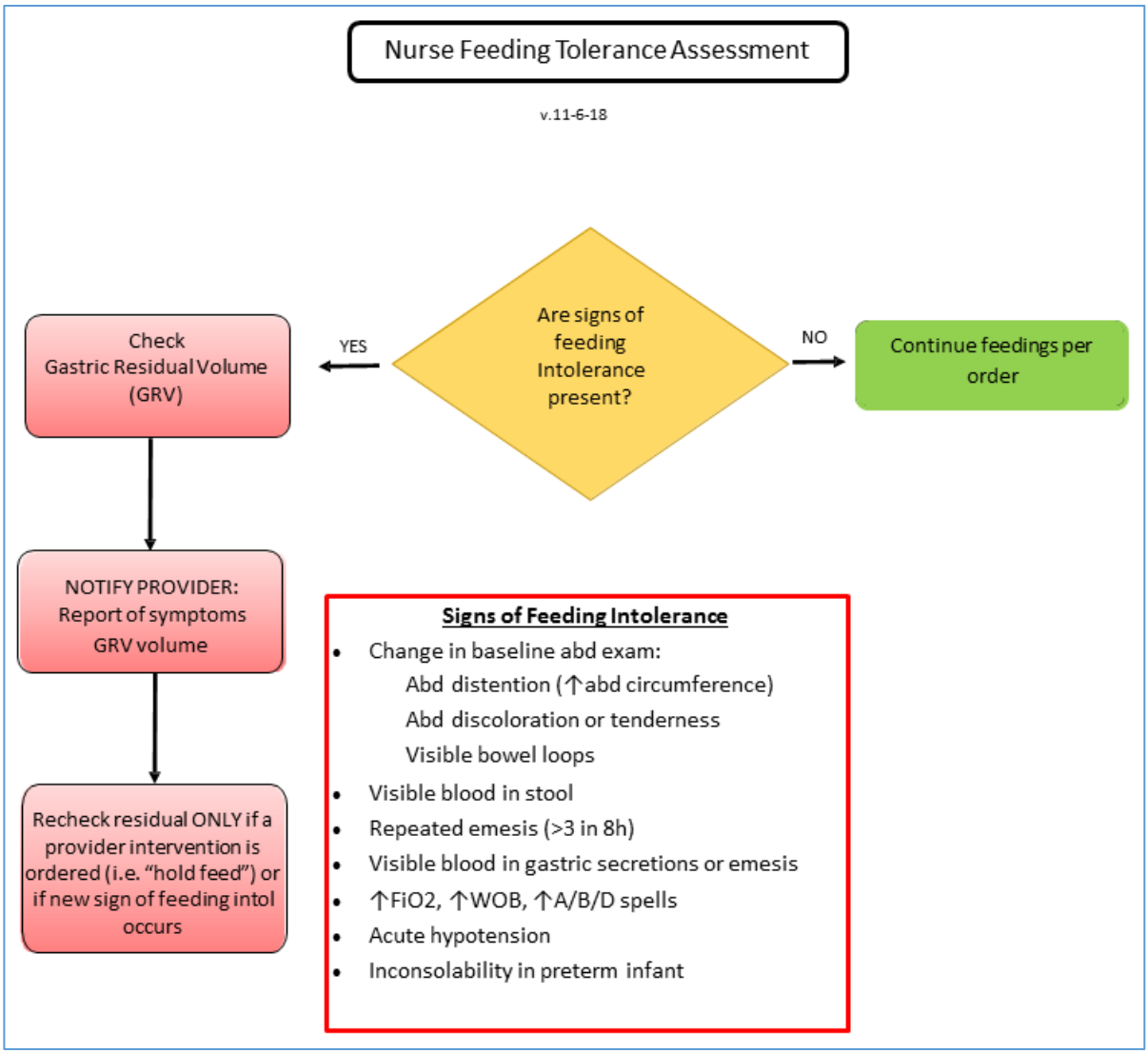
When issues with production or supply of EBM occur, the second most preferable enteral nutrition source is pasteurized donor human milk (DHM) and this should be provided to all families of ELBW infants. While signed parental consent is not required, all families should be made aware of the recommendation for DHM prior to its use, and a family's declination of DHM should be respected. In situations where EBM is not available and DHM is declined, the next most preferable enteral nutrition source is a premature infant formula with iron that is specifically tailored to the needs of this patient population. In general, Similac Special Care is the St. Luke's Neonatology preferred formula for this purpose, as many of our secondary fortifications and nutritional approaches are tailored specifically to account for this product's constituents. Family requests for "designer formulas," such as certain organic and other products, should be highly discouraged as they are not appropriate for the ELBW nutritional needs.

Trophic feeds (10ml/kg/day) should be initiated as soon as possible after birth, ideally in the first 6h, with maternal colostrum if available. The use of standardized feeding advancement tables has been demonstrated to decrease length of time to full feedings, improve ease of ordering, preparation, and administration of feeds for staff, and may reduce the incidence of NEC. St. Luke's Neonatology group members and Registered Dietitians have spent substantial time and effort creating 4 categories of feeding advancement tables (FAT), two of which apply to the ELBW population and should be utilized whenever possible. The FAT for infants up to 750gm provides three days of trophic feedings, and then advances by 20ml/kg/day to goal feeds of 160ml/kg/day on Day #11 of advancement. Fortification to 22kcal/oz takes place at 110ml/kg/day, and fortification to 24kcal/oz occurs at 130ml/kg/day. The FAT for infants 751-1250gm provides two days of trophic feedings, and then advances similarly to full volume fortified feedings by Day #10 of advancement. The addition of protein and vitamin additives is also automated by use of the FAT, optimizing nutritional delivery as parenteral nutrition is weaned. While not included in this document, the FAT ordersets are readily available within Epic.

Gastric Residuals:

While there remains some debate regarding the utility of gastric residuals (GR) in NICUs across the country, the current state of the science suggests an approach that eliminates routine checking of GR and instead promotes checking GR only in the presence of other gastrointestinal symptoms (Parker 2015, Arave 2018). In summary of the rationale behind forgoing the routine checking of GR:

- GR volumes are highly unpredictable and often do not correlate with actual gastric contents
- While GR are higher in NEC, data does not show that regular GR checks lead to more timely diagnosis of NEC and less invasive GI and cardiopulmonary indicators can be utilized in evaluating for NEC
- Checking GR can have adverse effects by delaying time to full feeds (either contributing to feeding intolerance by disruption of normal digestive hormone cascade or leading to perception of poor feeding tolerance) and in turn increasing TPN, central line days, and potential for line infections.



Gastroesophageal Reflux (GER):

Gastroesophageal reflux, generally defined as the passage of gastric contents into the esophagus with or without regurgitation and/or vomiting, is a normal developmental phenomenon noted almost universally in preterm infants and typically resolves spontaneously with maturation (COFN 2018). It is a physiologic process related to transient lower esophageal sphincter relaxation (TLESR), a large-volume liquid diet, and age-specific body positioning. GER is considered to be pathologic and referred to as GER Disease (GERD) when the reflux leads to troublesome symptoms (excessive crying, back arching, regurgitation and irritability) and/or complications, such as esophagitis, weight loss, or the development of strictures (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) 2018). The presence of an indwelling gastric tube through the LES increases the frequency of GER (COFN 2018).

GERD is also known to be prominent in children who have other underlying medical conditions such as neurologic impairment, congenital anomalies, or surgical issues (lack of integrity of the gastric lining, esophageal atresia, ENT surgery or vocal cord edema and erythema with airway compromise, short bowel syndrome or the presence of ostomy-due to association with gastric acid hypersecretion) (Angelidou 2017). The following evidence is presented to support the subsequent guidelines which have been developed. These guidelines are meant for premature infants and not meant to address these other specific populations.

Positioning: Prone positioning vs supine positioning decreases episodes of GER. Infants have fewer TLESRs in the left-side-down position after feeding. Gastric emptying is facilitated by the right-sided down position after feeding (COFN 2018). The guidelines below attempt to optimize this evidence. There is no evidence that head of bed (HOB) up positioning decreases GER in term infants, and in fact car seat positioning has been shown to elicit *worse* acid GER in term infants (COFN 2018). HOB up positioning hasn't been studied in preterm infants.

Feeding Strategies: Smaller volume feedings given more frequently might result in fewer GER episodes. A randomized controlled trial (RCT) of 40 VLBW infants demonstrated that superior mesenteric artery doppler ultrasound flow was better in infants fed by bolus versus continuous feeds (Bozzetti 2016). No randomized trials have been used to compare the effects of continuous intragastric or transpyloric feeds versus bolus intragastric tube feedings on GER symptom severity (Cochran rev 2014, COFN 2018). The use of transpyloric feeding as a diagnostic test for GERD has not been studied (ESPGHAN 2018). There was a small retrospective single center cohort study of 72 VLBW infants in the early 2000s which demonstrated that transpyloric feedings, especially when limited to human milk, may safely reduce episodes of apnea and bradycardia in preterm infants with suspected GER (Malcolm 2009). It is important to note, however, that nutrient composition of breast milk may be compromised by longer feeding times on a pump (fat, calcium, phosphorous) (Abrams 2010).

Hydrolyzed/Elemental Formula/Dairy-Free feedings: It is suggested that elemental or extensively hydrolyzed protein formulas reduce GI transit time and reduce symptoms in term

infants with symptomatic GER. While there is no evidence to support the use of extensively hydrolyzed formula or amino acid-based formula for the treatment of GERD in infants and children who do not have cow milk protein allergy (CMPA), symptoms of GERD and CMPA are identical. Therefore a trial of extensively hydrolyzed protein-based formula may be reasonable in age-appropriate preterm infants with signs of severe reflux not to treat the reflux, but rather to rule out an unrecognized CMPA (COFN 2018, ESPGHAN 2018). In breast-fed infants, the mother can achieve similar results by restricting all dairy, including casein and whey, from her diet.

Impedance Testing: The most accurate method for detecting GER is impedance monitoring- it is a reliable and reproducible technique for diagnosing GER in preterm infants and can be combined with pH monitoring. Reflux is non-acidic approximately 70% of the time. Studies have used impedance to evaluate the relation of infant behaviors as well as apnea and bradycardia events to GER episodes and found that they are rarely temporally related (COFN 2018). This testing should be done if possible prior to initiation of acid suppression therapy (Silvalingam 2017).

Acid Suppression/Prokinetic Therapy: There is no evidence that pharmacologic treatment of GER with agents that decrease gastric acidity or promote gastrointestinal motility decrease the risk of recurrent apnea or bradycardia in preterm infants (COFN 2018). Five RCT trials of proton pump inhibitors (PPIs) in preterm and term infants with treatment periods ranging from 2-4 weeks have not shown reduction in symptoms when compared to placebo (JPGN 2018). Infants with BPD have not been shown to have an increased incidence of GER (COFN 2018). Appearance of the airway, as evaluated by an ENT, does not correlate with pathologic reflux (ESPGHAN 2018). Mechanisms to protect the esophagus and airway from GER appear to be intact in the preterm infant (Jadcharla 2017, COFN 2018). While there have not been many quality studies done in premature infants, a recent systematic review in 2014 showed insufficient evidence for an association between GER and apneas in infants (Smits 2014, Poets 2011). The adverse effects of anti-reflux medications are now well documented. Reduced gastric acidity, alteration of the gut microbiome, and interference with neutrophil function result in increased risk of GI infections in term infants and NEC in premature infants. These medications also increase the rates of community-acquired pneumonia in healthy term infants as well as ventilator-associated pneumonia (VAP) in PICU patients and late-onset sepsis in NICU patients. Alterations in gastric pH can impede calcium absorption with potentially harmful effects on bone development and increased risk of fractures. Drug metabolism may also be delayed in premature infants due to immature liver function (Angelidou 2017). ESPGHAN recommends to use PPIs as first line treatment for erosive esophagitis only, and H2 blockers only if PPIs are unavailable or contraindicated. If a trial is considered, it should be done for 1 week (due to drug pharmacokinetics) and discontinued if not effective based on objective criteria (Angelidou 2017). Prokinetics are not recommended (ESPGHAN 2018).

Thickened Feeds: Thickening does improve visible regurgitation, but the impact on non-regurgitation symptoms is less clear (ESPGHAN 2018). Only small trials of thickeners have been performed in the preterm population, and there is evidence to suggest that some thickeners may increase risk of NEC. This has been thoroughly reviewed in our thickening protocol and is not meant for routine use in infants <42 weeks CGA. In the rare cases where thickeners are considered, this should only been done in conjunction with NICU dietitian consultation.

Fundoplication: Largely based on expert opinion due to lack of proper RCTs, ESPGHAN recommends fundoplication (laparoscopic) only for life threatening complications (e.g. cardiorespiratory failure) of GERD after failure of optimal medical treatment, symptoms refractory to optimal therapy after appropriate evaluation to exclude other underlying diseases, chronic conditions with a significant risk of GERD-related complications (CF, neurologic disorders), and the need for chronic pharmacotherapy.

Discharge Positioning: There are a couple of important points from the 2016 AAP Policy Statement regarding Sudden Infant Death Syndrome (SIDS) and other Sleep-Related Infant Deaths as they pertain to GER. The first is that the supine sleep position does not increase the risk of choking and aspiration in infants, even those with GER, because infants have airway anatomy and mechanisms that protect against aspiration. The AAP concurs with the North American Society for Pediatric Gastroenterology and Nutrition that "the risk of SIDS outweighs the benefit of prone or lateral sleep position on GER; therefore, in most infants from birth to 12 months of age, supine positioning during sleep is recommended" (AAP, 2016). Postprandial prone positioning is acceptable when the infant is awake and observed, but should only be considered in infants with certain upper airway disorders in which the risk of death from GERD may outweigh the risk of SIDS (AAP, 2016). The second point is that elevating the head of the infant's crib is ineffective in reducing GER and is not recommended. In addition, elevating the head of the crib may result in the infant sliding to the foot of the crib into a position that may compromise respiration.

Premature Infant GER Guidelines:

Red Flags that may require additional testing/Immediate Intervention:

- Persistent forceful vomiting
- Bilious vomiting
- Hematemesis
- Chronic diarrhea
- Rectal bleeding
- Abdominal distension
- Concern for increased intracranial pressure (bulging fontanel), or seizures

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Steps for Assessment and Treatment

First: Anti-Reflux Positioning

- Consult OT/SLP for high-risk infants (ELBW or preterm infants with IUGR).
- Hold infant during the feed and for 20-30 min following feed as able.
- If not held for feeding, position the infant left side down during the feeding and for the first 30 minutes after the feeding, followed by right side down.
- May consider prone positioning instead of supine.
- Consider a trial for 3-5 days of positioning the head of the bed up. If this does not help, return the bed to a flat position.

Second: Feeding Strategies

- May consider more frequent, smaller volume feeds for certain infants (if growth supported).
- May prolong feeds on pump up to an hour, but return to 30 min if no improvement after several days. May consider prolonging pump feeds longer than 60 min, up to continuous gastric feeds, prior to initiating more invasive therapies.
- Pump times for partial oral feedings are adjusted to the remaining volume of feeding.
- Transpyloric feeding – may consider this after maximizing above therapies. For the ELBW population: May consider if >1000 g, >30 days of age, and breast milk used for feeds. Time to not exceed one week if symptoms do not improve.

Third: Alternative Formula Trial – ≥36 weeks; already incorporated OT interventions

- Consult NICU RD for recommendations/implementation
- If suspected cow's milk protein allergy (CMPA) and >/= 36 wks, trial one of the following:
  - If formula fed: trial protein hydrolysate, or elemental/AA-based formula for at least 2-wks.
  - If using breast milk: eliminate cow's milk in maternal diet x2-4 weeks. Continue to give breast milk as available during this trial if mother agrees to dairy free diet (use protein hydrolysate or AA-based formula to fortify).
  - Note: this trial is not intended to treat reflux, rather to rule out CMPA.
- If suspected prematurity related GER/D that significantly impacts growth/feeding progression (including associated ABD events with feeds), may consider trial of an anti-reflux formula (Added Rice Starch infant formula).
  - Consult OT, if not already following, for oral feeding evaluation and parent feeding education.
  - Trial Added Rice Starch/anti-reflux formula for up to 1-week, with the following items in place:
    - Must hold acid-blocking medications which interfere with the thickening function.
    - Cannot use with maternal milk due to amylase enzyme activity within maternal milk which breaks down the rice starch, negating the thickening effect.
    - If maternal milk IS available, consider alternate plan to avoid eliminating maternal milk.
  - Anti-Reflux/Rice Starch formulas are NOT intended for use in treatment of infants with dysphagia.
  - Anti-Reflux/Rice Starch formulas are NOT intended for small bowel feeding tubes.

Fourth: Referral to Pediatric GI if above fails – 38-40 weeks:

- Impedance testing first, then:
- Acid suppression trial (recommend objective data from impedance testing first).

Fifth: Thicken Feeds – 42 weeks

- If >42 weeks and not improved with Elemental/Dairy-free feeds – thickened feeds require OT&RD consultation prior to implementation.
- Refer to Children's Protocol on Thickening for additional guidance.

Sixth: Consider fundoplication – 44 weeks

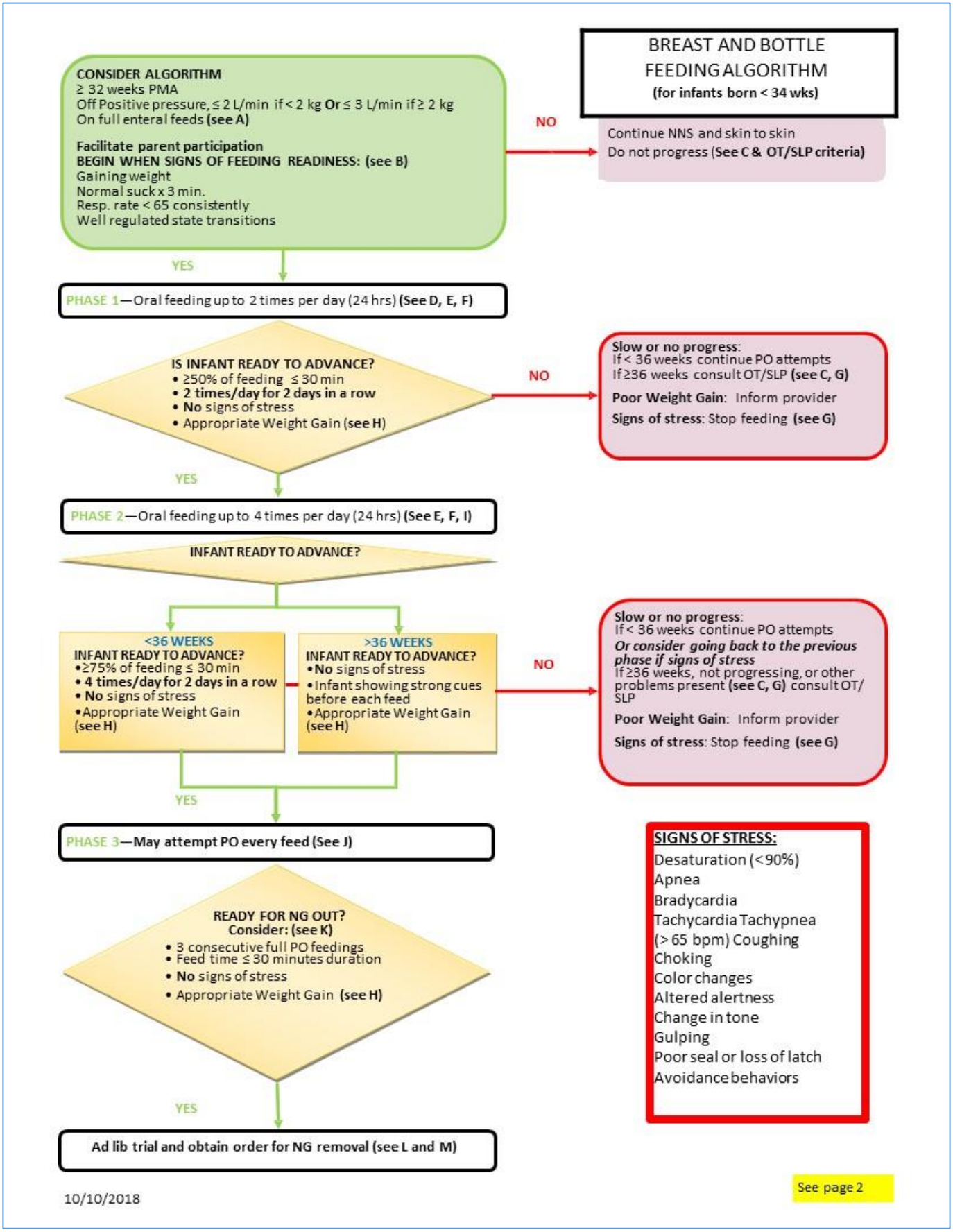
- If all above fails or other special circumstances. GI consultation should be obtained if not already done.

Discharge Considerations:

- A trial of the infant in a flat recumbent position should be considered by 32 weeks CGA and at the very latest several days prior to anticipated discharge.
- If ordered, give discharge instructions for elevating the head of the bed to parents (only special circumstances).

Breast and Bottle Feeding Algorithm (BBFA):

The breast and bottle feeding algorithm is an individualized, developmentally appropriate approach to feeding that enables the infant to participate and control their own feeding. This approach has been shown to decrease the time to achieve full oral feeds and ultimately shorten length of stay. It allows more parent involvement and promotes both breast and bottle feeding. Using readiness scores and documenting disengagement cues also empowers nurses to use sound evidence based on judgment on whether to feed or not to feed. The specific strategies used to continue feeding in the volume driven model places the infant at risk for unstable vital signs, hypoxia, increased energy expense and poor weight gain.



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	Breast and Bottle Feeding Algorithm Explanation Sheet (for infants born < 34 wks)
A	**Consider Algorithm:** For infants born < 34 wks, tolerating full enteral feedings that still require gavage tube. Please encourage parental involvement in their infant's feedings. Update parent/caregiver of feeding schedule and any changes in the schedule (e.g. bathing, feedings, cares). Provide a comfortable chair for them to sit while feeding their infant. Provide privacy for breastfeeding and skin to skin holding. ***Once infant enters the algorithm, place the Breast & Bottle Feeding tracking sheet at bedside.***
B	**Readiness for oral feedings**: The infant is: 1)growing appropriately **(see H)**, 2) able to suck on a pacifier for 3 minutes with normal suck/burst/rest pattern, 3) RR ≤ 65 when held for feeding, 4)transitioning from sleep to awake gradually; & is in a drowsy, alert, or fussy state prior to cares; rooting and/or hands to mouth; awakens at scheduled feeding times and has good tone. A lactation consult is requested if mother is interested in breastfeeding.
C	**Infants ≥ 32 wks that are NOT ready to PO feed:** Hold infant and offer pacifier during the gavage feeding if possible. Mother may hold infant skin to skin to suck at a pumped breast. Non-nutritive breast feeding does not count as attempts. Transitioning from non-nutritive breast feeding to full breast feeding may require mother to partially pump before breastfeeding attempts. **Always consult OT/SLP: with infants who are ELBW, IUGR, ≤ 1,000 gm, and born < 28 weeks.** **Consider OT/SLP consult for infants with: swallowing dysfunction, poor management of oral secretions, posturing with feedings, oral aversion/nipple avoidance, absent gag reflex, oral motor/feeding concerns not related to prematurity, craniofacial deformities, neurological disorders, physiological distress with feedings and persistent spells with feedings (≥ 2 feeding in a row). If OT/SLP is seeing infant, they may change to an individualized feeding plan. Do not make changes to an individualized feeding plan without collaboration with OT/SLP.**
D	**Timing and initiation of the first PO feed:** Discuss with parents their desire to participate in the first oral/ gavage feeding. Allow the infant to wake up on his own and come to an alert state. If external pacing is needed, follow OT/SLP recommendations. Stop a feeding when signs of stress are noted (see signs of stress on algorithm). Reassess for PO feeding opportunity at a later time and discuss in rounds.
E	**Cue-based infant driven feeding schedule:** Offer a PO feeding when the infant is awake, alert, showing hunger cues prior to feeding. If an infant is sleeping at the time of a feeding, wait to attempt PO feeding when infant awakens and shows feeding cues. Observe for signs of stability or stress and adjust oral feeding attempts accordingly. **Signs of stability include: awake and alert, showing hunger cues, smooth and regular RR, stable HR, demonstrating self-regulatory behaviors, coordinated suck/swallow/breathe pattern, good tone and color.** PHASE 1: Oral feeding up to 2 times per 24 hrs; prefer not back to back. Offer milk on pacifier with gavage feeding if awake. PHASE 2: Oral feeding up to 4 times per 24 hrs; prefer not all back to back. Offer milk on pacifier with gavage feeding if awake.
F	**Estimating how much to gavage after breast feedings:** Goal mother's milk supply is the following: Week 1 post birth, mother expresses ≥ 375 mls in 24 hours; week 2 post birth, ≥ 750 mls in 24 hours. If milk supply is less, mothers may still breastfeed. Use AC/PC weight with the infant on the same scale, clothing and diaper, to estimate the volume of milk transferred during a breast feeding. If needed, specific supplementation plan will be developed by lactation, RD, RN and provider.
G	**Slow or no progress:** If an infant has not progressed and is <36 weeks PMA, continue PO attempts and expect improvement by 36 weeks. If ≥36 weeks and not progressing, **consult OT.** At any time, if the infant is regressing, inform the provider. Persistent stress is when the infant exhibits signs of stress for 2 or more feedings in a row (see signs of stress). If persistent signs of stress are noted, discuss on rounds.
H	**Appropriate weight gain:** Infants < 2 kg, desired weight gain is 18-22 grams/kg/day. Infants > 2 kg, desired weight gain is 25-35 grams/day. If infant fails to meet growth goal, inform provider. For breastfed infants, use AC/PC weight to ensure adequate supplementation.
I	**Giving bottle feedings to breast fed infants:** Do not introduce bottle feedings before 35 weeks PMA or before the infant has had at least 2 breast feedings a day, with acceptable latch and transfer of milk, unless mother desires. When the breastfeeding mother cannot come in for every feeding, discuss starting bottle feeding with mother, in order to continue feeding progression.
J	PHASE 3: **May PO each feeding:** PO can be breast and or bottle feeding (continue to use AC/PC weights to estimate volumes as long as using gavage). Have parents bring bottles they will be using at home.
K	**NG OUT:** Poor endurance may result in the infant terminating the feeding before taking the required volume, **OR** demonstrating poor weight gain *despite* **ACCEPTABLE** intake. Endurance is a reflection of the infants ability to maintain homeostasis. If they are able to complete 3 consecutive feeds in ≤ 30 min, feeds without signs of stress, and maintains appropriate weight gain, consider NG out. Endurance is the infants ability to meet this criteria multiple times consecutively.
L	**Ad lib trial:** Infants are fed PO as much (or as little) as they want on demand per feeding readiness cues. They can be fed every 2-4 hours. Contact the provider for D/C NG order and 12-hr minimum volume if desired. Stop AC/PC weights (may use daily weight gain if breast feeding). **If the infant is not meeting 12-hr minimum volume, or not awakening to feed, or no wet diapers in 5 hours, *notify the provider.***
M	**Feeding status for discharge:** 1) The NG tube is out for a minimum of 48-72 hours. 2) The infant is accepting adequate volumes of ***home feeding***, with no distress, and gaining weight appropriately (see H). 3) The parents/caregivers are educated regarding feeding preparation, feeding and OT/SLP feeding recommendations.

10/10/2018

Monitoring of Growth:

ELBW infants are at extremely high risk for postnatal growth failure. To ensure consistent and detailed measurement and monitoring of length and occipitofrontal circumference (OFC), Registered Dietitians (RDs) will perform weekly length board and OFC measurements on all ELBW infants (RDs also perform measurements on all other infants who screen for nutrition risk, including those <1500gm, <30 weeks GA, and those who are IUGR/SGA). ELBWs are not measured before at least 4 weeks of age. Measurements are obtained weekly (Tues-Thurs) based on infant's condition. Infants who are not clinically stable, are ventilated, or are on pressors or pain management will have their measurements deferred.

After full oral feedings have been established and babies have been discharged home, they continue to have specialized nutritional needs. Our team has a role to play in recommending follow up nutritional care to maximize long term outcomes. These guidelines and procedures will be addressed in the discharge section of our Small Baby Guidelines.

Respiratory

Airway and breathing management are the two first components of the 'ABCs' of resuscitation, and the respiratory system is the most immediate need of all of the systems addressed within these Guidelines. Nearly all ELBW infants will have respiratory distress syndrome (RDS), also known as surfactant deficiency. Most will also have some degree of either partial or complete respiratory failure, meaning an inability of the pulmonary support systems to be compatible with life in the absence of significant assistance from the team of care. This assistance begins in the delivery room, and requires coordination, procedural skill, thorough knowledge of resuscitative techniques, and proficiency in adherence to the AAP Neonatal Resuscitation Program (NRP).

Many of these infants will require intubation in the delivery room, however growing evidence and our own experience has shown that in many cases, infants can be managed successfully with non-invasive techniques. As we attempt to master newer techniques such as Non-Invasive Positive Pressure Ventilation (NIPPV), our overarching goal is to minimize, and where possible even eliminate, the need for invasive ventilation. While in many cases intubation may be inevitable and may be required for prolonged periods, substantial evidence now exists that shows that simply having an endotracheal tube, even for a brief period of time, leads to significant elevation of polymorphonuclear cells and inflammatory cytokines such as TNFα, IL-6, and IL-1β (Puyo 2012). These cytokines, as well as the positive pressure mechanics of mechanical ventilation, have been strongly implicated in the development of chronic lung disease (CLD). There has been much debate regarding whether lung injury from mechanical ventilation occurs primarily from excessive pressure (barotrauma), excessive stretch on the delicate premature lung architecture (volutrauma), or repetitive shear forces from frequent collapse and reinflation of alveoli (atelectatrauma). In reality, it is likely all of these components, combined with the highly immunologically active lung tissue itself, that lead to the long-term condition of CLD.

It is important to remember that embryologically these infants, particularly the 22-24 weekers, are just beginning to transition from the canalicular to the saccular stage of lung development. They have minimal Type 2 pneumocytes, whose function is the production of surfactant. The development of alveolar sacs is at a very early stage for these infants, and this alveolar development and overall lung growth occurs well into childhood, not reaching a full complement of alveolar development until around 8 years of age. This ongoing growth is important to recognize, as even infant who sustain prematurity-related lung trauma and scarring can continue to grow new and healthy lung tissue long after discharge. Most infants who are discharged home with CLD and O2 requirement will outgrow their oxygen need by 1-2 years of age.

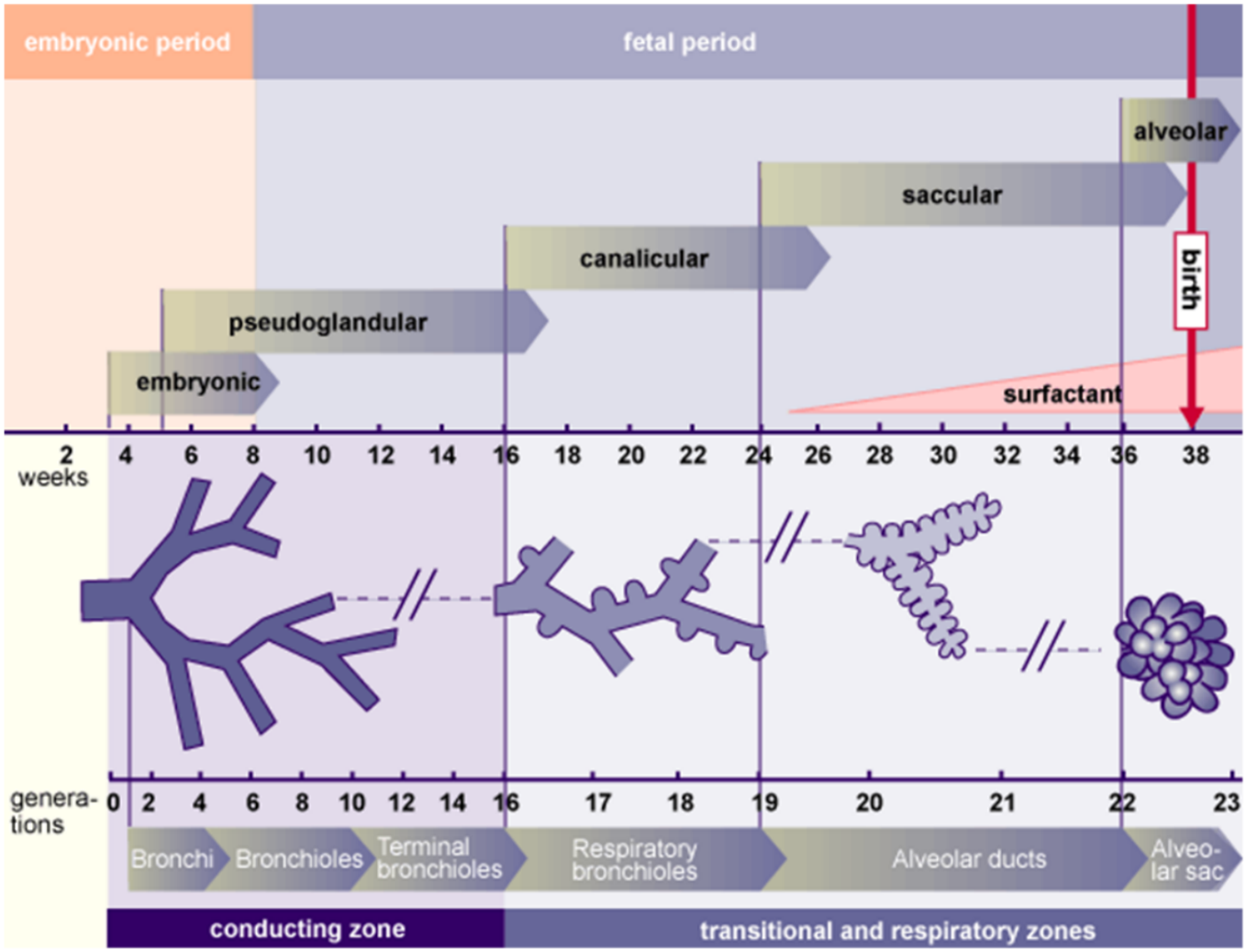


Image borrowed from Klein, J presentation, WNPPS Meeting 2019, Scottsdale. Source not identified.

These Guidelines will attempt to summarize our approach to utilizing various strategies, invasive, and noninvasive techniques with an overarching goal to minimize long-term pulmonary morbidity and CLD.

Delivery Room Approach:

All infants born to mothers with good dating techniques at 22-23wk EGA should be intubated in the delivery room. Most 24wk EGA infants will likely also warrant intubation in the DR, however for vigorous infants a trial of NIPPV should be entertained and initiated promptly in the DR. Infants 25-27wks have a greater likelihood of avoiding intubation, and once again NIPPV should be initiated promptly in the DR if intubation is not clearly indicated. This should be the standard for all non-intubated 25-27wk infants to reduce or prevent need for future intubation.

Due to the critical importance of rapid airway establishment in this population, and the propensity for long-term negative consequences of trauma from multiple intubation attempts, the most experienced person with intubation skills should perform DR intubations. These

patients are not in an ideal situation for trainees or less experienced intubators to improve their skills.

Hyperoxia should be strictly avoided in the DR, and NRP guidelines followed for FiO2 delivery and SpO2 monitoring.

Surfactant administration should be performed quickly if intubation takes place, however ideally this should take place in NICU immediately after CXR confirmation of appropriate ETT placement. Asymmetric distribution of surfactant due to a malpositioned ETT can have significant long-term consequences, hence our decision to obtain the CXR first whenever possible. In the DR, if efforts to achieve NRP-targeted SpO2 goals require >60% FiO2, then surfactant administration may be warranted prior to transport to NICU for CXR.

Standardized Premedication for Non-Emergent Neonatal Intubations

While not specific to the <28wk population, a discussion of intubation premedication is included in the SBG due to the high frequency of intubation in these infants. All non-emergent intubations, regardless of GA, should be performed with the following approach if at all possible.

Tracheal intubation is associated with adverse events that may include cardiac arrest, elevated intracranial pressure, esophageal intubation, hypotension, hypertension, direct airway injury, significant bradycardia, and severe desaturation (Foglia 2015, Hatch 2016). The number of attempts and intubation urgency are associated with increased adverse events. Premedication (in the absence of a muscle relaxant) alone does not decrease the odds of an adverse event (Hatch 2016). The Committee on Fetus and Newborn, Section on Anesthesiology and Pain Medicine, made the following statement in 2010: "An ideal approach to tracheal intubation would be to administer supplemental oxygen as needed, via properly sized face mask, then a vagolytic agent, followed by an analgesic and/or hypnotic medication before infusion of a muscle relaxant" (COFN 2010). Several studies have been done to inform and attest to this statement (Roberts 2006, Norman 2011, Feltman 2011, Hatch 2016, McPherson 2018). We have thus developed an EPIC order set (NICU Rapid Sequence Intubation, or RSI) of the following medications to be used (in order) for pre-medication for non-emergent intubation:

1. Atropine (0.02mg/kg/dose)
2. Fentanyl (2mcg/kg/dose given over 3-5 min)
3. Rocuronium (0.5mg/kg/dose).

These medications were chosen as they are the quickest acting and can even be used if the goal is to quickly extubate (i.e. INSURE method for surfactant administration) (Hatch 2016, Van Alfen-van der Velden 2006). As fentanyl can have an elimination half-life of up to 5 hours in term, or ~9 hours in preterm infants, naloxone may be beneficial if rapid extubation is the goal (McPherson 2018).

Midazolam is to be used only for infants >34 weeks as it is associated with decreased cerebral blood flow velocity, desaturations, and hypotension in premature infants (Van Alfen-van der Velden 2006, Whyte 2000, McPherson 2018).

Surfactant:

While there are many contributing factors to respiratory distress syndrome (RDS) of the newborn, surfactant deficiency often plays a critical role in RDS. Surfactant is a naturally occurring mixture of phospholipids and proteins produced by the lung that reduces alveolar surface tension thereby preventing alveolar collapse. Surfactant deficiency will lead to progressive atelectasis with worsening pulmonary function. Fortunately, there are commercially available surfactant preparations that can be instilled into the neonatal lung to treat surfactant deficiency. Despite the widespread use and success of this revolutionary treatment for RDS, there is still not clear evidence as to the ideal way to administer surfactant and criteria for when both the initial and repeat doses of surfactant should be given. The Committee of the Fetus and Newborn in 2014 stated the "optimal method of surfactant administration in the preterm infant has yet to be determined" and there is "insufficient evidence to recommend the optimal number of doses".

What is clear is that while prophylactic surfactant generally does not improve outcomes, getting surfactant to those who need it in a timely fashion is best. Other conclusions that can be drawn from the literature support performing a gentle alveolar recruitment maneuver by increasing PIP just prior to surfactant delivery, followed by rapid bolus delivery via manual administration. The goal is to achieve a homogenous and symmetric distribution to improve pulmonary function.

The approach below drew from the above conclusions as well as querying multiple additional NICUs as to their processes surrounding use of surfactant with the goal of creating a standardized approach of surfactant use for St. Luke's Neonatology.

For infants intubated in the delivery room our stated goal is for surfactant administration by 20 minutes of age. As mentioned above, in most cases this should be done after obtaining a STAT CXR for ETT placement immediately upon arrival in the NICU. Whenever possible, the NICU Abbreviated Admission Orderset should be used as soon as possible after delivery (before the infant leaves the DR) to facilitate having the Xray technician standing by at the bedside upon arrival. Once appropriate tube placement is confirmed, the infant should receive surfactant immediately and prior to placement on the ventilator. The appropriate administration technique is outlined in the table below. Surfactant should always be given prior to placing lines, as failure to do so could result in a significant delay.

Note that surfactant should still be taken to all deliveries of infants born at <28wks EGA. While the preferred approach is to confirm tube placement first, it is appropriate to administer surfactant in the DR if unable to obtain NRP-targeted SpO2 despite >60% FiO2 via ETT.

For infants not intubated in the DR, the criteria for meeting initial intubation threshold should be followed, and surfactant administration should occur as soon as tube placement is confirmed. In rare cases of intubation for apnea without RDS, surfactant may not be indicated.

Surfactant Delivery Guidelines:

St Luke's Children's Hospital

Surfactant Delivery Guidelines

v. 9-30-19

	22-24 weeks*	≥25 weeks
Medication/ Dose	Curosurf (2.5ml/kg)	≤1.2kg: Curosurf (2.5ml/kg) OR >1.2kg: Infasurf (3ml/kg)
Criteria for Initial Dose	• ASAP following intubation, ideally in NICU after CXR confirmation of ETT placement. • Take surf to all deliveries. Consider giving in DR if FiO2 needs are >60% to achieve NRP-targeted SpO2.	• ASAP if intubated OR • FiO2 need >0.4 for 2h on NIV (Initial intubation) • Ideally administer in NICU after CXR confirmation of ETT placement. • Take surf to all deliveries. Consider giving in DR if FiO2 needs are >60% to achieve NRP-targeted SpO2.
Administration Technique	• Increase PIP by ~2-5cm H20 for ~10 breaths just prior to administration. • Rapid (5-10sec) administration of single aliquot in midline position with NeoTee @ 60 bpm. • Continue until surf completion, then decrease PIP to lowest pressure that creates gentle chest movement.	• Increase PIP by ~2cm H20 for ~10 breaths just prior to administration. • Rapid (5-10sec) administration of single aliquot (Curosurf) or in two aliquots (Infasurf) in midline position with NeoTee @ 60 bpm. • Continue until surf completion, then decrease PIP to lowest pressure that creates gentle chest movement.
INSURE?	No. Follow 22-24wk vent/extubation guideline	Yes if at all possible. If plan to remain intubated, obtain pre/post-surf P/V loops on Avea and follow 25-27wk vent/extubation guideline
Repeat dosing	• Curosurf (1.25ml/kg) q12h x 2 if FiO2 >0.4 and MAP >10	• ≤1.2kg: Curosurf (1.25ml/kg) OR • >1.2kg: Infasurf (3ml/kg) q12h x 2 if FiO2 >0.4 and MAP >10 • If s/p INSURE (and now extubated) then FiO2 >0.5 for 2h on NIV

*Provider discretion for some robust 24 weekers who may be candidate for INSURE or may avoid intubation altogether

Initial Ventilator Settings, Weaning, and Extubation Guidelines:

A full and thorough discussion of neonatal ventilatory management across the spectrum of ventilators available on the market is beyond the scope of these Guidelines. Ventilator management generally requires a tailored approach with much nuance depending on individual patient circumstances. SLN has agreed, however, to embark upon a standardized approach to initial ventilator settings, goals for weaning, specific blood gas criteria, and recommended thresholds for initial intubation, extubation, failed extubation, and reintubation.

While some feel that High Frequency Ventilation (HFV) may confer some advantages over Conventional Ventilation (CV) in the tiniest babies, the evidence is not clear on this. An internal review of our own data shows that HFV comes with a significant risk of overventilation. Therefore, our Guidelines recommend very stringent criteria regarding blood gas monitoring and strict adherences to avoiding hyperventilation/hypocarbia. Due to the pressure-passive nature of the preemie cerebral vasculature and the inability to autoregulate cerebral blood pressure, especially in the first few days of age, avoidance of low pCO_2 is paramount. Elevated pCO_2 may also impact cerebral perfusion, albeit likely to a lesser extent than hypocarbia. Nonetheless, hypercarbia contributes to decreased serum pH and respiratory acidosis, which can impair cardiac output and interfere with critical enzymatic and metabolic functions throughout the body. Our Guidelines incorporate a slightly tighter range of pCO_2 control (which therefore requires more frequent blood gas monitoring) in the first 72h of life. Frequency of blood gases decreases thereafter, and as metabolic compensation begins to improve with the slow maturation of renal function, our tolerance of hypercarbia is liberalized slightly. Ventilatory maneuvers should never be used to correct pH issues related to metabolic acidosis.

As can be seen from the guidelines below, the initial ventilator of choice is High Frequency Oscillatory Ventilation (HFOV) for infants 22-24wks, and Conventional Ventilation (CV) for infants 25-27wks who require intubation. HF Jet Ventilation (HFJV), should generally be reserved for infants with known or suspected air leak syndromes such as Pulmonary Interstitial Emphysema (PIE) or pneumothorax (PTX), or for infants who fail to oxygenate or ventilate effectively on optimal HFOV settings.

The goal for extubation for intubated infants at 25-27wks is by 24h of age whenever possible, and ventilator management should be performed with this target in mind. Infants 22-24wks are likely to be more difficult to wean to extubatable settings, nonetheless the goal should be to achieve extubatable settings within 5 days.

See also the Neurology chapter for perspective regarding sedation of intubated patients.

Initial Ventilator & Extubation Guideline (22-24wks):

INITIAL VENTILATOR & EXTUBATION GUIDELINE (22-24 WKS)

v.10-8-20

PLACE ON HFOV: Initial settings: Hz 14; ΔP 16; MAP 8

LAB WORK:

1. I-stat gas at time of UAC placement, 2h after, then q4h and PRN for first 24h
2. I-stat gases q6h and PRN for 25-48h
3. I-stat gases q8h and PRN for 49-72h

MEDICATIONS:

4. See Surfactant Delivery Guidelines.
5. Caffeine 25 mg/kg IV x 1 load upon admission, then 10 mg/kg IV q 24hrs.

IMAGING:

6. CXR at least q6h for first 24h to monitor expansion. If post-surfactant CXR is <1h after surf, repeat in 2h.
7. CXR at least q12h from 25 - 72h to monitor chest expansion
8. CXR at least daily from 72h – 5d to monitor chest expansion

BLOOD GAS CRITERIA FOR VENTILATOR MANAGEMENT:

Age		Immediate Evaluation *Notify Provider* Recheck gas 30-60" after intervention	Increase ΔP pCO2	Hold pCO2	Wean ΔP pCO2	Immediate Evaluation *Notify Provider* Aggressive Wean Recheck gas 30-60"
0-72h	ABG/CBG	pH <7.2 OR pCO2 >70	56-70	45-55	40-45	pH >7.45 OR pCO2 <40
3+days	ABG/CBG	pH <7.2 OR pCO2 >70	61-70	50-60	40-49	pH >7.45 OR pCO2 <40

- Notify Provider if FiO2 >50% or rapidly increasing.
- Any value in "immediate evaluation" category takes precedence.
- Any gas rechecks due to "immediate evaluation" category are in addition to routinely scheduled gases.
- Wean as tolerated with goal to achieve extubatable settings within 5 days. Consider HUS just prior to extubation if >72h of age.

EXTUBATION CRITERIA:

9. **HFOV:** FiO2 <0.4; MAP ≤8; Delta P ≤15; pCO2 <60
   Avea: FiO_2 <0.4; Rate 20; PEEP 5. PIP based on weight:

Weight	<750 gm	750-1000 gm	1001-1500 gm	>1500
PIP	13 cm H_2O	14 cm H_2O	15 cm H_2O	16 cm H_2O

10. Hold all sedation for at least 12h prior to extubation. Consider Narcan/Flumazenil rather than reintubation if oversedation occurs post extubation.
11. Call MD/NNP just prior to extubation.
12. Refer to NIV order set.
13. Follow Intubation & Extubation Criteria, post-extubation gas criteria (on NIPPV order set).
14. If extubation fails, consider conventional ventilation after reintubation.

Initial Ventilator & Early Extubation Guideline (25-27wks):

INITIAL VENTILATOR & EARLY EXTUBATION GUIDELINE (25-27 WKS)

v.10-8-20

PLACE ON CONVENTIONAL VENTILATOR: Initial settings: SIMV/VG; TV 4-6ml/kg; PEEP 6; Rate 30; Ti 0.3s; PIP 25 limiting pressure; PS 8 (Goal of PS is to attain comfortable WOB, not to match TV of vent breaths). Consider changing to PC/PS if unable to maintain on VG due to airleak

LAB WORK:

1. iSTAT gases every 4h x 24h and prn if intubated. Consider decreased frequency if TCOM in place and correlating, or after 24h.

MEDICATIONS:

2. See Surfactant Delivery Guidelines.
3. Caffeine 25 mg/kg IV x 1 load upon admission, then 10 mg/kg IV q 24hrs.
   If extubation is 12-24hrs after loading dose, give 1st maintenance dose just prior to extubation.

ADDITIONAL CONSIDERATIONS:

4. CXR at least q day until extubated to monitor chest expansion. CXR within 2h after any surfactant.
5. Transcutaneous pCO_2 monitor.

BLOOD GAS CRITERIA FOR VENTILATOR MANAGEMENT:

Age		Immediate Evaluation *Notify Provider* Recheck gas 30-60" after intervention	Increase PIP pCO2	Hold pCO2	Wean PIP pCO2	Immediate Evaluation *Notify Provider* Aggressive Wean Recheck gas 30-60"
0-72h	ABG/CBG	pH <7.2 OR pCO2 >70	56-70	45-55	40-45	pH >7.45 OR pCO2 <40
3+days	ABG/CBG	pH <7.2 OR pCO2 >70	61-70	50-60	40-49	pH >7.45 OR pCO2 <40

- Notify Provider if FiO2 >50% or rapidly increasing.
- Any value in "immediate evaluation" category takes precedence.
- Any gas rechecks due to "immediate evaluation" category are in addition to routinely scheduled gases.
- Wean as tolerated with goal to achieve extubatable settings in ≤ 24 hrs.

EXTUBATION CRITERIA:

6. **HFOV:** FiO2 <0.4; MAP ≤10; Delta P ≤15; pCO2 <60
   Avea: FiO_2 <0.4; Rate 20; PEEP 5. PIP based on weight:

Weight	<750 gm	750-1000 gm	1001-1500 gm	>1500
Total PIP	13 cm H_2O	14 cm H_2O	15 cm H_2O	16 cm H_2O

7. Hold all sedation for at least 12h prior to extubation. Consider Narcan/Flumazenil rather than reintubation if oversedation occurs post extubation.
8. Call MD/NNP just prior to extubation.
9. Refer to NIV order set.
10. Follow Intubation & Extubation Criteria, post-extubation gas criteria (on NIPPV order set)
11. If extubation fails, consider conventional ventilation after reintubation.

Criteria for Initial Intubation/Extubation Failure/Reintubation & Extubation:

v.5-10-19	Initial Intubation Criteria /Extubation Failure Criteria/Reintubation Criteria
Considerations	• With the exception of FiO2, all criteria are the same for initial intubation, extubation failure, and reintubation • Extubation failure is defined as replacement of ETT within 72h of extubation due to pulmonary/apnea causes (i.e. not surgical). Reintubation is defined as replacement of ETT beyond 72h. • Meeting criteria below should prompt escalation to next NIV modality, if possible: HFNC→CPAP→NIPPV • All infants 22-23wks will be intubated in DR. Most 24 weekers will be intubated in DR. • Intubation should occur if criteria below are met on NIPPV
FiO2	Initial intubation: >40% for >2h Extubation failure or reintubation: >50%
pH	<7.2 (and CO2 as below, i.e. not metabolic)
pCO2	0-72h: 65 3+days: 70
Apnea	≥6 apnea episodes or significant bradys requiring stimulation in 6 consecutive hrs OR >1 episode requiring PPV in 12h shift
Other	Always allow provider discretion for "urgent need"
	Extubation Criteria
	Follow SLN Extubation Guidelines
FiO2	22-27wks: <40%
pCO2	22-27wks: <60
MAP	22-24wks: ≤8 25-27wks: ≤10
Vent rate	22-27wks: ≤20
ΔP	22-27wks: ≤15
PIP	PIP based on wt (13-16, see Extubation Guidelines)

NonInvasive Ventilation (NIV):

NIV refers to all forms of positive pressure delivered via a format other than an endotracheal tube. These include: NonInvasive Positive Pressure Ventilation (NIPPV), Biphasic ventilation (SiPAP or BiPAP), Continuous Positive Airway Pressure (CPAP), and Heated Humidified High Flow Nasal Cannula (HHHFNC). True NIPPV is presently only proposed as actual PIP, PEEP, and rate delivered via the Avea ventilator and the Fisher/Paykel Flexitrunk nasal apparatus.

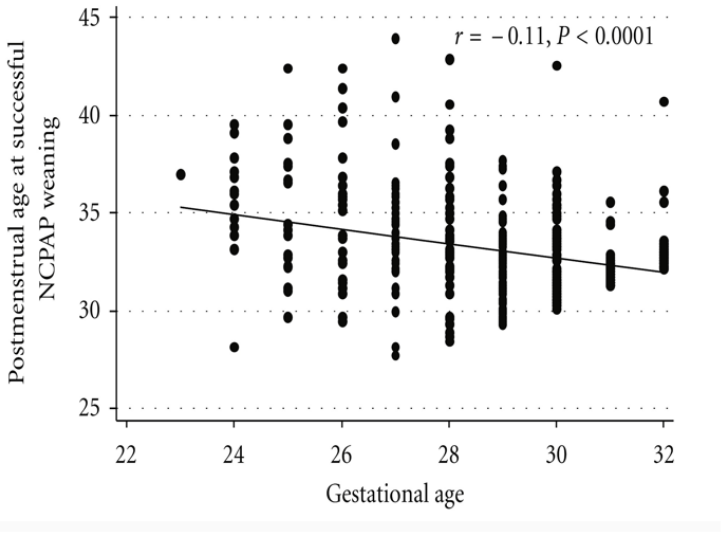
The following are the Basic Tenets of NIV:

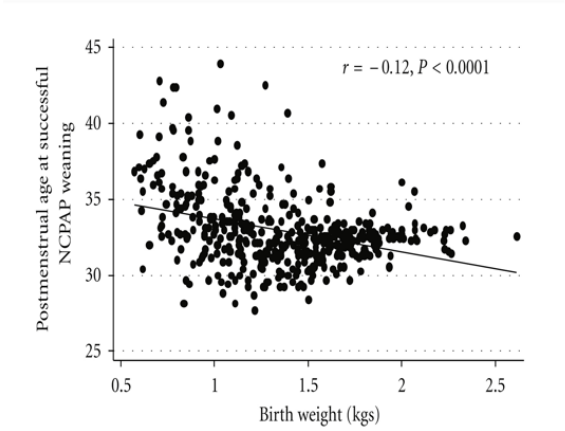
1. Evidence supports providing NIV for longer than we presently do (in 2019).
2. NIV should generally be continued until at least 32wks CGA.
3. Infants born >32wks likely warrant NIV for brief duration based on risk factors.
4. When HFNC is used to provide NIV, it should be used at higher flows, i.e. 5-7 lpm, and no less than 3 lpm.
5. As a general rule, NIV should be used as such:
    - NIPPV until at least 28 0/7wks CGA
    - CPAP from 28 wks to at least 32 0/7wks
    - HFNC (RAM or Infant Flow or VT) >32 0/7wks
6. Exceptions should be considered for issues such as severe head molding, skin breakdown.

The evidence supporting these tenets is based on multiple studies. Lam et al (2017) found that infants with an additional 2wks of CPAP had a significant increase in functional residual capacity (FRC) at the end of the two weeks. Spindel et al are, at the time of this writing, completing a primate study looking at pulmonary function studies following CPAP x 10d, with matched controls. Their study is based on other animal studies that have demonstrated increased lung volumes following positive pressure treatments, suggesting that CPAP may promote lung growth and development by mechanical stretching of the lung, similar to amniotic fluid during intrauterine life.

Jensen et al (2018) and Amatya et al (2015) both noted that successful weaning of CPAP prior to 32wks and 1600gm was rare in infants born less than 28wks EGA. Yang et al (2018) found similar results, and also noted that there were higher rates of BPD and ROP in both home O2 and low flow NC (≤2 lpm). Infants on home O2 also weaned faster but had higher rates of ROP and BPD. Based on these findings, it is recommended that infants be maintained on stable CPAP settings until at least >32wks and 1600gm.

Correlation btw GA/BW and PMA at successful CPAP weaning





Rastogi S, Rajasekhar H, Gupta A, Bhutada A, Tastogi D, Wong J. (2011). Factors Affecting the Weaning from Nasal CPAP in Preterm Neonates. Int J pediatr 2012: 416073. Doi: 10.1155/2012/416073

In the ELBW population, as a general rule, the pressure generated by HHHFNC is approximately 1cm H2O less than the flow rate, i.e. an infant on 6 lpm flow is likely experiencing ~5cm H2O distal airway pressure. This rationale, along with the above findings that infants on lower flow NC and home O2 had higher rates of ROP and BPD, lead to our recommendation that infants who are felt to truly need HHHFNC be maintained on no less than 3 lpm flow.

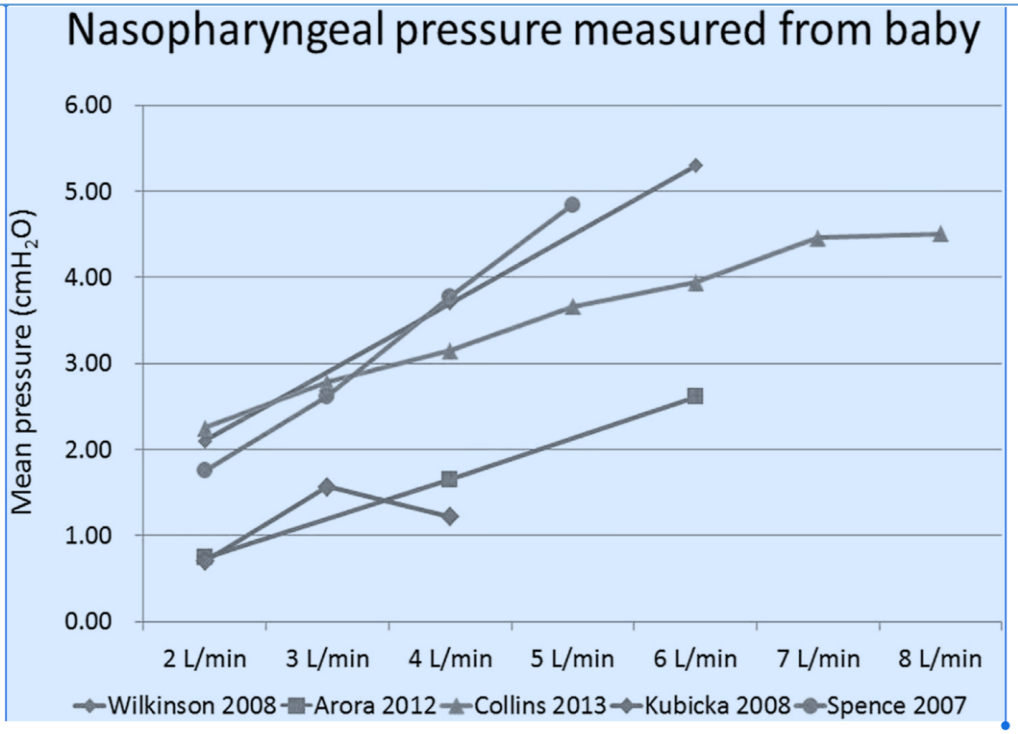


Figure 1 Nasopharyngeal pressure of infants during heated humidified high-flow nasal cannula.

Chao et al. 2017. *Pediatrics and Neonatology, 58*. 295-302.

The following guidelines have been developed to assist with the initiation, management, and weaning of the various forms of NIV. Note that while NIPPV Guidelines for infants ≥28wks at birth are technically outside the scope of these Small Baby Guidelines, they are included here for reference and convenience.

NIPPV Pathway <28wks:

INITIAL NIPPV AND WEANING GUIDELINE ON AVEA/FLEXITRUNK (<28 WKS AT BIRTH) v.12-11-20

INITIAL NIPPV SETTINGS: Total PIP 16, PEEP 6, Rate 20, i-Time 0.5 sec.

- Target initial MAP to approximate same as on ventilator, if just extubated
- Titrate to attain comfortable WOB, good 'roar,' appropriate blood gases
- MAX Settings: Total PIP 20-24, PEEP 8-10, Rate 50, i-Time 0.5 sec. (Note that max settings likely to be lower in acute phase; consider giving surfactant in acute phase if meets criteria.)

LAB WORK:

- POCT gases one hour following initiation and PRN (daily suggested if FiO2 >30%). Consider decreased frequency if TCOM in place and correlating, or if in chronic phase of lung disease.

MEDICATIONS:

- See Surfactant Delivery Guidelines.
- Caffeine 25 mg/kg IV x 1 load upon admission, then 10 mg/kg IV q 24hrs.

ADDITIONAL CONSIDERATIONS:

- CXR within 24 hours and PRN to assess for over/underinflation.
- Strict avoidance of overtightening headgear straps and pressure/folding of ear pinna.
- Transcutaneous pCO_2 monitor if skin integrity allows.
- Minimize time "off" NIPPV (<30sec) when switching mask/prongs to avoid atelectasis.

BLOOD GAS CRITERIA FOR NIPPV MANAGEMENT:

Age		Immediate Evaluation *Notify Provider* Recheck gas 30-60" after intervention	Increase PIP or rate pCO2	Hold pCO2	Wean PIP or rate pCO2	Immediate Evaluation *Notify Provider* Aggressive Wean Recheck gas 30-60"
0-72h	ABG/CBG	pH <7.2 OR pCO2 >70	56-70	45-55	40-45	pH >7.45 OR pCO2 <40
3+days	ABG/CBG	pH <7.2 OR pCO2 >70	66-70	50-65	40-49	pH >7.45 OR pCO2 <40

- Notify Provider if FiO2 >50% or rapidly increasing, or for worsening of A/B/D severity.
- Any value in "immediate evaluation" category takes precedence.
- Any gas rechecks due to "immediate evaluation" category are in addition to routinely scheduled gases.
- Titrate settings until stable in Hold range for 72h, then proceed to Weaning Approach.

WEANING APPROACH:

- Wean slowly as tolerated until Maintenance Settings reached.
- PIP changes should generally be by 1-2cm/change. Rate changes should be by 5-10 breaths/change.
- **Maintenance NIPPV Settings:** Total PIP 16; Rate 10-20; PEEP 5-7 (based on FiO2, inflation)
- At ~27wks CGA, begin weaning towards CPAP Criteria over ~1wk.

CPAP CRITERIA:

- Wean toward a mean airway pressure on NIPPV settings that can be approximated by straight CPAP by 28wks.
- Infants should generally be maintained on NIPPV until 28wks CGA prior to attempting CPAP
- Consideration may be given to trial of CPAP earlier than 28wks CGA in select infants with abd distention, however there should be low threshold for returning to NIPPV as evidence shows this decreases risk for reintubation.
- Once infant reaches 28wks CGA, refer to CPAP/BPD Guideline
- If unable to wean to CPAP by 29wks CGA, assess infant for other modifiable risk factors.

EXTUBATION FAILURE CRITERIA:

v.5-10-19	Initial Intubation Criteria /Extubation Failure Criteria/Reintubation Criteria
Considerations	• Intubation should occur if criteria below are met on NIPPV
FiO2	Initial intubation: >40% for >2h Extubation failure or reintubation: >50%
pH	<7.2 (and CO2 as below, i.e. not metabolic)
pCO2	0-72h: 65 3+days: 70
Apnea	≥6 apnea episodes or significant bradys requiring stimulation in 6 consecutive hrs OR >1 episode requiring PPV in 12h shift
Other	Always allow provider discretion for "urgent need"

- If extubation fails, consider conventional ventilation after reintubation.

NIPPV Pathway ≥28wks:

INITIAL NIPPV AND WEANING GUIDELINE ON AVEA/FLEXITRUNK (≥28 WKS AT BIRTH) v.12-11-20

INITIAL NIPPV SETTINGS: Total PIP 16, PEEP 6, Rate 20, i-Time 0.5 sec.

- Target initial MAP to approximate same as on ventilator, if just extubated
- Titrate to attain comfortable WOB, good 'roar,' appropriate blood gases
- MAX Settings: Total PIP 22-26, PEEP 8-10, Rate 50, i-Time 0.5 sec. (Note that max settings likely to be lower in acute phase; consider giving surfactant in acute phase if meets criteria.)

LAB WORK:

- POCT gases one hour following initiation and PRN (daily suggested if FiO2 >30%). Consider decreased frequency if TCOM in place and correlating, or if in chronic phase of lung disease.

MEDICATIONS:

- See Surfactant Delivery Guidelines.
- Caffeine 25 mg/kg IV x 1 load upon admission, then 10 mg/kg IV q 24hrs.

ADDITIONAL CONSIDERATIONS:

- CXR within 24 hours and PRN to assess for over/underinflation.
- Strict avoidance of overtightening headgear straps and pressure/folding of ear pinna.
- Transcutaneous pCO_2 monitor.
- Minimize time "off" NIPPV (<30sec) when switching mask/prongs to avoid atelectasis.

BLOOD GAS CRITERIA FOR NIPPV MANAGEMENT:

Age		Immediate Evaluation *Notify Provider* Recheck gas 30-60" after intervention	Increase PIP or rate pCO2	Hold pCO2	Wean PIP or rate pCO2	Immediate Evaluation *Notify Provider* Aggressive Wean Recheck gas 30-60"
0-72h	ABG/CBG	pH <7.2 OR pCO2 >70	56-70	45-55	40-45	pH >7.45 OR pCO2 <40
3+days	ABG/CBG	pH <7.2 OR pCO2 >70	66-70	50-65	40-49	pH >7.45 OR pCO2 <40

- Notify Provider if FiO2 >50% or rapidly increasing, or for worsening of A/B/D severity.
- Any value in "immediate evaluation" category takes precedence.
- Any gas rechecks due to "immediate evaluation" category are in addition to routinely scheduled gases.
- Titrate settings until stable in Hold range for 24-72h, then proceed to Weaning Approach.

WEANING APPROACH:

- Wean as tolerated until CPAP Criteria reached.
- PIP changes should generally be by 2cm/change. Rate changes should be by 5-10 breaths/change.

CPAP CRITERIA

- Wean toward a mean airway pressure on NIPPV settings that can be approximated by straight CPAP.
- Infants who are ≥ 28wks and require NIPPV may be considered for wean to CPAP after 24h of stability on above settings.
- Consideration may be given to trial of CPAP sooner in select infants with abd distention, however there should be low threshold for returning to NIPPV as evidence shows this decreases risk for intubation/reintubation.
- Refer to CPAP/BPD Guideline

EXTUBATION FAILURE CRITERIA:

v.5-10-19	Initial Intubation Criteria /Extubation Failure Criteria/Reintubation Criteria
Considerations	• Intubation should occur if criteria below are met on NIPPV
FiO2	Initial intubation: >40% for >2h Extubation failure or reintubation: >50%
pH	<7.2 (and CO2 as below, i.e. not metabolic)
pCO2	0-72h: 65 3+days: 70
Apnea	≥6 apnea episodes or significant bradys requiring stimulation in 6 consecutive hrs OR >1 episode requiring PPV in 12h shift
Other	Always allow provider discretion for "urgent need"

- If extubation fails, consider conventional ventilation after reintubation.

CPAP/BPD Pathway:

CPAP/BPD PATHWAY (<32 WKS AT BIRTH) v.12-11-20

CONSIDERATIONS:
- Infants <28 0/7wks CGA should generally be maintained on NIPPV.
- Maintain on CPAP until no WOB and baseline FiO2 <25% and at least 32 wks gestation.
- HHHFNC (RAM, Infant flow, or Vapotherm) should generally be reserved for infants born ≥32 0/7wks or those with skin breakdown or significant cranial molding issues.
- When weaning, goal is <10% increase in FiO2, comfortable WOB, RR<60 and pC02 50-65. No more than 6 apnea spells in 24 hours requiring stimulation.

INITIAL CPAP SETTINGS: Discontinue NIPPV rate and continue at approximate MAP achieved on NIPPV.

LAB WORK/IMAGING:
- POCT gases one hour following initiation and PRN.
- Weekly CBG
- Consider CXR within 6-24 hours with change in mode of support and PRN. Avoid hyperinflation.

ADDITIONAL CONSIDERATIONS:
- Transcutaneous pCO_2 monitor. May wish to avoid in chronic phase of disease.
- Minimize time off CPAP.
- Refer to NIV Skin Care Guidelines (TBD)
- Two staff members present for cares and/or when switching mask/prongs to avoid atelectasis.
- Weekly skin care rounds by respiratory team to evaluate for skin breakdown

WEANING DOWN CRITERIA*:
- Stability Criteria (must meet all criteria to wean)
  - FiO2 <25%
  - No significant apnea (>2 moderate episodes in 12h or >3 in 24h or any spell requiring PPV)
  - Saturations within criteria 90-95% most of the time.
  - Blood gas pH >7.25 pC02 <65 and base deficit <8 (if available)
- If any 2 or more failure criteria are met (see below) return to previous settings

WEANING OFF CRITERIA*:
- Maintain on CPAP+5 until ≥32 0/7wks and ≥1600gm. Once Stability Criteria met for 24-48 hrs and FiO2 21% proceed as below.
- Infant should be able to tolerate time off CPAP during cares up to 15 min or more
- Goal to get to PEEP 5 FiO2 21%, and hold until all criteria are met, then trial straight to RA
- If fails room air due to desaturations, then may trial LFNC: if significant ROP may use 0.5LPM NC blended oxygen (goal baseline FiO2 need <30%), if no sig ROP may use home O2 (max for 2-3 kg is ⅛ LPM, 3-4 kg is ¼ LPM, 4-5 kg is ½ LPM)

FAILURE OF WEAN OR WEAN OFF:
- Significantly increased work of breathing
- Tachypnea >60 for >2hrs and retractions
- Significant apnea (>2 episodes in 12h or >3 in 24h or any spell requiring PPV)
- Increased FiO2 >10% (follow graph in room for infants on home oxygen)
- Abnormal blood gas with pCO2 >65
- If failure criteria met after RA/LFNC attempt, and infant remains <34wks, return to CPAP 5 for one week
- Monitor for failure criteria for 7 days once off support.

***IF STILL CPAP DEPENDENT AT 36 WEEKS:**
- Consider airway evaluation if clinical indication
- Consider GER pathway
- Weekly blood gas to evaluate for chronic retention
- Consider continuing caffeine until no longer requiring positive pressure
- Echo at 36 wks and prior to d/c to evaluate for PHN (consider monthly in severe cases)
- Pulmonology consult around 38-40 weeks
- OT to work with infants on oral feedings
- Older infants with BPD may require higher PEEP (+8/+9) to maintain FRC- goal to keep FiO2 < 25% and they may do RA/LFNC trial q 1-2 weeks directly from higher PEEP
- **May consider prolonged CPAP up to 50 weeks CGA if improving and no significant issues other than BPD**

Vitamin A:

Multiple studies have been undertaken to assess the potential benefit of using intramuscular Vitamin A administration to decrease chronic lung disease (CLD) in ELBW infants. While some studies have shown benefit, others have been inconclusive. The most recent Cochrane review from 2016 provides the following background: "Vitamin A is a group of fat-soluble compounds used by the body for regulation and promotion of growth and differentiation of many cells, including cells in the retina of the eye and the cells that line the air passages in the lungs. Preterm infants have low vitamin A levels at birth. This may contribute to an increased risk of developing chronic lung disease and hence a requirement for oxygen. It is possible that an additional vitamin A supplement may reduce complications of prematurity, including abnormal development of the retina (retinopathy), bleeding in the brain (intraventricular hemorrhage), and damage to the gut from inflammation (necrotizing enterocolitis) as well as reducing respiratory infections."

Further review of the literature by the St. Luke's Neonatology team suggests that with our current rates of CLD, Vitamin A has potential to benefit our population, with a predicted number needed to treat (NNT) of 13. Recent historical challenges have included a multiyear lack of availability of Vitamin A due to pharmaceutical constraints. Once it was released back to the market, the cost per vial had been raised to cost-prohibitive levels. Those costs have now come down substantially, and our team now believes that the cost-benefit ratio supports implementation of Vitamin A treatment for all infants <28wks of GA at birth. The dosing regimen is included below.

- Vitamin A 5000 international units IM 3x per week (Mon/Wed/Fri) x 12 doses
    - If day of birth is on Sun/Mon, begin dosing on Wed.
    - If day of birth is on Tue/Wed, begin dosing on Fri.
    - If day of birth is on Thu/Fri/Sat, begin dosing on Mon.

Vitamin A must be given as a series of 12 intramuscular injections. It cannot be reliably delivered enterally due to erratic absorption, or IV due to photosensitivity and tubing adherence (and IV preparation is not presently available). Care should be taken to manage pain during the injections. For infants who are receiving other types of pain management (such as scheduled or PRN opiates), it would be appropriate to slightly alter the timing of Vitamin A administration to coincide with this pain management. If opiates are not presently prescribed, then the use of sucrose and comfort measures and timing with other painful procedures is encouraged.

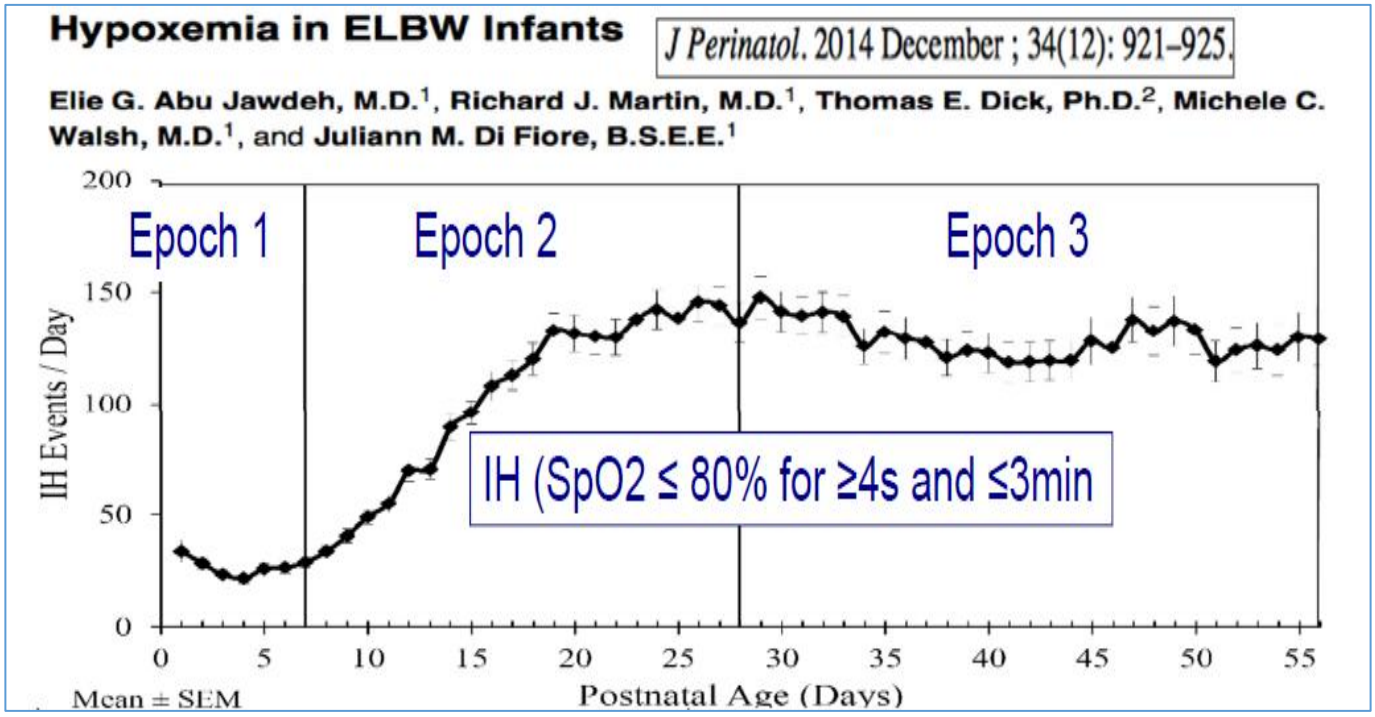
Apnea and Bradycardia:

Apnea occurs frequently in preterm infants due to multiple factors. Apnea of prematurity (AOP) is defined as the sudden cessation of breathing that lasts for at least 20 seconds or is accompanied by bradycardia or oxygen desaturation in an infant younger than 37wks postmenstrual age. Most apneic events are central (ie, cessation of respiratory effort), and the disorder is thought to be caused by immaturity of neurologic and respiratory control mechanisms.

The pathophysiology of AOP is secondary to the ventilatory response to CO_2 which increases with advancing postnatal and gestational age in preterm human infants. The breathing response to CO_2 in preterm infants is impaired when compared with term neonates or adults, and it appears that this difference is both quantitative and qualitative. While term neonates and adults increase their ventilation through an increase in both tidal volume and frequency, preterm infants do not appear to increase frequency in response to CO_2.

Bradycardia that accompanies apnea and resultant desaturation is attributed to hypoxic stimulation of carotid body chemoreceptors, especially in the absence of lung inflation. This likely explains why maintaining positive end expiratory pressure, through either invasive or noninvasive means, tends to decrease both apnea and bradycardia spells.

ELBW infants typically experience a predictable increase in apnea, bradycardia, and desaturation (A/B/Ds) spells over the first weeks of life. The frequency of these spells tends to peak at around 3 to 4 weeks chronologic age, then slowly decrease over the next several weeks. While infection is always in the differential for infants with increasing A/B/Ds, anticipating this natural increase can be helpful in avoiding unnecessary workups for sepsis when other factors do not suggest active infection. Additionally, avoiding significant weaning of noninvasive ventilatory support during this 3-6 week time frame appears to increase stability and decrease overall frequency of A/B/Ds. The study graph below shows an excellent representation of the natural progression of spell frequency over time (please disregard the Epochs, they are related to other aspects of the study).



The neonatal breathing pattern matures with increasing postmenstrual age. Nonetheless, preterm infants continue to have more episodes of prolonged apnea than infants born at term until about 43 weeks postmenstrual age. Some infants, especially those born ≤28 weeks gestation, may have persistent apneic spells at 37 to 40 weeks postmenstrual age (PMA) when

they may otherwise be ready for discharge to home from the hospital. The earlier the gestational age at delivery, the longer AOP may be expected to persist.

Late preterm infants and occasionally term infants may also have symptomatic periodic breathing with corresponding bradycardia and desaturations. These tend to be of shorter duration and often peak around 3-5 days of age, when the catecholamine surge from delivery typically reaches its nadir.

Caffeine:

Caffeine is one of a subclass of medications known as methylxanthines which are competitive inhibitors of adenosine receptors. Adenosine is an inhibitory neuromodulator of respiratory drive. Blockage of adenosine receptors by methylxanthines results in increased ventilatory responsiveness to carbon dioxide, reversal of central hypoxic depression of breathing, enhanced force of diaphragmatic contraction, and improved pharyngeal muscle tone. All of these effects contribute to a significant reduction in A/B/Ds, with the effect increasing with increasing GA.

Unlike many medications in neonatology, caffeine has been heavily studied with numerous well-designed randomized controlled trials demonstrating safety and efficacy. The CAP trial (Schmidt 2006) demonstrated improved survival without neurodevelopmental disability and long-term safety of caffeine therapy. Even when intubated, infants should remain on caffeine therapy unless side effects are present as this may improve respiratory drive and facilitate weaning from the ventilator. There may also be some beneficial diuretic effect that is conferred.

Caffeine should be initiated on all ELBW infants on admission. Dosing is 25mg/kg load then 10mg/kg per day unless tachycardic. The dose should be weight adjusted weekly until at least 32wks, then only weight adjust as necessary for increasing or persistent A/B/Ds. If the infant has minimal spells and is off all positive pressure, consider discontinuing at 36wks CGA or phase II on new feeding guideline (PO up to 4x per day). Note that due to caffeine's long half-life, and the extended duration of symptomatic apnea of prematurity in the SBG population, these infants should be monitored for at least 7 days post discontinuation. Infants greater than 27 weeks may be considered for caffeine discontinuation at 34wks.

Caffeine may need to be continued for longer duration in infants who remain on positive pressure (HFNC or greater) at the time of usual discontinuation.

Bronchodilators:

Bronchodilators improve lung compliance by relaxing smooth muscle cell and decreasing airway resistance. Albuterol is most commonly used, however ipratropium bromide has also been well-studied. Changes in pulmonary mechanics may last as long as 4-6 hours after administration. Adverse effects are typically limited to transiently increased blood pressure and heart rate. Ipratropium bromide is a muscarinic antagonist that is related to atropine; however, it may have bronchodilator effects more potent than those of albuterol. Improvements in pulmonary mechanics were demonstrated in patients with bronchopulmonary dysplasia after they received ipratropium bromide by inhalation. Combined therapy with albuterol and

ipratropium bromide may be more effective than either agent alone, with few adverse effects noted.

Infants <28wks should be considered for a trial of albuterol at 3-4 weeks of age (1.25 -2.5mg dosing), particularly for infants remaining mechanically intubated or with an increase in spells over preceding week. Start dosing at q6h x 48h. If improvement is noted, continue treatment until off positive pressure with minimal spells. Consider decreasing frequency to q12h, but monitor for increased spells and note that typical improvement wanes after 4-6h. Consider changing to Xopenex if the infant develops significant tachycardia. Note that PRN dosing is unlikely to be effective. It is also important to note that improvement in spells and pulmonary mechanics may lead to staff suggestions to discontinue treatment, at which point it is imperative to educate that this improvement is actually an indication to *continue* treatment.

Corticosteroids:

Many researchers have evaluated the effects of early administration of dexamethasone to prevent bronchopulmonary dysplasia, often demonstrating short-term improvements in clinical outcome. However, Papile et al (1998) reported that early use of dexamethasone during the first 2 weeks of life did not prevent bronchopulmonary dysplasia and may worsen neurologic outcome. Infants who received a combination of dexamethasone and indomethacin were at increased risk of spontaneous intestinal perforation. Neurodevelopmental follow-up studies of infants treated with prolonged and high-dose dexamethasone suggest that, though this therapy improves short-term pulmonary outcome, long-term outcomes appear to considerably worsen (Stark 2001).

Studies of inhaled glucocorticoid therapy have suggested that the only beneficial effect was a reduction in the use of systemic corticosteroids in infants receiving inhaled steroids. However concerns about systemic absorption (hypertension), associated complications, drug delivery, and current restrictions on systemic dexamethasone use have markedly decreased the use of this therapeutic approach.

The *routine* use of dexamethasone in infants with bronchopulmonary dysplasia is not currently recommended. The American Academy of Pediatrics and the Canadian Society of Pediatrics do not advocate the routine use of corticosteroids in preterm neonates to treat bronchopulmonary dysplasia. Despite these recommendations, dexamethasone is still used in carefully selected patients who have substantially increased ventilatory requirements when approaching 1 month of age.

Based on agreement reached by SL Neonatology in May 2020, we plan to use the NICHD BPD calculator to guide our use of postnatal dexamethasone. Data from the NICHD Neonatal Research Network were used to develop a web-based BPD estimator that accurately predicts the risk of bronchopulmonary dysplasia (BPD)-defined according to the Eunice Kennedy Shriver National Institute of Child Health and Human Development consensus definition of no, mild, moderate, and severe BPD (Jobe 2001) - as well as the competing outcome of death, by

postnatal day. The population includes infants 23-30 weeks gestation and 501-1250 grams birth weight.

Using meta- regression analysis, the authors demonstrated that rates of cerebral palsy and mortality were greater in infants treated with steroids when underlying risk for BPD was low but lower when BPD risk was high. Although the optimal threshold for treatment has not been determined, it has been proposed to use a 40% combined risk of death or severe BPD (Schmidt and Kirpalani, 2019).

DART Protocol dosing should be followed and is available via order sets within Epic (10d and 6d courses both available, however based on May 2020 group agreement, in most cases 10d course is preferred). Dosing should be avoided at <14d of age due to concerns with increased negative neurodevelopmental impact. Additionally, short-term efficacy is reduced the later that dosing is initiated. Therefore, the data would suggest that the optimal time for dosing is ~21d of age in order to attain greatest benefit while minimizing risk. It is strongly recommended that parents are made aware of the risks, benefits, and alternatives of corticosteroid therapy prior to administration, and that these discussions are documented within the medical record.

Our agreed upon approach to steroid therapy utilizing the NICHD BPD calculator is as follows:

NICHD BPD Calculator for Steroid Use:

St Luke's Children's Hospital

NICHD BPD Calculator for Steroid Use
v. 5-6-20

WEBSITE: https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start

1. Utilize BPD Outcome Estimator for all infants <28wks GA
2. Input data at 21 days of life
3. Utilize ≥ 40% combined risk of death or severe BPD as treatment threshold
4. If combined risk at 21d is 30-40%, consider inputting data again at 28d
5. If decision to treat, complete full 10d DART course

Of note, routine use of *inhaled* steroids should not be initiated unless recommended by SL Peds Pulmonology.

Diuretics:

Little data exists supporting the effectiveness of routine diuretic use. Significant electrolyte and nutritional disturbances are common when utilizing both short-acting and chronic diuretics.

As of January 2019, there is insufficient evidence from prospective randomized controlled trials of diuretics that have shown improvements in either the prevention of BPD or alteration in the long-term course of the condition that would justify widespread use of diuretics in this population. Per Micheal et al, Boston Children's, 2018, "…current evidence does not support routine use of furosemide for the prevention of BPD. However, symptomatic management of pulmonary edema justifies its use for selected patients."

Short term improvements in pulmonary function (improved compliance, decreased pulmonary vascular resistance, decreased pulmonary edema) have been documented with furosemide (Micheal 2018). However, the most recent Cochrane Review (2011) of enteral or IV furosemide concluded the following:

1. In infants > 3 wk of age with BPD, a single 1 mg/kg dose of furosemide improves lung compliance and airway resistance for only 1 hr.
2. Chronic administration of furosemide improves oxygenation and compliance.
3. Overall routine or chronic administration of furosemide cannot be recommended based on current evidence.

A Phase II multicenter trial of furosemide in infant's < 29 wk is underway as of December 2018 to assess safety, however it is not powered to assess outcomes.

Potential side effects of furosemide include hypokalemia, hyponatremia, hypochloremia, contraction alkalosis, hypocalcemia, osteopenia, nephrocalcinosis, ototoxicity, and possibly increased risk for PDA.

Overall data on the use of chlorothiazide (Diuril) and spironolactone (Aldactone) in the modern era are sparse. A Cochrane Review of 6 studies suggested some improvement in lung mechanics and less need for furosemide with a 4-week course of chlorothiaze and spironolactone (Cochrane Review 2011).

Based on the paucity of data showing efficacy or improvement in long-term outcomes, St. Luke's Neonatology's position is that diuretics should not be routinely utilized, however there may be case-specific instances where a brief trial of diuretics may be entertained. When utilized, the recommended approach is to employ a brief, 3-day course of furosemide. If there is objective evidence of improvement, as indicated by at least 5% reduction in baseline FiO2, then fluids should be restricted by as much as nutritional delivery will allow (ideally at least 10-20ml/kg/day) and then furosemide should be discontinued. Suggested dosing is 1mg/kg IV or 2mg/kg PO daily x 3 days, and if no significant increase in UOP is noted after the first 24h, then bid dosing may be attempted on day 2 and 3. Electrolytes should be monitored closely during treatment.

It is worth noting that in almost all historic cases of infants who have been discharged on chronic diuretics, SL Peds Pulmonology allows infants to outgrow the dose and then discontinues the medication. Per the Pulmonologist, diuretics are seldom if ever used in outpatient management.

Chronic Respiratory Care for the Infant with BPD:

Definitions of BPD vary, but the most accepted is the need for oxygen or respiratory support at 36 wks PMA. Mild BPD may be defined by an effective FiO2 <30% and NO positive pressure requirement. Severe BPD may be defined by an effective FiO2 >/= 30% AND/OR a requirement for positive pressure. There are 2 types of severe BPD:

- Type 1 = CPAP or HHHFNC >2LPM at 36 wks PMA
- Type 2 = Ventilator dependence at 36 wks PMD

There are some important concepts about risk of acquiring BPD. We know that early attempts at extubation and less time on a ventilator decreases the risk of BPD (Subramaniam 2016, Robbins 2015, Walsh 2005). We also know that early cumulative oxygen predicts BPD in ELBW infants (Wai 2016) and that CPAP can better support infants with RDS and decrease length of time of oxygen requirement when compared to HHHFNC (Murki 2018, Abdel-Hady 2011). Another study showed that prolonging CPAP 2 weeks beyond meeting stability criteria in infants born </+ 32 wks CGA increased FRC through discharge (Lam 2020). This CPAP need is based on both chest wall compliance (which decreases as the baby gets older) as well as lung compliance (which improves as a baby's lung disease resolves). CPAP can support the baby until these processes are improved enough for the baby to generate enough negative pressure with a breath to maintain an optimal FRC (typically at least 32-34 weeks CGA, longer if poor lung compliance due to more severe disease). Oxygen, therefore, should not be traded for pressure due to this physiology. The goal is to use enough pressure to maintain optimal inflation and avoid atelectasis with the least amount of oxygen necessary to maintain proper saturations.

Our guideline for the non-invasive respiratory support of the ELBW, therefore, emphasizes the use of CPAP until at least 32 weeks CGA. At that time, RA may be attempted if the baby is in 21% oxygen, and not having significant A/B/D events or work of breathing. Failure requires return to CPAP. Low flow oxygen trials may be started at 34 weeks for infants that are not meeting saturation criteria in RA and have no work of breathing or significant apnea/bradycardia events. The flow rate of the low flow oxygen should be **no more** than the effective fraction of inspired oxygen of 30% - this is dependent on the size of the baby (~⅛ LPM for 2-3 kg baby, ¼ LPM for 3-4 kg baby, ½ LPM for 4-5 kg baby). For babies that have severe BPD, a higher peep may be required to maintain an optimal FRC until they meet criteria for a low flow oxygen trial (i.e. no work of breathing or significant apnea/bradycardia events, Fio2 <25%, proper linear growth).

Infants with severe BPD require a significant amount of multidisciplinary care. To address controversies and promote research to improve the care of children with severe BPD, the "BPD Collaborative" was formed. This collaborative includes a group of multidisciplinary clinicians from interdisciplinary care programs for infants with severe BPD from several major medical center. Their recommendations have informed our approach to these infants. (Abman 2017). Evaluation may include workup for GER/aspiration, airway evaluation, and echocardiography to assess for pulmonary hypertension. Infants with Type 2 severe BPD who are still ventilator dependent at term may be assessed for tracheostomy. While tracheostomy should not be significantly delayed in babies that will definitely need it (DeMauro 2014, Jun Luo 2018, Cammack 2020), babies with Type 1 severe BPD on CPAP may be able to wean off (in the

absence of other severe pathology) by 50-52 weeks CGA and thus avoid tracheostomy given the significant amount of growth that occurs during this time. It is very important for these infants to receive developmental care (especially by their families) as well as feeding therapies (by occupational therapy) and range of motion/movement therapies (by PT).

BPD Chronic Care Guidelines:

BPD Chronic Care Guidelines
For Infants Born <32wks w Evolving CLDz of Prematurity
v.12-11-20

1. CPAP need is based on both chest wall compliance (becomes less compliant as baby gets older (~>32-34 weeks gestation) as well as lung compliance (becomes more compliant as baby's lung disease resolves).

2. Oxygen should not be traded for pressure due to this physiology.

3. Goal of CPAP is to help baby maintain FRC as both above improve (i.e. minimize work of breathing). If this is being done optimally, O2 requirement should ideally be low (≤25%) while maintaining SpO2 >90% (more optimally 95%).

4. An infant should be maintained on CPAP until no significant WOB (baseline RR <80, no significant retractions or A/B/D spells- at rest as well as when active) and baseline O2 need ≤ 25% and at least 32 weeks gestation. CPAP may be weaned weekly toward a PEEP of +5 if criteria are met. At this time, the infant may trial RA (if stable on 21%) or low flow NC oxygen.

-If no significant ROP may use home oxygen (max for 2-3 kg is ⅛ LPM, 3-4 kg is ¼ LPM, 4-5 kg is ½ LPM)
-If significant ROP may need to use ½ LPM NC blended oxygen (goal baseline FiO2 need <30%)

An infant with severe BPD may need a higher peep on CPAP as they grow to maintain FRC (particularly those >36 weeks). LFNC trials may be done directly from these higher PEEPs if infant does not have increased WOB and baseline FiO2 need ≤25% (as above).

5. If an infant develops WOB on low flow O2 (or RA), infant needs to go back to CPAP for a week to allow time for growth, improvement in chest wall compliance/lung compliance. If an infant only has low baseline sats or mild desats on RA, low flow O2 may be tried (as above).

6. Histograms should be used if available to help optimize time in target saturations (90-95%). If unavailable, may need to consider having baseline SpO2 always >92%.

7. Medications – Systemic or inhaled steroid administration may have a beneficial effect in treating or preventing BPD exacerbations (based on data from other similar pulmonary diseases) but are not well studied in this population. They should be considered on an individualized basis and in consultation with Peds Pulm. Consider scheduled bronchodilators for infants with evidence of reactive airway disease.

8. If there are concerns for pathologic GER (and possible aspiration) – see GER pathway for management.

9. Airway evaluations (flexible laryngoscopy, rigid bronchoscopy) should be considered if clinical indication (stridor, suprasternal retractions, inability to tolerate ANY time off of CPAP, etc.).

10. Consider weekly blood gas to evaluate for chronic CO2 retention (this really should be relatively normal if the infant truly has no significant increased work of breathing).

11. HHHFNC is not a part of this pathway unless there are extenuating circumstances such as skin breakdown. When it is used, it should be used for the **SHORTEST** duration possible.

12. Consider continuing caffeine until infant no longer requires positive pressure.

13. Echo at 36 wks GA and prior to d/c as these infants are at risk for developing pulmonary hypertension. Infants with more severe BPD may require additional imaging (i.e. every 1-2 months) if hospitalization expected beyond 42-44 weeks CGA. If pulmonary hypertension is diagnosed, consult Peds Cardiology for ongoing management.

14. Peds Pulmonology consultation around 38-40 weeks.

15. OT should be involved with all of these infants to work on oral feeding stimulation, possibly limited oral feeding once they show stability with holding and readiness signs (likely >35-36 weeks). PT and PMR consultation is also appropriate to assess and maximize proper development.

16. Weekly skin care rounds by respiratory team are an essential part of CPAP success (as well as daily by nursing and RT).

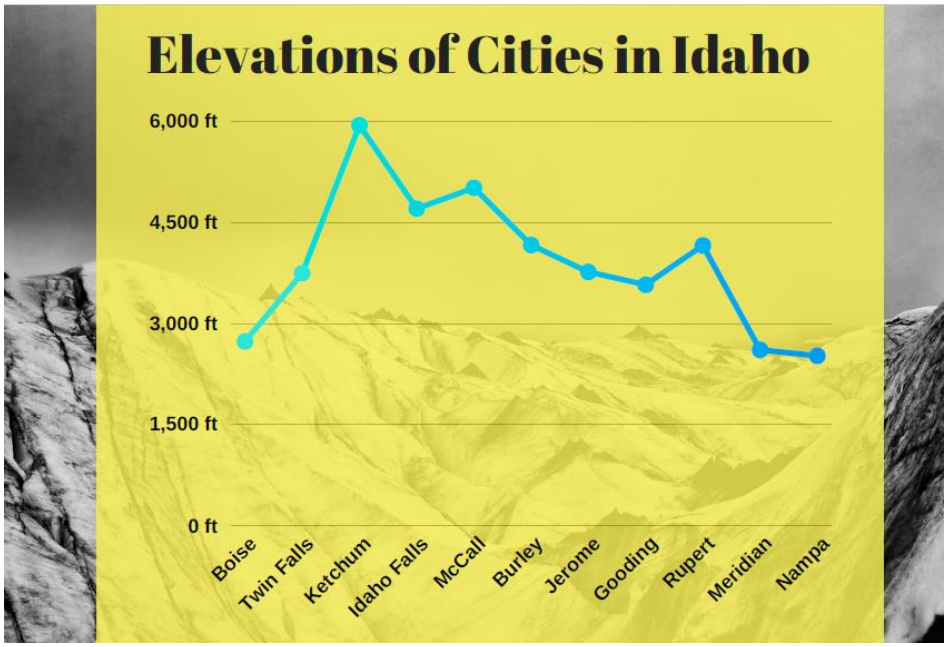
17. GT should be considered at time of trach if a baby is not able to wean from CPAP (for most kids with BPD – this would be around 50-52 wks) or once weaned to LFNC and not progressing on oral feeding in timely manner. Consider a PEG tube at this point and limiting intubation/mechanical ventilation as much as possible (discuss with Peds Surgery/Peds GI to determine best course of action). May consider GT earlier if indicated especially if baby needs another surgical procedure.

See also references in the Small Baby Guideline – Full Version

Home Oxygen and High-Altitude Recommendations:

Infants born <28wks are at increased likelihood for requiring home oxygen at discharge to maintain adequate saturations and to decrease metabolic demand, thereby improving growth. Due to the nature of Idaho's geography and our referral area, infants with stable SpO2 and reasonable growth at Boise's 2700ft altitude may experience desaturations and/or growth failure if discharged to higher altitudes. As such, the following recommendations have been developed for these infants.

- If the patient is on oxygen, nearing d/c, and going to higher elevation, do not attempt further weaning and allow that to take place at home facility or under the supervision of home pediatrician.
- If the patient is on RA and going to higher elevation, educate the parents that there is a possibility of the infant going back on oxygen due to the higher elevation and that this is not a setback, but rather just the infant acclimating to the higher altitude.
- If the infant is on RA and is going to a higher altitude, have a system of oxygen saturation monitoring in place when the infant arrives in their home community (PMD office, local ED) to ensure there is no need for supplemental oxygen while the infant is acclimating to the higher elevation.



St. Luke's Pediatric Pulmonology Consultations:

We are fortunate to have a skilled Pediatric Pulmonologist at our disposal for consults and curbside questions. The following are indications which should prompt consideration for a Peds Pulmonology consult.

- Any infant discharged home with O2. Consult Peds Pulm 1-2 weeks prior to anticipated discharge. Infants will be seen in-hospital prior to discharge.
- Any infant under consideration for tracheostomy placement. Peds Pulm supports PICU transfer for post-operative trach management unless significant ongoing prematurity-related issues suggest more appropriate ongoing management in NICU.
- All infants with confirmed or suspected cystic fibrosis. A 24h On-Call Service now exists which will engage all appropriate members of the CF team.
- Infants discharged home on caffeine and apnea/SpO2 monitor.

Cardiovascular

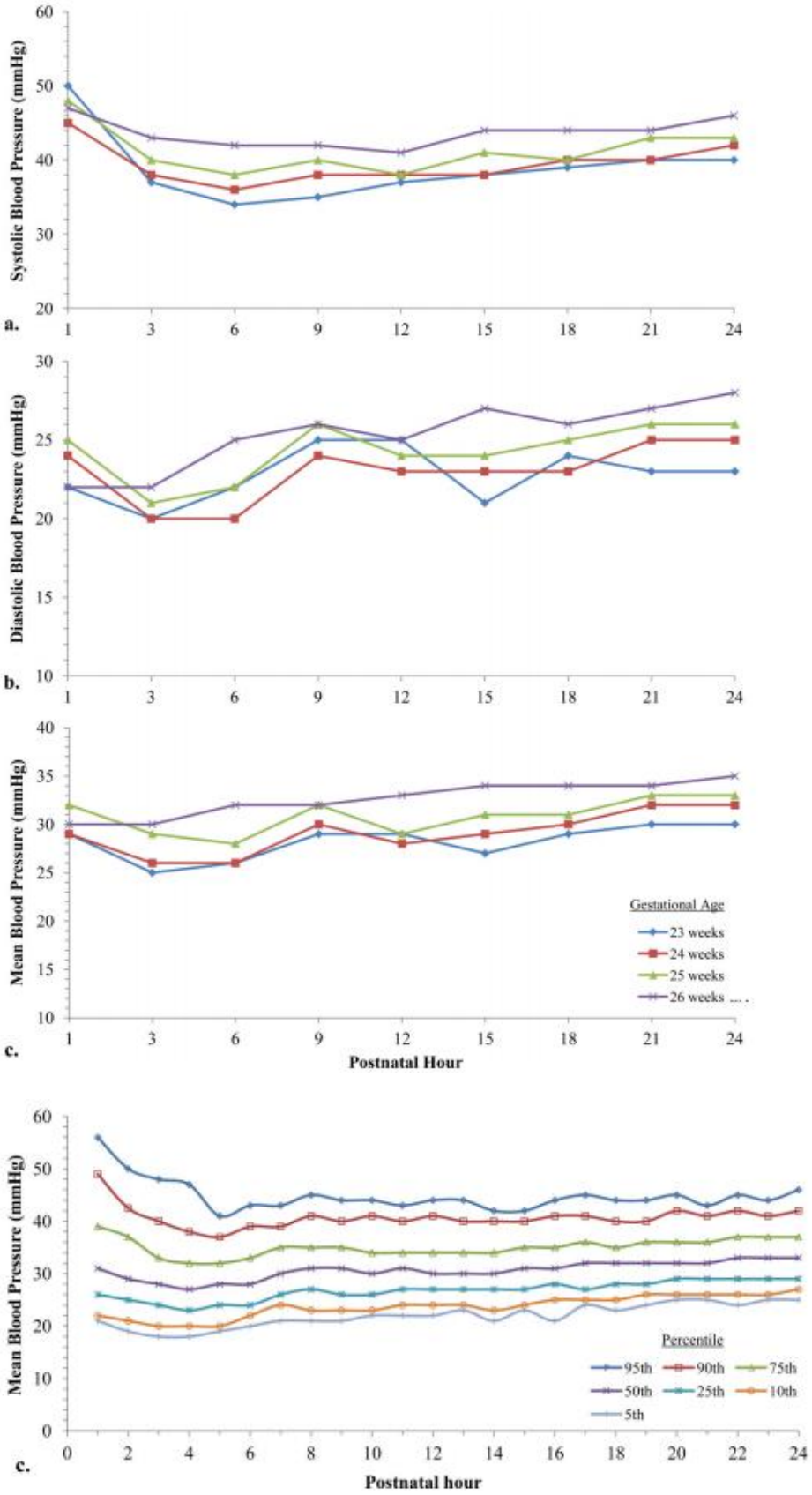
Management of Hypoperfusion and Hypotension:

Perfusion pressure is what provides adequate oxygen and nutrient delivery to end organs. Blood pressure is only one measurement of perfusion pressure and depends on vascular tone. An adequate blood pressure in one patient may not be adequate in another patient with different vascular resistance. Other measurements of perfusion include capillary refill time, renal perfusion (Cr, urine output) and tissue oxygenation (lactic acidosis/metabolic acidosis). Because a "normal" blood pressure has not been identified in the ELBW population, our goal is to ensure adequate perfusion to end organs using these other measurements/assessment tools. Due to the fragile nature of the skin in this population, BP should be measured via the UAC transducer if a line is in place with a good waveform.

In a patient with low BP but what seems like adequate perfusion pressure (normal capillary refill, perfusion to extremities, pulses, labs), NIRS and/or bedside echo for venous flow may be of use to assess need for intervention as well as determine if intervention is working.

Most infants are euvolemic to volume overloaded at birth unless there is clear indication of volume loss such as abruption or other bleeding. This is even truer with the advent of delayed cord clamping. Given the negative impact of volume overload on RDS and PDA, volume should be used restrictively. When giving fluid boluses, rapid infusion is associated with IVH, therefore only in cases of severe blood loss should the bolus be given faster than 30 minutes. Inotropes and hydrocortisone can be very effective at improving hypotension and hypoperfusion without resulting in excessive fluid administration. When used, hydrocortisone should be dosed in mg/kg. Always use caution with concomitant use of ibuprofen or indomethacin. While hydrocortisone does not appear to have the same deleterious effects of dexamethasone and appears instead to have a fairly favorable safety profile, judicious use seems to be prudent. If fluid resuscitation and low dose dopamine do not resolve hypotension, infants should be given a "test dose" of 1 mg/kg with an objective assessment of response. If no objective response is noted, it should not be continued. If response is noted, as demonstrated by improvement in BP, decrease in vasopressor requirements, and/or improvement in UOP, then dosing should be continued. Once off vasopressors for at least 24h, hydrocortisone should be weaned slowly over the next 10 days while monitoring closely for signs of new-onset adrenal insufficiency. An ACTH stim test should be considered prior to discharge for any infant who has received >21 days of steroids.

The following figures demonstrate the gestational age specific changes in the systolic, diastolic, and mean arterial blood pressure 50th percentile curves over the first 24 hours, followed by the average mean blood pressure percentiles of a large cohort (n=367) of extremely preterm infants. The subsequent algorithm should be used when possible for the management of hypotension and hypoperfusion in this population.



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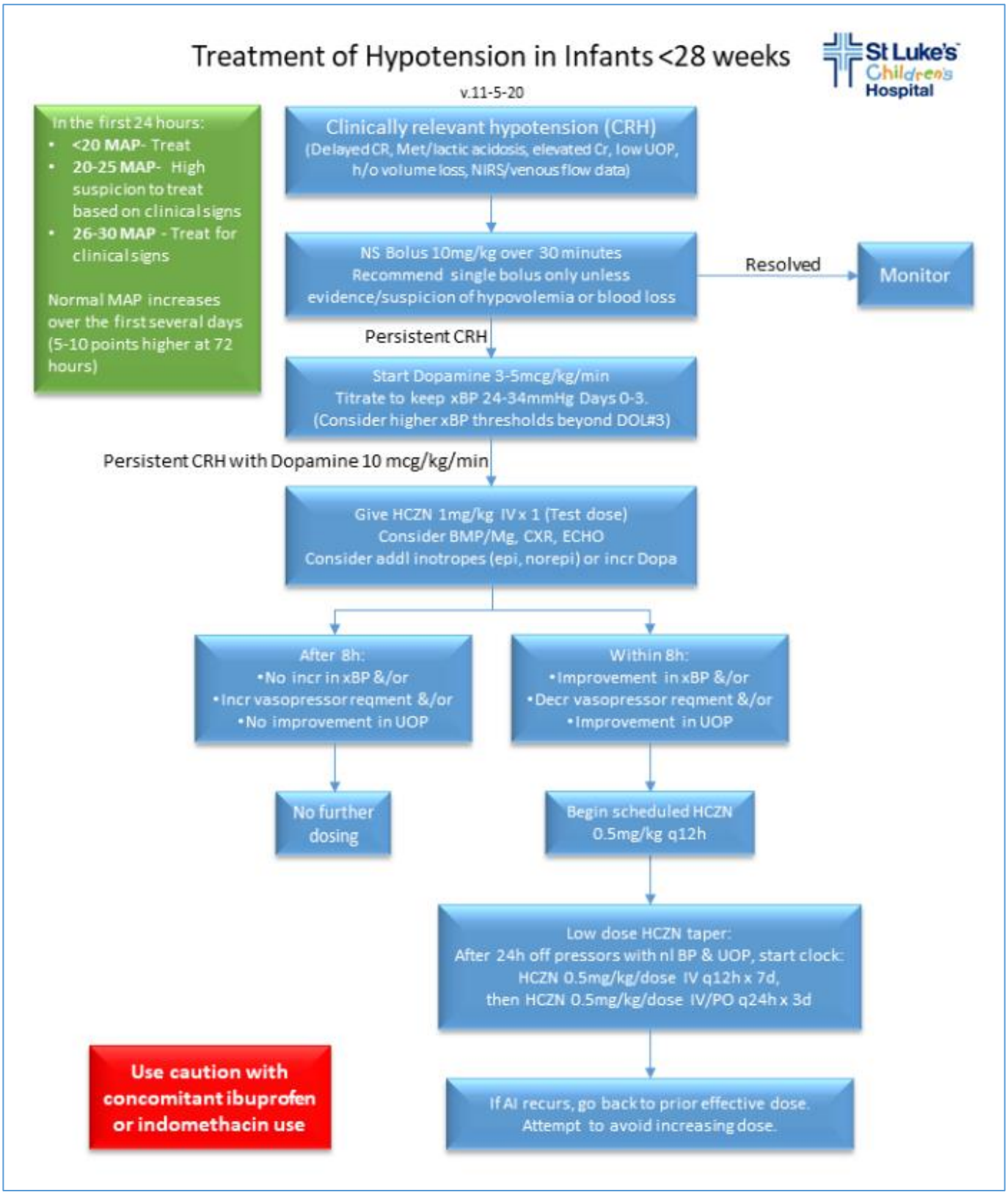
Treatment of Hypotension in ELBW Infants:



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Patent Ductus Arteriosus:

Patent ductus arteriosus (PDA) is a common problem in the ELBW infant with rates that are inversely proportional to gestational age[1]. A PDA has been associated, but importantly not proven to be causative, of multiple morbidities including bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage. Treatments, both prophylactic and rescue, for the PDA have included the prostaglandin inhibitors (indomethacin and ibuprofen) and surgical ligation with the aim that PDA closure would prevent the aforementioned morbidities.

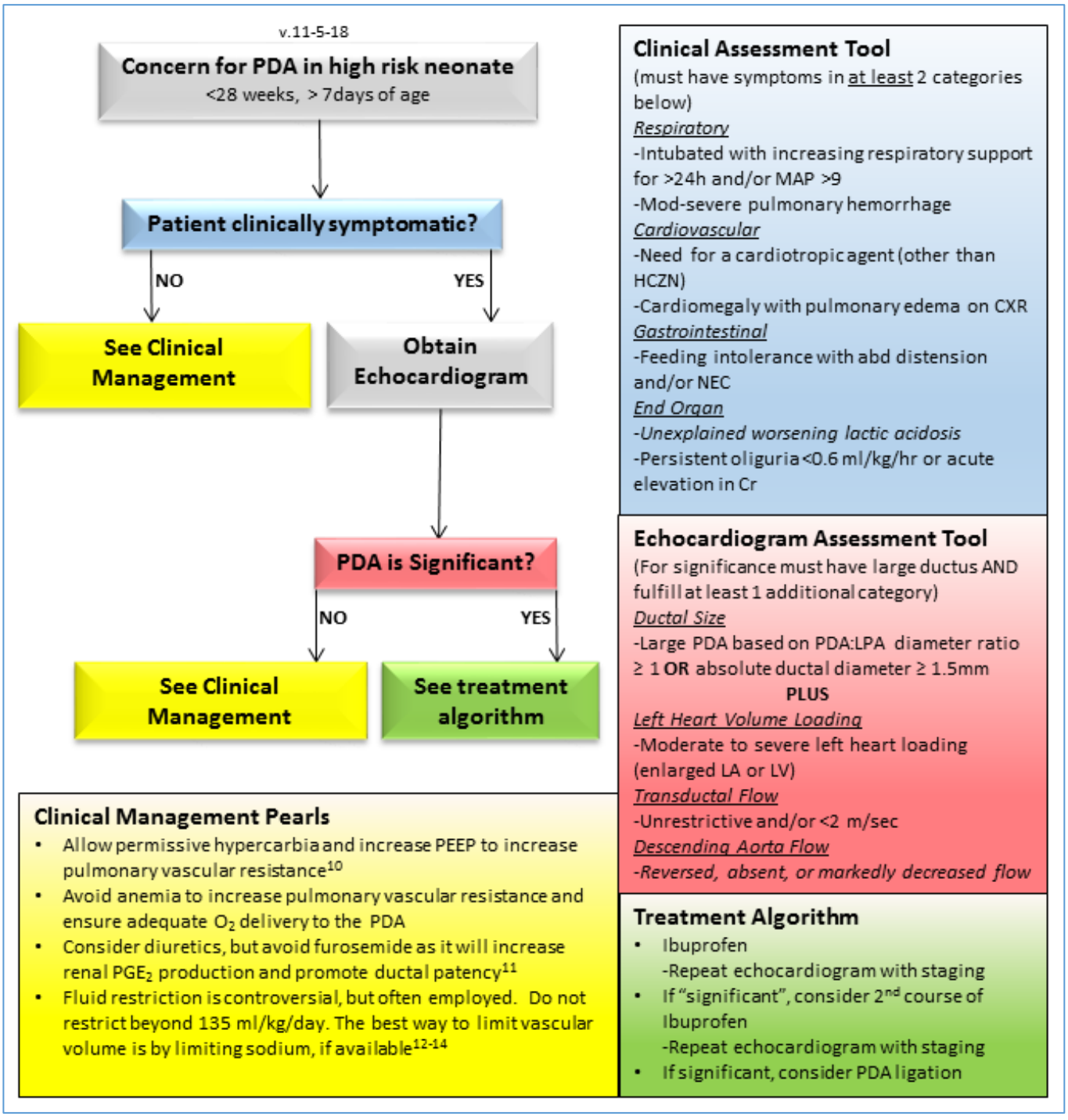
Current treatments for the PDA have come under great scrutiny in recent years due to lack of evidence for improvement in neonatal outcomes[2-4]. Many centers are now moving away from aggressive treatment of the PDA to a more conservative approach[5-9]. In addition to the risks of immediate operative complications of ligation such as bleeding, infection, pneumothorax, chylothorax, and inadvertent ligation of the pulmonary artery, there are also increased risks of long term complications such as vocal cord paresis, diaphragm paresis, and spinal and chest wall deformities from the thoracotomy incision.

In an effort to standardize echographic interpretation of PDA size, it is recommended that the PDA to left pulmonary artery (LPA) ratio be used.

- PDA:LPA ratio < 0.5 indicates small PDA
- PDA:LPA ratio ≥ 0.5 but < 1 indicates moderate PDA
- PDA:LPA ratio ≥ 1 indicates large PDA

The algorithm below is aimed at aligning our management of the PDA with best available evidence.

PDA Management Algorithm:



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Hypertension:

Neonatal hypertension is defined as persistent systolic and/or diastolic blood pressure (BP) that exceeds the 95th percentile for corrected gestational age. As there is a lack of normative data as well as many factors that affect normal BP values during the neonatal period, it has been difficult to develop a standardized definition of hypertension for clinical use in this age group.

A reference table of normal BP values at or after two weeks of age in infants between 26 and 44 weeks post-conceptual age (PCA) has been published (Dionne 2012).

PCA (weeks)	SBP (mmHg) – 95th percentile	DBP (mmHg) – 95th percentile	MAP (mmHg) – 95th percentile
26	72	50	57
28	75	50	58
30	80	55	63
32	83	55	64
34	85	55	65
36	87	65	72
38	92	65	74
40	95	65	75
42	98	65	76
44	105	68	80

Common etiologies of hypertension in premature infants:

1. Renal (renal artery thrombosis, renal vein thrombosis, renal artery stenosis, renal parenchymal disease, severely obstructed urinary tract, low renal mass/impaired nephrogenesis, nephrocalcinosis, acute tubular necrosis, cortical necrosis)
2. Cardiovascular (coarctation/interrupted aortic arch, distal aortic thrombosis, fluid overload)
3. Endocrine (congenital adrenal hyperplasia, hyperaldosteronism, hyperthyroidism, adrenal hemorrhage, hypercalcemia)
4. Bronchopulmonary dysplasia
5. Medications (dexamethasone, caffeine, adrenergic agents, bronchodilators)
6. Neurological (pain, seizures, intracranial hypertension, drug withdrawal, HIE)

Measurement:

The gold standard for blood pressure measurement is an appropriately calibrated intra-arterial catheter. If there is not a catheter in place, blood pressure is most commonly measured with an oscillometric manometer (e.g. Dinamap). Blood pressure should be taken in the right upper arm unless contraindicated (e.g. PICC line, fracture, etc.) when babies are asleep or quietly awake and not feeding (systolic BP is 5mmHg lower in sleeping babies and is higher after a feed) with an appropriate sized cuff. The cuff bladder should measure 2/3 of the length of the extremity, and 0.44 to 0.55 of the arm circumference (Flynn 2014). If the choice is difficult, err

on the side of choosing the larger rather than smaller cuff. After cuff placement, the infant should be left undisturbed for 15 minutes and then 3 successive BP readings obtained at 2-minute intervals (Flynn 2014). The first reading (when taken with an oscillometric monitor) should be disregarded.

Initial Hypertension Evaluation:

1. Ensure proper measurement technique and cuff size – check q6h trend for a couple of days and obtain multiple readings at given measurement session
2. Review of history (h/o umbilical catheters, diuretic use (increases risk of obstructive stones), recent discontinuation of narcotics, etc.)
3. Review medication list
4. Evaluate for pain
5. Obtain 4 extremity blood pressures
6. Echocardiogram (evaluate for coarctation, LVH)
7. Obtain both renal ultrasound (done by radiology) and renal dopplers (done by vascular)
8. Obtain labs: urinalysis, renal function panel, renin/aldosterone

Consult nephrology for further evaluation once these studies are obtained. They may consider further laboratory studies such as cortisol, thyroid function, and evaluate need to start treatment.

Neurology

Extremely low birth weight infants are born prior to the critical organization stage of central nervous system (CNS) formation, characterized by the development of synaptic networks, dendritic growth, myelination, apoptosis and pruning. In addition, maturation of arterial vasculature in the CNS does not complete in the basal ganglia and diencephalon until 24-28 weeks GA and even later in the cortex and germinal matrix. Despite many advances in care of these ELBW infants in the NICU, avoiding neurologic injury and interference with appropriate CNS development remains challenging. Since the critical CNS organization and maturation are taking place during the period that ELBW infants experience NICU care, diligent multidisciplinary approaches are warranted in order to promote better cognitive, behavioral, and motor outcomes. (Altimier 2018).

The incidence of any-stage IVH remains ~25% for infants born < 1500gms or 22-28 weeks gestation. The incidence of severe IVH (Grade 3-4) in VLBW infants appears to be decreasing. Rates dropped from 19% in 1993 to 15% in 2012 but remained about the same for infants of 22-24 weeks gestation (Stoll 2015). Importantly for therapeutic strategies, most IVH occurs within the first 24 hours of life with 90% diagnosed by DOL #4 (Al-Abdi 2014).

While we know that both lower gestational age and birth weight increase the relative risk of incurring CNS injury, the mechanisms of these injuries are not completely understood. One could postulate that the earlier an infant is born, the less time normal CNS development has had to occur and the more frequent and intense are the noxious stimuli experienced in the extra-uterine environment. Similarly, one could argue that the less mature infant's developing brain has less adaptable circulation and stability leading to higher rate of injury. It is not difficult to postulate that both physiologic immaturity of these extremely premature infants and the required NICU environment can lead to profound neurologic injury during this critical phase of brain development.

Recommendations for Minimizing Neural Injury:

We have divided the most recent recommendations from the literature review of ELBW care into two main parts. This first part, "Recommendations for Minimizing Neural Injury," addresses common practices that may help to ameliorate injury and is detailed below and summarized at the end of this chapter. The details and summary of the second part, "Recommendations to Maximize Normal Development," can be found in the SBG Developmental chapter. As with all care of the ELBW infant, some recommendations may conflict with other systems-based recommendations and the risk and benefits of each should be evaluated to determine the ideal approach. For instance, ideally, pH and CO_2 should be kept as normal as possible for neuroprotection, however, ventilation and early extubation strategies allow for permissive hypercapnia in order to decrease lung injury and improve other outcomes (see Respiratory chapter).

Mechanisms of ELBW Neural Injury:

Most of the neural injuries to ELBW infants can be traced to the combination of fragile, immature cerebral blood vessels, primarily in the germinal matrix, and a reduced capacity to regulate Cerebral Blood Flow (CBF). In adults and children, CBF is tightly autoregulated so that for a relatively large range of systemic blood pressure, CBF remains constant. CBF is dependent on both mechanical and metabolic components. Perfusion pressure (PP, which is essentially systemic BP), intracranial pressure (ICP) and arterial resistance all interact to determine CBF. For a given BP and ICP, the body regulates the resistance (through multiple signals) to auto-regulate CBF.

Extremely premature infants have a significantly decreased ability to autoregulate cerebral blood flow often resulting in "passive" cerebral circulation, where changes in systemic or intracranial pressure result in similar changes in cerebral flow, placing them at higher risk for intracranial hemorrhage and/or hypoperfusion injury (Figure 1). Acute increases in BP can result in acute increase in CBF and therefore bleeding. Conversely, acute decreases in BP or increases in ICP can lead to neuronal death due to decreased oxygen and nutrient delivery to the brain followed by subsequent reperfusion injury. Autoregulation can also be negatively affected by aberrations in electrolytes, glucose levels, acid/base balance, and carbon dioxide as well as many signaling molecules (Figure 2).

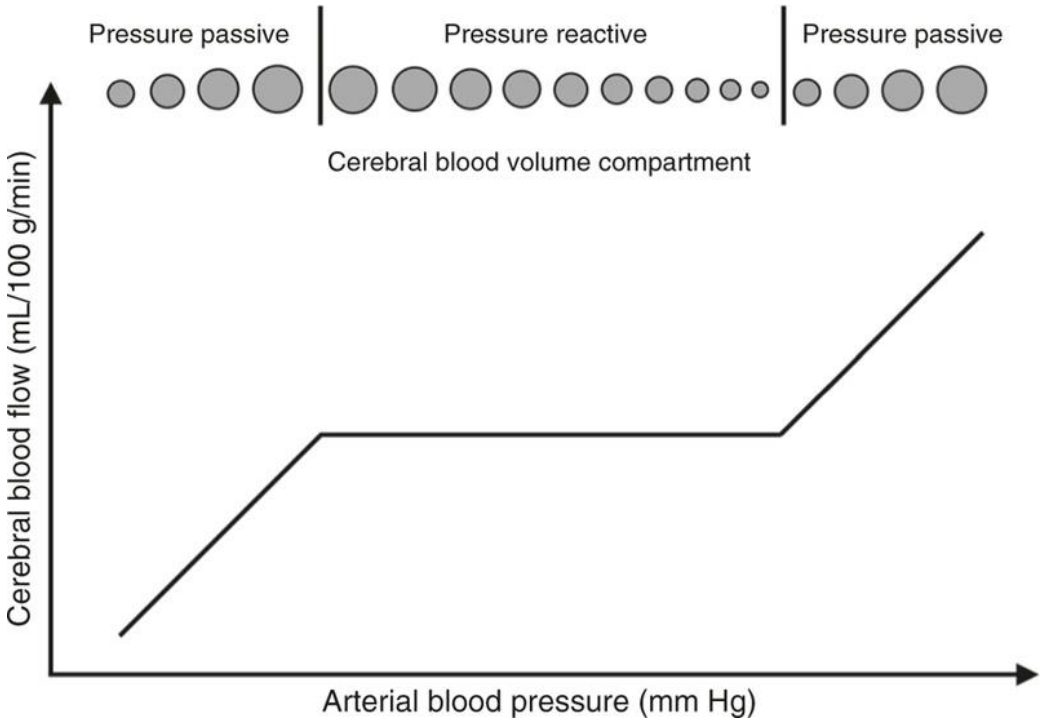


Figure 1. Autoregulation is the physiologic mechanism that maintains a constant blood flow to the brain constant across a range of blood pressure. The flat area of the curve is a state of pressure reactivity where BP and blood flow go in opposite directions. However, outside the range of auto-regulation on the two ends is a state of pressure passivity where blood flow is purely dependent on BP. There is no more reactivity in the vessels. Low arterial BP would then result in ischemia, while high arterial BP results in edema and possible further ischemia and/or hemorrhage.
Pediatr Res. Author manuscript; available in PMC 2019 Mar 18.

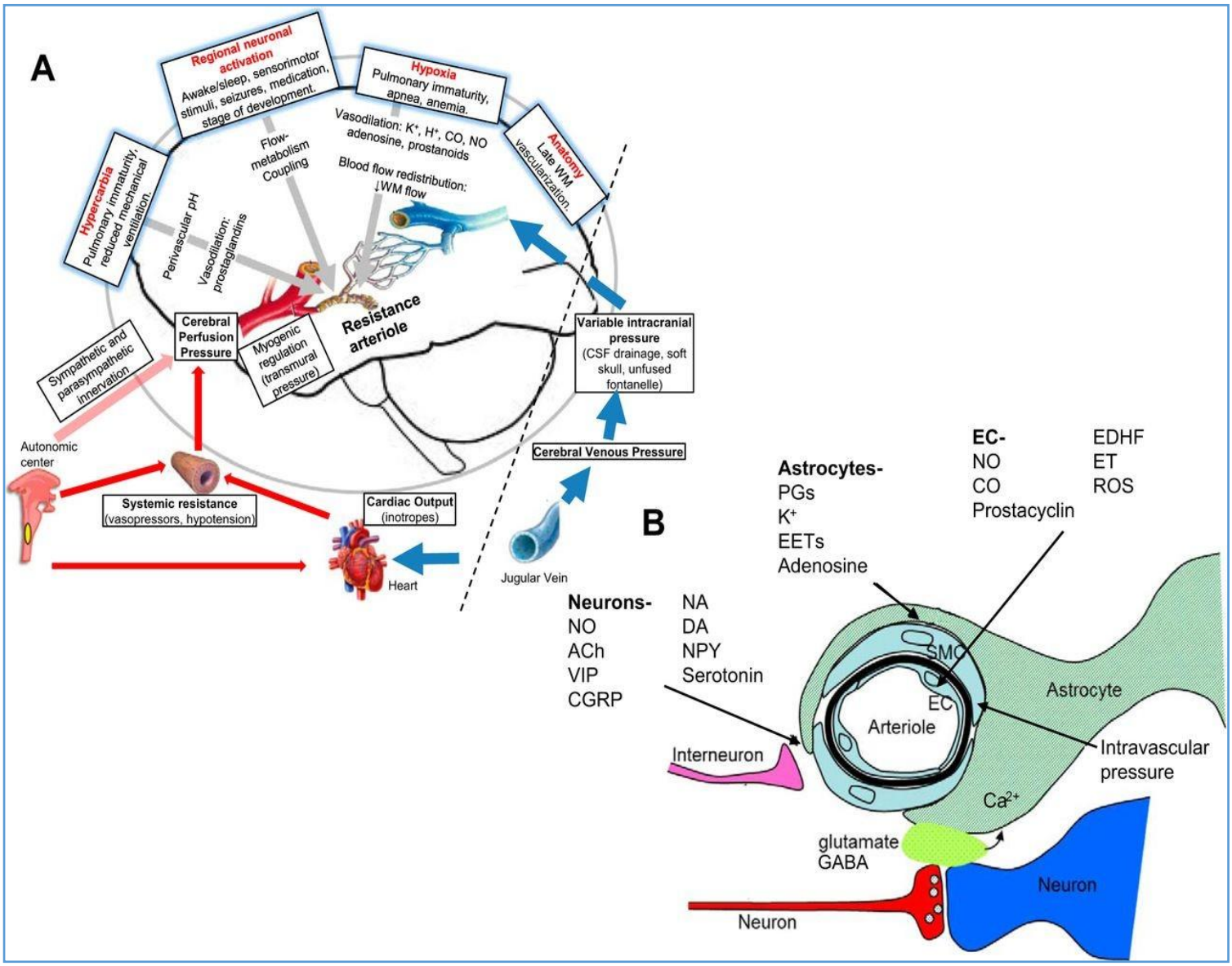


Figure 2. A: Major factors contributing to cerebral blood flow (CBF) regulation in newborn infants. Cerebral perfusion pressure, hypercarbia, hypoxia, regional neuronal activation, and immature vascular anatomy (left side of dotted line) are major determinants of CBF in newborns. The vascular tone of cerebral resistance arterioles is modulated by numerous factors, primarily transmural pressure, perivascular pH, neuronal metabolism, and numerous vasodilatory molecules such as potassium (K^+), hydrogen ions (H^+), carbon monoxide (CO), nitric oxide (NO), prostaglandins, prostanoids, and adenosine. Intracranial pressure and cerebral venous pressure (right side of dotted line) play a more significant role in CBF regulation in the adult brain. B: Neurovascular unit in cerebral resistance arteriole, illustrating relationship between arteriole, interneuron, astrocyte, and neuron-secreted factors on smooth muscle cells, which regulate vascular diameter. (WM: white matter; SMC: smooth muscle cell; EC: endothelial cell; Ach: acetylcholine; PGs: prostaglandins; EETs: epoxyeicosatrienoic acids; VIP: vasoactive intestinal polypeptide; CGRP: calcitonin gene related peptide; NA: noradrenaline; DA: dopamine; NPY: neuropeptide Y; EDHF: endothelium derived hyperpolarizing factor; ET: endothelin; GABA: γ-aminobutyric acid; ROS: reactive oxygen species. https://doi.org/10.1152/ajpregu.00487.2013

The following is the rationale and data (where available) to support the subsequent summary of recommendations for minimizing neural injury.

ANTENATAL CARE

Antenatal Corticosteroid Administration:

The benefits of antenatal corticosteroid (ACS) administration have been well demonstrated for infants delivered as early as 24 weeks, however there are limited data and no current recommendations in the literature to support the use of ACS at gestational ages less than 24 weeks. Despite this paucity, there are many institutions providing a comprehensive, proactive approach for mothers and infants beginning at 22 weeks gestation and demonstrating improving outcomes for these periviable infants. Given the clear benefit at 24 weeks, and the lack of data for 22-23 week gestational infants, we feel it is more likely that steroids provide greater benefit than risk of harm at these extreme gestations. Therefore, SL Neonatology supports the administration of antenatal corticosteroids as early as 21 5/7 weeks gestation if proactive support is desired by parents facing eminent delivery at 22 weeks. See also Perinatal chapter above.

Magnesium Sulfate:

The American College of Obstetricians and Gynecologists continues to support the administration of magnesium sulfate to mothers with anticipated early preterm delivery to reduce the risk of cerebral palsy in surviving infants. Meta-analyses of five RCTs using magnesium sulfate as a neuroprotectant showed amelioration of cerebral palsy at 2 years. A meta-analysis of individual participant data from these trials showed an equally strong decrease in cerebral palsy and the combined risk of fetal/infant death and cerebral palsy at 2 years (Chollat 2018).

Maternal Transport:

Conflicting studies suggest that neonatal transport of the ELBW infant is associated with increased rates of IVH and other morbidities. Given this possible association, maternal transport to a tertiary care center, whenever possible and safe for the mother, is preferable to transport of a critically ill ELBW infant (Lim 2019).

POSTNATAL CARE

Delayed Cord Clamping (DCC):

In multiple studies, DCC has been shown to decrease the incidence of all grades of IVH, but did not show any benefit in severe IVH (Obstet Gynecol 2017). In addition, DCC may help maintain a more consistent target mean blood pressure and decrease the need for volume boluses. Conflicting studies on the safety of Umbilical Cord Milking (UCM) in the ELBW due to the acute rise in ICP prevent us from recommending UCM < 28 week infants until further

studies have been completed (Perlman 2015). See also Hematology chapter. We therefore recommend DCC in vigorous ELBW infants but not UCM as has been recommended by AAP and ACOG.

Intubation:

Neonates with birth weights less than 750gm who experienced more than 3 intubation attempts in the first 4 days after birth were 28 times more likely to develop severe IVH (J Peds 2016). Therefore, we recommend that the most experienced provider available attempt intubation when needed in this gestational age group. Similarly, trials of extubation should be done with relative confidence of success. Again, the most proficient provider available should attempt reintubation if necessary and if possible, Rapid Sequence Intubation methodology should be employed. See also Respiratory chapter.

Temperature Regulation:

Appropriate temperature regulation is important for many bodily functions from cellular metabolism to cardiac function. One cohort study of 8782 VLBW infants with 52% demonstrating some degree of hypothermia demonstrated no increased risk of IVH with mild hypothermia (36.0-36.4˚C) but higher risk for severe IVH with moderate hypothermia (32.9-35.9˚C) (Miller 2011). Therefore, we recommend maintaining tight control of temperature using the NRP guidelines for prewarming the delivery room and the SLHS isolette/humidity protocol. See also Thermoregulation/Integumentary chapter.

Cerebral Perfusion:

In order to maintain the most stable cerebral perfusion, it is necessary to address the 3 components that determine perfusion: BP, ICP, and autoregulation through vessel constriction.

1) Blood Pressure

The data supporting the role of blood pressure and hypotension on cerebral perfusion pressure (CPP) in neonatal brain injury is mixed. Given that CBF measurement is difficult in premature infants, indirect inferences often are made about the integrity of CPP which may be inaccurate. Recent studies suggest that during the early period after premature birth, blood pressure may be a poor indicator of cerebral perfusion pressure (du Plessis 2008). Evans and colleagues have used functional echocardiography to measure cardiac output and superior vena cava (SVC) flow as a surrogate for cerebral blood flow to show that during the first 12 hours of life a substantial minority of premature infants develop low-flow states in the systemic and cerebral circulations. These low-flow states are poorly associated with blood pressure and are not improved by the use of pressor-inotropes (Osborn 2002). This may account for data suggesting that while hypotension is harmful, our interventions (pressors and volume) often don't improve outcomes. See also Cardiovascular chapter. Other studies have corroborated the poor relationship between cerebral perfusion and systemic blood pressure in the early

premature period (Weindling 2001). Using continuous cerebral NIRS and arterial blood pressure measurements, Soul et al (2007) showed an association between the prevalence of hypotension and cerebral pressure passivity in premature infants. However, the ability to predict cerebral pressure passivity from the blood pressure was poor. Using NIRs and EEG, there is some suggestion that the lower BP limit of the cerebral autoregulatory plateau is between 23 and 30mmHg in very preterm infants (Brew 2014). Given this information we recommend that BP be optimized through a combination of physical exam and monitoring that could include NIRS and Point of care Ultrasound to assess cardiac output and inferior vena cava return (as a surrogate of central venous pressure) combined with the judicious use of volume and pressors. See also Cardiovascular chapter.

2) Intracranial Pressure (ICP)

CBF can be markedly affected by acute changes in ICP. ICP can be affected by multiple transient factors, most of which affect central venous pressure, such as overdistension of the lungs, tension pneumothorax, acute increases in venous return (rapid IV infusions), and occlusion of jugular veins (acute head turning).

In order to avoid lung overdistension it may be necessary to obtain frequent CXRs in the first 72 hours of life depending on the type of ventilation strategy (see also Respiratory chapter). Similarly, avoid and treat tension pneumothorax aggressively.

Volume boluses are to be given slowly (over 30 minutes) and flushes slowly (see also Cardiovascular chapter).

While there is ample evidence in adult studies regarding the impact of maintaining midline and elevated head positioning in ICU patients, the data in ELBW infants is much less rigorous. However in a 2018 study, 180 ELBW infants of <1000gm were randomized into either FLAT (supine and head rotated 90 degrees Left/Midline/Right every 4 hours, n=90) or ELEV (head midline up 30 degrees with no rotation, n=90) for the first 4 days of life. The ELEV group developed significantly fewer grade 4 hemorrhages (p=0.036) and survival to discharge was significantly higher in the ELEV group (p=0.037)(Kochan 2018).

We recommend that following delivery, there should be meticulously careful handling of the infant with as little movement as possible. The head should be kept midline and once in isolette and films obtained, the head of the bed should be elevated for the first 72 hours of life (we do not feel development and insertion of a device to raise the bed completely to 30 degrees as opposed to 12-15 degrees obtainable in the Giraffe isolette are warranted given the difficulty of their use). Minimize movements during repositioning that could increase ICP acutely (like lifting legs higher than head to place diaper) or care that is noxious like suctioning or lab testing without sedation.

3) Maintain Autoregulation by Avoidance of Vasodilation and Vasoconstriction

Eucapnia:

Extremes of pCO2 levels have been implicated in prematurity-related brain injury. Hypercapnia during the first 3 days of life increased the risk for severe IVH probably through vasodilation and engorgement of cerebral microvasculature. In addition, hypercapnia may limit the normal response to stimuli such as hypotension and hypoxemia, predisposing to hypoxic-ischemic insults, although this is temporary and resolves in the face of chronic hypercapnia (Kaiser 2006).

Conversely, severe hypocapnia may cause sustained vasoconstriction and an increase in oxygen-hemoglobin affinity thereby limiting cerebral oxygen delivery. Severe hypocapnia from the first 7 DOL has been associated with cystic periventricular leukomalacia in premature infants (du Plessis 2008). Therefore, we recommend normalization of pCO2 levels (40-55) especially in the first 72 hours as is reasonable within the requirements of other recommendations (see also Respiratory chapter).

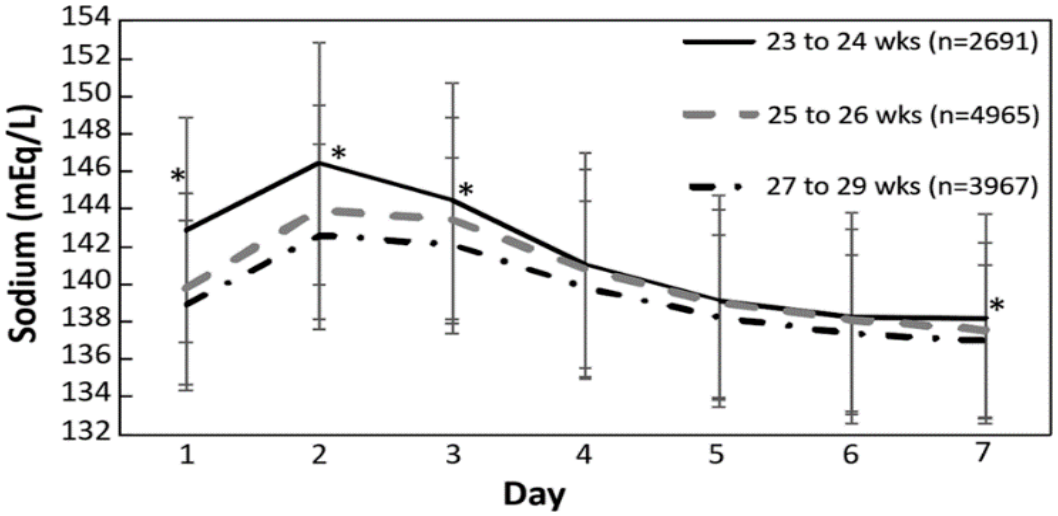
Oxygenation:

Because a fundamental goal of the cerebral circulation and its regulatory systems is to maintain an appropriate oxygen supply responsive to cerebral demands, hypoxemia is a potent and robust vasodilatory stimulus. Hypoxemia contributes to cerebral vasodilation and increased CBF to maintain oxygen delivery (Brew 2014). Any form of reduced arterial oxygen content—a reduction in hemoglobin, oxygen-hemoglobin affinity, or partial pressure of oxygen—increases cerebral blood flow. It is also important to note that the vasodilation response to hypoxemia is more potent and overrides vasoconstriction caused by hypocapnia. Furthermore, hypoxemic vasodilation can persist during sustained hypoxemia but can be rapidly reversed with restoration of normoxia (du Plessis 2008).

Conversely, hyperoxemia has been shown to trigger vasoconstriction and a decrease in cerebral blood flow in an immature canine model and this effect may be most prominent in earlier gestations. Numerous recent studies have led to our recommendation to target saturations in the 90-95% range (see also Respiratory chapter). Every attempt should be made to attempt tight control of saturation during the first 72 hours of life, avoiding frequent desaturations and/or hyperoxia. Additionally, Hct should be maintained as recommended per the transfusion guidelines (see also Hematology section).

Electrolytes:

Control of electrolyte levels, in particular Na, can be very difficult in the ELBW infant especially in the first week of life. A recent retrospective study demonstrated abnormal Na levels in up to 85% of ELBW infants.



Daily sodium levels (mean ± SEM) over first 7 days of life. N=11,623 (excludes 805 infants with renal insufficiency). 27-29wk infants had significantly lower sodium values on all measured days compared with the two younger gestational age cohorts. Repeated-measures ANOVA with Tukey–Kramer correction where *$p < 0.0001$ between 23/24 weeks and 25/26 week.

This study also demonstrated an increased rate of mortality but not necessarily specific neural injury. Dysnatremia in extremely low birth weight infants is associated with multiple adverse outcomes (Monnikendam 2019). Other literature suggests that hypernatremia during the first week of life has an association with greater severity of IVH and adverse neurodevelopmental outcomes (Dalton 2015. Baraton 2009). We recommend meticulous fluid and Na management to attempt to maintain Na within a normal range.

Glucose:

The importance of avoiding hypoglycemia for neuroprotection remains self-evident from numerous studies, although defining what level of hypoglycemia and the duration to cause harm remains undefined in the ELBW population. Hyperglycemia is also potentially harmful due to both changes in osmolality and coupling between circulating glucose levels and cerebral blood flow. One study retrospectively looked at 859 infants <32wks, 66 of whom developed hyperglycemia, at 2 years of age. Mortality was higher and neurological and behavioral development was more frequently abnormal among those with hyperglycemia treated with insulin. It remains unclear whether this association was due to hyperglycemia or due to the infusion of insulin (van der Lugt 2010). We therefore recommend that glucose control be maintained within relatively tight parameters (especially for the first 72 hours) as outlined in the insulin and glucose algorithms located within the FEN chapter. If possible, management without the use of insulin is ideal.

Prophylactic Indomethacin (PI):

Mixed evidence exists with regard to prophylactic use of indomethacin for IVH prevention. Routine use in ELBW infants remain controversial. PI is defined as 0.1mg/kg IV given within 6-24 hours of age x 3 doses q24h. PI reduced the incidence of severe IVH and need for PDA ligation in infants <1000-1250g BW in two landmark studies (Ment 1994, TIPP 2001). However, PI did not affect the outcomes of mortality or long-term neurodevelopmental

impairment (TIPP 2001). Furthermore, PI did not affect the outcomes of BPD, pulmonary hemorrhage, pneumothorax, NEC/SIP, or ROP (TIPP 2001, Cochrane 2010, Jensen 2017).

In addition to indomethacin's well-documented side effects (acute kidney injury and platelet inactivation), plausible risks for routine use of PI have been suggested. Further analysis of the TIPP trial by Schmidt et al (2006) suggested a possible link between PI and early pulmonary edema, thereby increasing the risk for later development of BPD. A few smaller studies also observed that indomethacin exposure was associated with severe respiratory distress by decreasing pulmonary prostacyclin (Lassus 2002) and worsened lung inflammation and fibrosis by increasing elastase activity and fibronectin levels (Gerdes 1988).

There may, however, be possible benefits of use of PI. A more contemporary, large, retrospective analysis of the NICHD National Research Network database (Jensen 2017) revealed that although PI was not associated with change in BPD risk, PI exposure was associated with decreased mortality in two subgroups (among infants with BW $\geq$10th percentile; and among infants who did not require any treatment for PDA). Mortality rate was found to be better among centers with high usage of indomethacin.

Based on the above evidence, consensus within the SLHS Neonatology group is not to give routine prophylactic indomethacin for IVH prevention in ELBW infants. However, PI administration can be considered for specific circumstances when benefits may outweigh the risks. Development of severe IVH is associated with lower GA, lower BW, inadequate antenatal steroids, outborn status, and lower 5-minute Apgar score. Male gender and mode of delivery have not been consistently associated (Singh 2013, Luque 2014). Mixed evidence exists whether PI is beneficial for the infants with highest severe IVH risk (Luque 2014, Foglia 2018).

Caffeine:

The CAP trial provides evidence demonstrating improved survival without neurodevelopmental disability as well as long-term safety of caffeine therapy. A caffeine loading dose of 25 mg/kg will be ordered on admission and maintenance caffeine therapy of 10 mg/kg/day will continue until 34-36 weeks CGA. See also Respiratory chapter.

Pain Control and Sedation:

Repeated pain exposure endured by ELBW infants can result in short-term adverse effects such as physiologic instability, and long term adverse sequelae including abnormal neurodevelopment, somatosensory, and stress response systems which can persist into childhood. Ascending pain pathways are mature and functional by about 24 weeks of gestation. However, due to immaturity of the dorsal horn synaptic connectivity and descending inhibitory circuits, there is poor localization and discrimination of sensory input and poor inhibitory modulation of noxious stimuli facilitating central nervous system sensitization to repeated noxious stimuli. The best pain management strategy in these infants is to prevent it. Since that

is not always an option, the use of a valid pain scoring tool such as the PIPP can help to assess an infant's level of pain and guide the appropriate management.

Pain can be minimized with judicious use of procedures. Mild procedural pain, such as that experienced with heel stick or venipuncture, can be treated with the use of non-pharmacologic interventions such as facilitated tuck, swaddling, and skin to skin holding with a parent. Non-nutritive sucking and the use of sucrose or mother's expressed breast milk should be used approximately 2 minutes prior to a painful procedure. For more invasive procedures, morphine or fentanyl can be used as deemed appropriate for the situation. RSI should be used for all non-emergent intubations. There is insufficient evidence to support the routine use of opioids in infants receiving mechanical ventilation due to concerns around adverse effects such as respiratory depression, increased duration of mechanical ventilation, development of tolerance/dependence, hypotension, bradycardia, decreased GI motility and urinary retention. There is also conflicting evidence regarding the long-term neurodevelopmental effects of opioids on ELBW infants. As such, infants receiving mechanical ventilation should only receive morphine as needed for pain based on PIPP scores indicating need for intervention. Due to concern for neurotoxicity, midazolam should be used very cautiously in this population.

Near InfraRed Spectroscopy (NIRS):

Although critically important, it is very difficult to assess whether a given perfusion pressure is providing appropriate CBF. Advances in the use of NIRS with correlating algorithms are increasingly being used to roughly assess optimal mean arterial pressure (MAP) for each infant. Using NIRS, variability in cerebral oxygenation relative to MAP suggests presence or loss of autoregulation. The figure below suggests the infant's optimal MAP is 23-27mmHg to maintain consistent cerebral oxygenation and autoregulation.

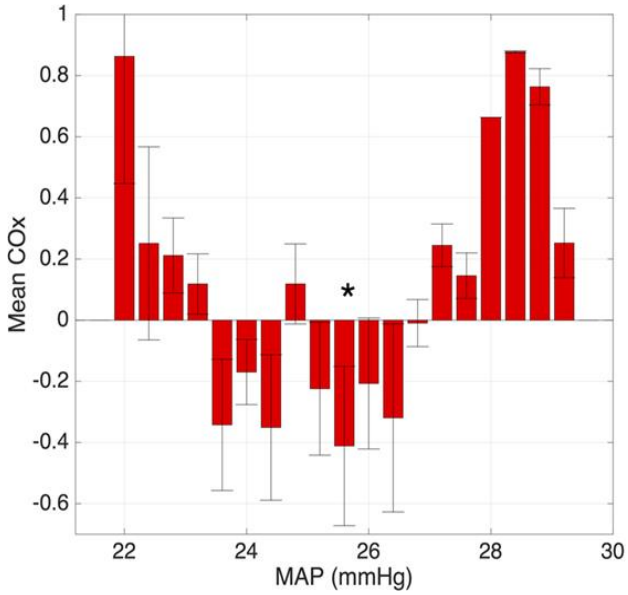


Figure 3. Plot of the average correlation between the blood pressure and cerebral oxygenation (COx). Note the lack of correlation over the range of "normal" blood pressure and increased correlation at the extreme values, representing loss of autoregulation. The optimal MAP is denoted with an asterisk. Front. Pediatr, April 2017. https://doi.org/10.3389/fped.2017.00064

In addition, NIRS can be used to monitor the effect of various NICU interventions such as suctioning, positioning, bolus infusion, pressors, etc., on cerebral oxygenation (Sood 2015). While the interpretation of NIRS data is fraught with potential errors, only through routine use can its utility be assessed. Therefore, we recommend that where technically possible, both cerebral and renal NIRS should be used routinely in ELBW management during the first 72 hours and possibly during periods of significant illness such as sepsis or NEC. Mepitac tape should be used underneath NIRS probes at all times to protect skin integrity. We also recommend continued assessment of future research data in the use and interpretation of NIRS in the ELBW infant.

Head Imaging:

Ultrasound:

The risk for intraventricular hemorrhage is greatest during the first several days of life, with the vast majority occurring prior to 4 days of life. Based on an internal review of our local IVH/PVL incidence and timing of diagnosis, as well as a recently published Clinical Report from the AAP (Hand 2020), the following screening guidelines were developed to allow appropriately judicious use of resources while still providing for timely diagnosis. As always, deviations from these guidelines may be entertained based on the unique patient course.

Routine IVH/PVL Screening Recommendations:

For Infants:	Screening Recs:
< 26wks EGA	DOL 5, DOL 10, DOL 30, and at TEA (38-40wks) or PTD (whichever 1st)
26-29 6/7wks EGA	DOL 10, DOL 30, and at TEA (38-40wks) or PTD (whichever 1st)
30-34wks for special circumstances	**Consider screening 30-34wks EGA infants (~DOL 10) or more frequently in earlier gestations if any of the following are present:** • Maternal chorioamnionitis with signs of neonatal sepsis • Placental abruption • Low 5-minute Apgar (<6) • CPR/Code event • Significant NEC • Sepsis without maternal steroids • Severe acidosis • Hypotension requiring pressor support • DIC • Unexplained seizures • Excessive head growth on chart • Tension pneumothorax requiring intervention v.12-2-20

Predischarge MRI for the ELBW infant:

There are no consistent recommendations regarding screening the former ELBW with brain MRI prior to discharge. Practice in the northwest U.S. varies widely from NICU to NICU. Of the 4 large regional NICUs polled, none routinely screen all former ELBW infants with term

equivalent age (TEA) MRI. Two of the four NICU's do not screen any former ELBWs with TEA MRI. Of the other two that do, they are done on targeted patients only and all have pediatric neuroradiologists on staff. Reasons for not screening included the following: recent articles have not supported benefit over predischarge HUS; screening provides limited utility in counseling of families; screening has poor prognostic value; considerable expense is incurred; and routine screening is not currently recommended by the AAP. Those that perform TEA MRI on targeted groups of former ELBW's do so on those that suffered grade 3 or higher IVH on early HUS, and/or have post hemorrhagic hydrocephalus and/or ventriculoperitoneal shunt placement, those with PVL/WMI on 36 week HUS, select patients with normal HUS when the clinical course was particularly complicated (generally infants that had confirmed sepsis or very prolonged ventilator courses with severe CLD) or when recommended by pediatric neurology. The literature is not conclusive on the benefit of TEA MRI. A recent study by Hintz et al (2015) looked at a large cohort of 480 infants < 28 weeks and the predictive value of early HUS and TEA HUS and MRI. In this study the predictive value of early and late HUS was only marginally improved with the addition of TEA MRI (which was read by a central pediatric-trained radiologist). This calls into question whether the increased cost and use of personnel is justified by such small additional predictive value, especially at our institution where we do not have pediatric neuroradiologists on staff.

Additionally, even in the face of severe abnormalities on either late HUS or TEA MRI, up to ¼ of patients were either only mildly impaired or unimpaired at 18-22 months CGA. It is clear that results of neuroimaging in the ELBW cannot be used to guide follow-up strategies or targeted interventions after discharge and thus may be of little to no benefit to parents. In August 2015, the American Academy of Pediatrics section on Perinatal Pediatrics published an article titled, "Choosing Wisely in Newborn Medicine: Five Opportunities to Increase Value." The results were based on a national survey followed by a literature search and evaluation by an expert panel.

After reviewing the literature, they concluded, "Findings on Term equivalent MRI correlate with neurodevelopmental outcomes at 2 and 5 years of age. There is however insufficient evidence that the routine use of term-equivalent or discharge brain MRI in preterm infants improves long term outcomes."

This is substantiated by a recent article published in May 2019 in the European Journal of Pediatrics which drew the same conclusion. They looked at the predictive value of TEA MRI in 75 former <28 week infants on neurodevelopment at 1 and 3 years of age. Their conclusion was, "TEA HUS can reliably identify severe brain abnormalities that would be seen on MRI imaging and positively predict abnormal neurodevelopment at both 1 and 3 years. Although MRI can pick up more subtle abnormalities that may be missed on HUS, their predictive value on neurodevelopmental impairment is poor. Normal HUS and MRI scan may not exclude abnormal neurodevelopment. Routine TEA-MRI scan provides limited benefit in predicting abnormal neurodevelopment in extremely preterm infants."

Based on the available evidence, and taking into consideration the fact that we do not have pediatric-trained neuroradiologists, nor any current standardized way to report MRI findings that would provide insight to an infant's long term prognosis, as well as the movement in medicine to a value based reimbursement model, we draw the conclusion that routine MRI does not presently add sufficient benefit/value to the care of the former ELBW infant and therefore cannot be routinely recommended, but may be considered on a case by case basis.

Summary of Recommendations for Minimizing Neural Injury:

The following summary of recommendations are aimed at preventing neurologic injury and minimizing pain.

Antenatal Care:

Antenatal Corticosteroid Administration as early as 21 5/7 weeks

Magnesium Sulfate Administration per OB guidelines

Maternal Transport to tertiary center rather than ELBW transport, when possible

Perinatal Care:

Delayed Cord Clamping but not Umbilical Cord Milking in this age group

Intubation by most experienced provider

Close Temperature monitoring and regulation

Optimizing Cerebral perfusion

1) Maintaining ideal BP (see CV)
2) Avoiding acute changes in ICP with HOB up and midline first 72 hours, slow bolus infusion and avoiding lung over distension and tension pneumothorax.
3) Maintain cerebral vascular auto regulation through tight control of CO2, Na, Glucose, pH (avoid acute infusions of bicarbonate), and oxygenation where possible particularly during the first 72 hours

Indomethacin -Routine prophylactic use is not recommended

Caffeine is recommended from birth and until 34-36 weeks CGA even if intubated

Pain and sedation

Minimize painful stimuli (especially the first 72 hours) as possible

For mild procedural pain - use nonpharmacologic interventions such as facilitated tuck, swaddling, skin to skin holding with a parent, non-nutritive sucking (age appropriate), and the use of sucrose or Mother's EBM

For more invasive procedures, morphine or fentanyl can be used as deemed appropriate for the situation

Avoid routine sedation due to ventilator alone

Use PIPP scores to help determine need for pain management

Cautious non-routine use of midazolam, ideally not <34wks

RSI for intubations whenever possible

Imaging

NIRS Monitoring - recommended the first 72 hours of life to help assess need for interventions (bolus, pressors, etc.) and to help optimize cerebral perfusion

Head U/S - should be obtained per SLHS protocol keeping in mind that this is the minimum recommendation and that once bleeding or other abnormalities have occurred, more frequent imaging may be indicated

Discharge MRI - routine completion of discharge MRI is not recommended except in unusual cases

Point of Care Ultrasound – Continue efforts to acquire and train.

Infectious Disease

Full recognition is given to the immunocompromised status and increased sepsis risk factors surrounding delivery at the extremes of prematurity. However, this must be balanced with acknowledgement that there is actually an *increased* risk of mortality and morbidity in the NICU with each additional day of antibiotics. Furthermore, increased antibiotic use and exposure negatively alters the neonatal microbiome and promotes the emergence of resistant organisms and fungal opportunists.

As such, we intend to attempt to end the culture of culture-negative sepsis in our NICU. There are three erroneous assumptions that can lead to a diagnosis of culture-negative sepsis:

1. Blood cultures are insensitive
2. Blood cultures are unreliable after maternal intrapartum treatment
3. Culture results are inferior to clinician's judgment

To achieve adequate sensitivity in ideal situations, a blood sample of at least 1 ml should be obtained before the infant receives antibiotics and placed in the proper bottle(s). Sensitivity decreases by 10-40% when 0.5 ml sample vs 1 ml sample is obtained. Sensitivity of blood cultures was nearly 100% (1 ml) if infant has growth of at least 4 CFU/ml (2007) and is even more sensitive now (2017) at 1-4 CFU/ml. Median CFU/ml for neonatal sepsis is > 100,000. If bacteremia is ultralow (CFU < 1) then sensitivity decreases. This may not be clinically significant if infant is treated empirically for 36-48 hours. Infants with sterile blood cultures and treatment for 36-48 hours virtually never require retreatment.

Intrapartum prophylaxis with adequate maternal treatment most often leads to ultralow neonatal bacteremia concentrations or sterility of the bloodstream, obviating the need for long-term antibiotic treatment.

While the clinician's judgment will always prevail, properly obtained cultures should provide enough additional information that empiric treatment should nearly always be able to be discontinued after 36-48h if the culture remains negative. "If the bacteria cannot grow in the blood culture bottle (an ideal medium at an ideal temperature, free of antibiotics, complement, or phagocytes) then why would they grow effectively in the infant's bloodstream?"

A formal Antibiotic Stewardship Program is presently under formation at the time of this writing, and we hope to fully implement within the NICU and Children's Hospital within the next year.

Delivery criteria that place the infant at low risk of neonatal infection include:

- C-section
- ROM at delivery
- Absence of clinical chorioamnionitis

Infants at <28wks EGA should whenever possible have a cord blood culture drawn and held at the bedside until the provider determines whether the culture needs to be sent. Cord blood cultures require meticulous cord preparation with chlorhexidine to avoid contamination. Volumes of 1-5ml should be obtained. Per the manufacturer, 3ml is optimal. Low risk infants should not have cultures routinely sent. If less than 1ml is obtained from the cord blood and the infant is not low risk and empiric antibiotics are to be started, then the cord blood sample should be discarded, and an attempt should be made to obtain an ideal 1ml sample from the infant.

Empiric Antibiotics for Early Onset Sepsis (EOS):

Empiric antibiotics of choice for EOS in the ELBW infant are nearly always ampicillin and gentamicin. Ampicillin should be dosed at 50mg/kg/dose q12h unless there is high suspicion for meningitis. Gentamicin should be dosed at 5mg/kg/dose per Neofax recommendations. End dates or finite doses should always be ordered to avoid inadvertent prolongation of administration. For presumed sepsis rule-out treatment, 3 doses of ampicillin and 1 dose of gentamicin should be ordered. If the provider feeds strongly that a diagnosis of "culture-negative sepsis" must be entertained, then treatment should be for 5 days rather than the typical 7-day course. For neonatal pneumonia with no pathogen identified, a 5-day course of treatment is preferred versus 7 days. EOS workup generally does not necessitate urine or CSF sampling unless there is a specific concern for urinary tract or central nervous system (CNS) infection.

Empiric Antibiotics for Late Onset Sepsis (LOS):

For infants >3 days of age without clinical signs of necrotizing enterocolitis (NEC) and with a central line in place, St. Luke's Pediatric Infectious Disease recommends use of vancomycin and cefotaxime* per Neofax dosing recommendations for broad coverage treatment until gram stain or organism identification. For infants without clinical signs of NEC and without a central line in place, empiric treatment should be with ampicillin and gentamicin. LOS is associated with as high as 10% CNS involvement even in the absence of documented bacteremia. Urinary tract infection is also more likely. As such, workup for LOS should include a lumbar puncture and catheterized or suprapubic urine specimen as well as blood culture, ideally prior to initiating antibiotics if at all possible and if clinical condition allows. Additionally, if Ampicillin is used, it should be dosed at 300mg/kg/day (frequency per Neofax recs) until CSF is determined to be negative. If there is a high suspicion for meningitis, based on either clinical symptoms and/or LP findings, and/or if gram-negative organisms are detected on gram stain, then cefotaxime

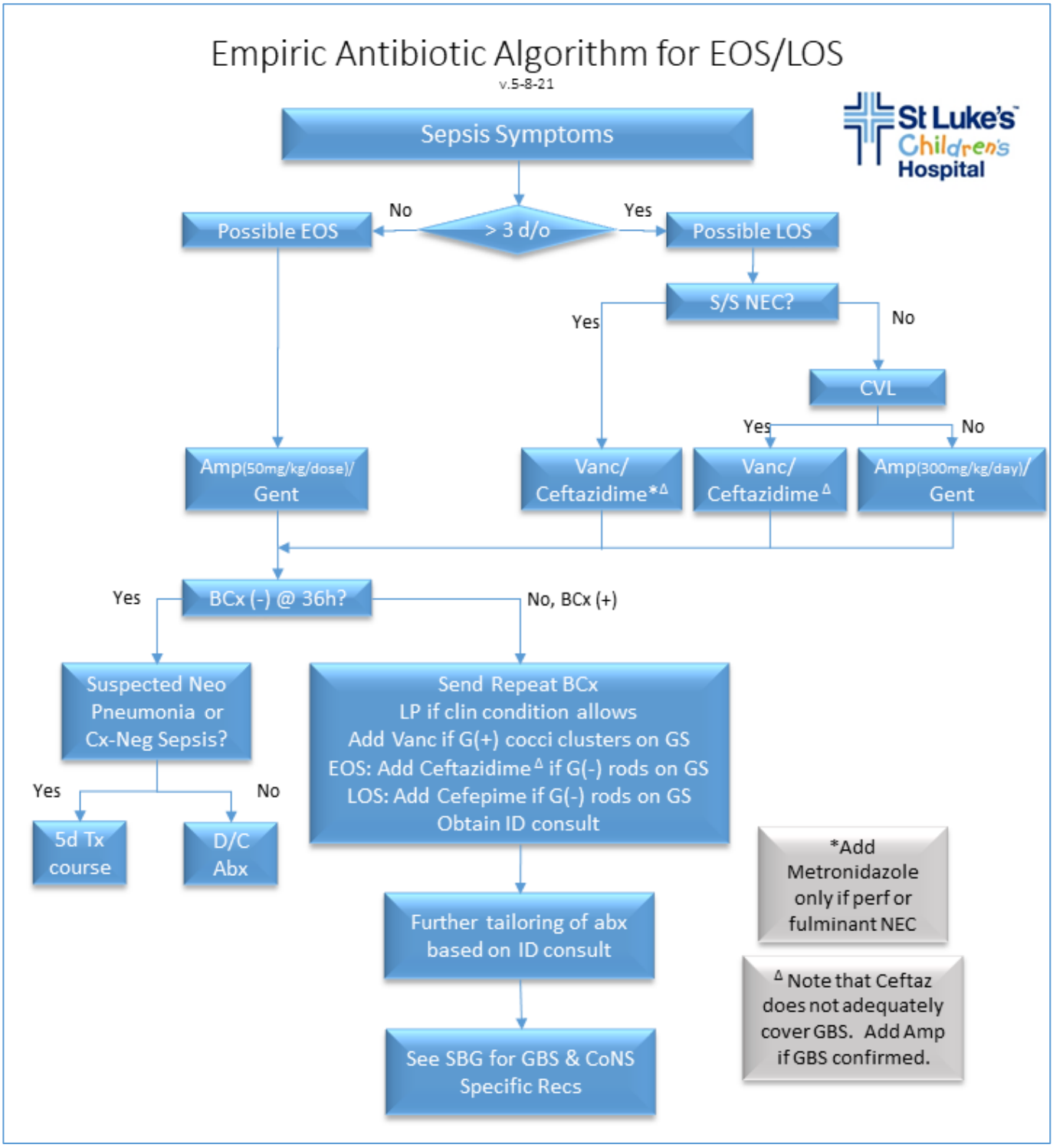
*Ceftazidime is second line agent in times of cefotaxime shortage.

should also be added. Alternatively, if gram-negative organisms are confirmed or suspected, empiric therapy with vancomycin and meropenem would be acceptable, per Peds ID.

Empiric Antibiotics for NEC:

While there is limited study data without specific recommendation, if clinical signs of NEC are present, treatment should be with vancomycin and cefotaxime*, with the addition of metronidazole only if there is evidence of intestinal perforation or concern for fulminant NEC. The rationale for minimizing the use of metronidazole relates to a potential increased risk of stricture formation with anaerobic treatment. Completion of the ongoing SCAMP trial may further inform and modify both our empiric and therapeutic treatment regimens for NEC.

Empiric Antibiotic Algorithm for EOS/LOS:



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Group B Streptococcus (GBS):

Per St. Luke's Peds ID, uncomplicated GBS bacteremia can typically be treated with a 10-day course of treatment. Uncomplicated GBS meningitis should be treated for 14 days. Fulminant GBS bacteremia/meningitis or illness that is slow to recover should be treated for 21 days. If fulminant disease is present, MRI should be obtained. If MRI reveals ventriculitis or brain abscess, then 28 days is the minimum course of treatment. Lumbar puncture (LP) is not routinely indicated for EOS workups, but should be obtained for LOS workups if the infant is able to tolerate clinically. If not already obtained, an LP should be performed when GBS bacteremia is diagnosed. Regardless of LP results, repeating the LP is generally not indicated unless there is clear clinical failure of treatment. Typically, in this situation imaging studies would also be obtained first.

Treatment for GBS is Ampicillin 300mg/kg/day IV divided per Neofax recommendations for age. Per Peds ID, this is the preferred therapy over penicillin (PCN) due to the increased risk for dosing errors and increased risk of toxicity of PCN, despite the fact that PCN does provide slightly more narrow coverage. High doses of PCN can cause seizures, hemolytic anemia, and interstitial nephritis.

Ampicillin Dosing:

Ampicillin dosing is quite variable and depends on gestational age, chronological age, and indication for use. See Neofax for the latest dosing recommendations.

See also the recommendations below from the AAP Red Book: 2018 Report, which were recently published within the 2019 AAP Clinical Report on Management of Infants at Risk for GBS Disease.

TABLE 1 Recommended Intravenous Antibiotic Treatment Regimens for Confirmed Early- and Late-Onset GBS Bacteremia and Meningitis

	GA ≤34 wk		GA >34 wk	
	PNA ≤7 d	PNA >7 d	PNA ≤7 d	PNA >7 d
Bacteremia				
Ampicillin	50 mg/kg every 12 h	75 mg/kg every 12 h	50 mg/kg every 8 h	50 mg/kg every 8 h
Penicillin G	50 000 U/kg every 12 h	50 000 U/kg every 8 h	50 000 U/kg every 12 h	50 000 U/kg every 8 h
Meningitis				
Ampicillin	100 mg/kg every 8 h	75 mg/kg every 6 h	100 mg/kg every 8 h	75 mg/kg q 6 h
Penicillin G	150 000 U/kg every 8 h	125 000 U/kg every 6 h	150 000 U/kg every 8 h	125 U/kg every 6 h

Adapted from Table 4.2. Antibacterial Drugs for Neonates (<28 Postnatal Days of Age). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:915-919. GA, gestational age; PNA, postnatal age.

Central Line Infections:

Vancomycin will commonly already be prescribed when a central line infection is diagnosed. This should be continued if the organism is gram + and believed to be susceptible. If Staph aureus is identified, therapy may be narrowed to nafcillin or cefazolin if the isolate is susceptible. Note that cefazolin does not penetrate the blood brain barrier and is slightly less effective against endocarditis but is generally tolerated better. Treatment for Staph aureus should be 10 days for an uncomplicated course, 14 days or longer if complicated.

Coagulase-negative Staph (CoNS) can be much more complicated due to the unreliability of susceptibilities for Staph epi. It is recommended to perform MecA gene testing to ensure that methicillin resistance has not been missed. (PBP2a testing can also be performed however is not available in St. Luke's laboratory). MecA testing is available at St. Luke's but requires a call to the micro lab to initiate. If CoNS is susceptible on our regular invitro panel, and the MecA isolate is negative, then therapy can be narrowed to nafcillin or cefazolin. If unable to obtain sensitivities or MecA then it is appropriate to treat with vancomycin for the full course of therapy. Length of therapy for uncomplicated CoNS with only one positive blood culture is 5-7 days if the line is removed, or 10 days if the line remains through treatment. If the line is left in place, antibiotic doses should always be administered through the line even if other IV access is in place, unless there are issues with compatibility of other infusions or inotrope requirement through the line. If there are multiple positive cultures, then an echocardiogram should be obtained, and the length of treatment extended. Repeat BCx should be obtained 48h after discontinuation of antibiotics to ensure clearance.

Fungal prophylaxis:

Based on the current low endemic rates of fungal infection in St. Luke's NICU, fungal prophylaxis is not routinely indicated. While other units have successfully used fungal prophylaxis protocols to reduce rates of secondary opportunistic fungal infections in infants requiring long-term antibiotics, those units frequently start with much higher fungal infection rates than St. Luke's. Per our Vermont Oxford Network data, the total number of fungal infections at St. Luke's NICU from 2008-17 was 7 cases. Following 7 years with no cases reported, we have now experienced several systemic fungal infections since 2018 that warrant recognition and consideration within these Guidelines.

In infants <1kg with a central line who are not suspected to have a systemic fungal infection, prophylaxis may be considered on a case by case basis if:

- 10 or more days of treatment with 3rd generation cephalosporin (cefotaxime, ceftazidime, ceftizoxime and cefoperazone)
- Treatment with carbapenem (meropenem)
- Suspected fungal rash being treated topically with nystatin (located in creases near line insertion sites, not just in diaper area)

The drug of choice should fungal prophylaxis be considered is IV fluconazole per the Neofax prophylactic dosing regimen. Both oral fluconazole and nystatin decolonize the gut well but are less effective systemically and are associated with higher incidence of NEC (speculated to be associated with higher sucrose content and osmolality) (Lollis & Bradshaw 2014, Kaufman & Manzoni 2010).

Antibiotic Levels:

Levels only need to be checked when antibiotics are planned for a full course of treatment. Gentamicin may be checked just prior to the third dose with a goal level of <1. Due to dosing that follows first order kinetics, gent dosing does not require waiting for steady state prior to

checking levels. Gent may need to be checked prior to the second dose in cases where renal failure or significant total body fluid perturbations are present. Vancomycin trough levels are typically obtained after three doses, just prior to the fourth dose, when it should have achieved approximately 88% of steady state. With the presence of Pediatric Pharmacy services now at St. Luke's Children's Hospital, the pharmacists can assist in performing kinetics to determine the best dosing intervals for infants with known infection.

St. Luke's Pediatric Antibiograms:

While not inclusive of many of the most common pathogens recovered in the NICU, the following antibiograms represent the typical sensitivities of some notable bacteria at St. Luke's Children's Hospital.

St Luke's Children's

2019 PEDIATRIC ANTIBIOGRAM - PERCENT SUSCEPTIBILITY

GRAM NEGATIVE ORGANISMS	AMK	GEN	TOB	ERT	MER	CFZ	CFU	CTX	CTZ	CFP	AMP	A/S	A/C	P/T	CIP	LEV	TCN	T/S	NIT*
Escherichia coli	100	96	96	100	100	91	95	97	97	98	63	67	89	98	95	95	83	82	100
Kleb. pneumoniae	100	96	96	98	98	92	92	94	94	94	-	80	-	98	96	98	84	86	43
P. aeruginosa	100	96	98	-	97	-	-	-	94	90	-	-	-	90	94	94	-	-	-

AMK-Amikacin
AMP-Ampicillin
A/C-Augmentin
A/S-Unasyn
CIP-Cipro
CFU-Cefuroxime
CFP-Cefepime
CFZ-Cefazolin
CTX-Ceftriaxone
CTZ-Ceftazidime
ERT-Ertapenem
GEN-Gentamicin
LEV-Levofloxacin
MER-Meropenem
NIT-Nitrofurantoin
P/T-Zosyn
T/S-Bactrim
TCN-Tetracycline
TOB-Tobramycin

Antimicrobial Stewardship Coordinator:
Charles Jensen 381-2472
email: jensench@slhs.org

Duplicates excluded by 1st Isolate Criteria
Cystic fibrosis isolates excluded
*** Indicated for UTI only**

Green = Strongly Favored, Susceptibility 90-100%
Yellow = Less Favored, Susceptibility 80-89%

St Luke's Children's

2019 PEDIATRIC ANTIBIOGRAM - PERCENT SUSCEPTIBILITY

GRAM POSITIVE ORGANISMS	AMP	PCN	NAF	ERY	CLN	DPT**	GEN	LEV	LZD	RIF	TCN	T/S	VAN	NIT*
E. faecalis	100	100	-	-	-	98	-	-	100	-	-	-	100	100
MRSA	-	-	-	-	92	100	100	37	100	99	96	97	100	100
MSSA	-	-	100	-	81	100	99	96	100	100	96	95	100	100

AMP-Ampicillin
CLN-Clindamycin
DPT-Daptomycin
ERY-Erythromycin
GEN-Gentamicin
LEV-Levofloxacin
LZD-Linezolid
NAF-Nafcillin
NIT-Nitrofurantoin
PCN-Penicillin
P/T-Zosyn
RIF-Rifampin
T/S-Bactrim
TCN-Tetracycline
VAN-Vancomycin

Duplicates excluded by 1st Isolate Criteria
Cystic fibrosis isolates excluded
*** Indicated for UTI only**
**** Daptomycin is NOT indicated for the treatment of pneumonia**

Green = Strongly Favored, Susceptibility 90-100%
Yellow = Less Favored, Susceptibility 80-89%

St. Luke's Pediatric Infectious Disease Consultations:

We are fortunate to have a number of skilled Pediatric Infectious Disease specialists at our disposal for consults and curbside questions. Per their feedback, the following list of problems

or diagnoses should prompt consideration for a call to Peds ID. They can assist us in determining whether a formal consult or curbside is most appropriate for a given situation.

- Neonatal sepsis with complications or questions beyond routine management
- Any known or suspected congenital infection (TORCH, HSV, HIV, hepatitis B or C, Parvovirus or other), or exposures to these maternal infections – consult ASAP after birth or when suspected infection is apparent
- Known or suspected central line associated bacteremia
- Any invasive Candidal or other fungal infection
- Group B Strep invasive disease, especially meningitis
- Any infection with a drug-resistant organism (ESBL or others)
- Meningitis
- Any device-associated infection – such as VP Shunt
- Fever or rash of unknown etiology
- Bone or joint infection, known or suspected
- Suspected immunodeficiency – call as soon as this is suspected
- Any abnormal newborn screen for Severe Combined Immunodeficiency (SCID TREC Screen) or a baby with family history of serious primary immunodeficiency – call immediately upon receipt of abnormal lab result
-
- Strongly consider consult for infections due to Serratia, Proteus, Providentia, Citrobacter, Enterobacter, Morganella (all GNR that are typically resistant or difficult to treat)

Utilization of PCR Panels:

St. Luke's currently offers respiratory pathogen PCR, enteric pathogen PCR, and CSF PCR meningitis/encephalitis panels. We are not currently using any rapid PCR identification for blood specimens. In the NICU population, it would be only for rare and very specific circumstances for which the respiratory or enteric pathogen PCR would be useful. Peds ID does not suggest ordering these routinely, as most NICU patients are not at high risk of acquiring these infections. The exception would be for rapid respiratory panel PCR for infants admitted from outside the hospital setting, or in circumstances where respiratory pathogen outbreaks are suspected in the NICU. CSF PCR meningitis/encephalitis panel may prove to be quite useful in cases of pre-treated meningitis (as there is often a delay in collecting CSF after a baby stabilizes from septic episode).

Procalcitonin (PCT) and C-Reactive Protein (CRP):

Procalcitonin may have a role in the first hours of life or first couple days, when trying to predict risk of neonatal sepsis. However, for most other indications outside of the immediate newborn period, CRP performs more reliably and is more useful for trending over time to assess response to treatment. Procalcitonin is appropriate for use in assessing questionable cases of

EOS when history, clinical findings, and CBC are marginal or equivocal. For LOS, however, CRP should be utilized if acute-phase inflammatory information is needed.

DEFEND the Line:

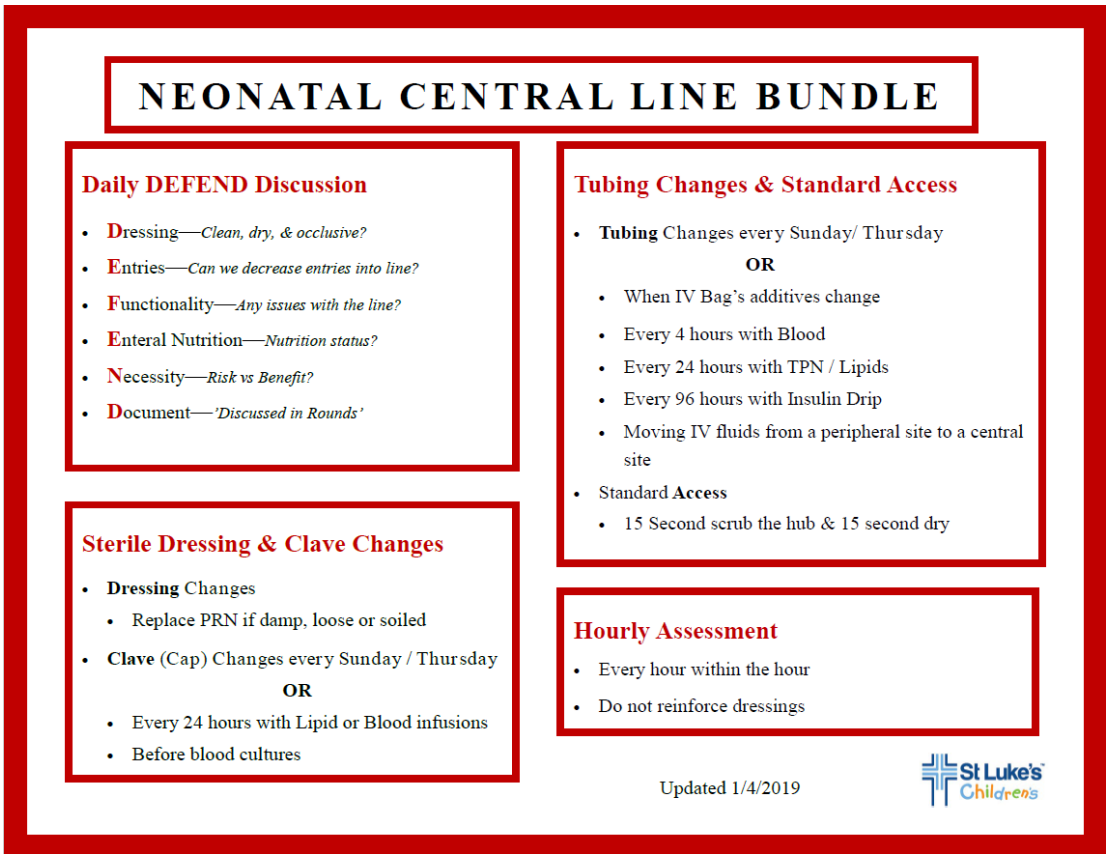
As part of the continual effort to protect our patients against nosocomial central line blood stream infections (CLABSI), nursing staff are to follow a central line bundled approach with specific standards for line monitoring, dressing changes, tubing changes, line access frequency, and clave changes. Providers can assist this approach by supporting the daily DEFEND discussion at the bedside, which is outlined below.

DEFEND Discussion Guide

D	Dressing: Change needed? ▪ Clean, dry and occlusive? ▪ Last changed?
E	Entries in Line: Reduce the use? ▪ How often is line accessed? ▪ Can we bundle entries? ▪ Change PRN to drips or d/c? ▪ Change IV to PO?
F	Functionality: Are there any issues with the line?
E	Enteral Intake: Is the line needed for nutrition? ▪ ≥120ml /kg /day
N	Necessity: Risk vs Benefit? ▪ Access issues? ▪ Unstable? ▪ Central line meds? ▪ Nutrition?
D	Document: Did you document 'Discussed in Rounds' in *my*StLuke's?

Infection Prevention Bundles:

St. Luke's Children's Hospital has developed care bundles for the prevention of central line, urinary catheter, and ventilator-associated infections and which should be regularly reviewed and adhered to.



NEONATAL CENTRAL LINE BUNDLE

Daily DEFEND Discussion

- **D**ressing—*Clean, dry, & occlusive?*
- **E**ntries—*Can we decrease entries into line?*
- **F**unctionality—*Any issues with the line?*
- **E**nteral Nutrition—*Nutrition status?*
- **N**ecessity—*Risk vs Benefit?*
- **D**ocument—*'Discussed in Rounds'*

Sterile Dressing & Clave Changes

- **Dressing** Changes
  - Replace PRN if damp, loose or soiled
- **Clave** (Cap) Changes every Sunday / Thursday

OR

  - Every 24 hours with Lipid or Blood infusions
  - Before blood cultures

Tubing Changes & Standard Access

- **Tubing** Changes every Sunday/ Thursday

OR

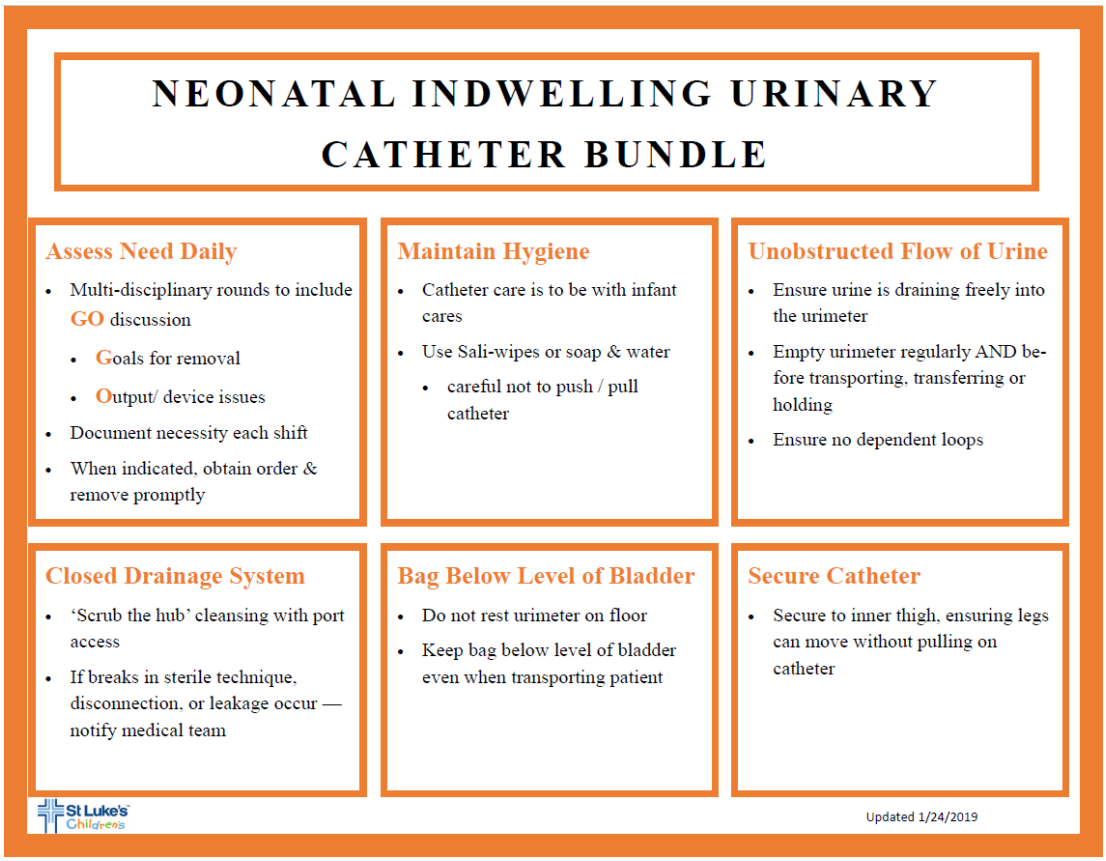
  - When IV Bag's additives change
  - Every 4 hours with Blood
  - Every 24 hours with TPN / Lipids
  - Every 96 hours with Insulin Drip
  - Moving IV fluids from a peripheral site to a central site
- Standard **Access**
  - 15 Second scrub the hub & 15 second dry

Hourly Assessment

- Every hour within the hour
- Do not reinforce dressings

Updated 1/4/2019

St Luke's Children's



NEONATAL INDWELLING URINARY CATHETER BUNDLE

Assess Need Daily

- Multi-disciplinary rounds to include **GO** discussion
  - **G**oals for removal
  - **O**utput/ device issues
- Document necessity each shift
- When indicated, obtain order & remove promptly

Maintain Hygiene

- Catheter care is to be with infant cares
- Use Sali-wipes or soap & water
  - careful not to push / pull catheter

Unobstructed Flow of Urine

- Ensure urine is draining freely into the urimeter
- Empty urimeter regularly AND before transporting, transferring or holding
- Ensure no dependent loops

Closed Drainage System

- 'Scrub the hub' cleansing with port access
- If breaks in sterile technique, disconnection, or leakage occur — notify medical team

Bag Below Level of Bladder

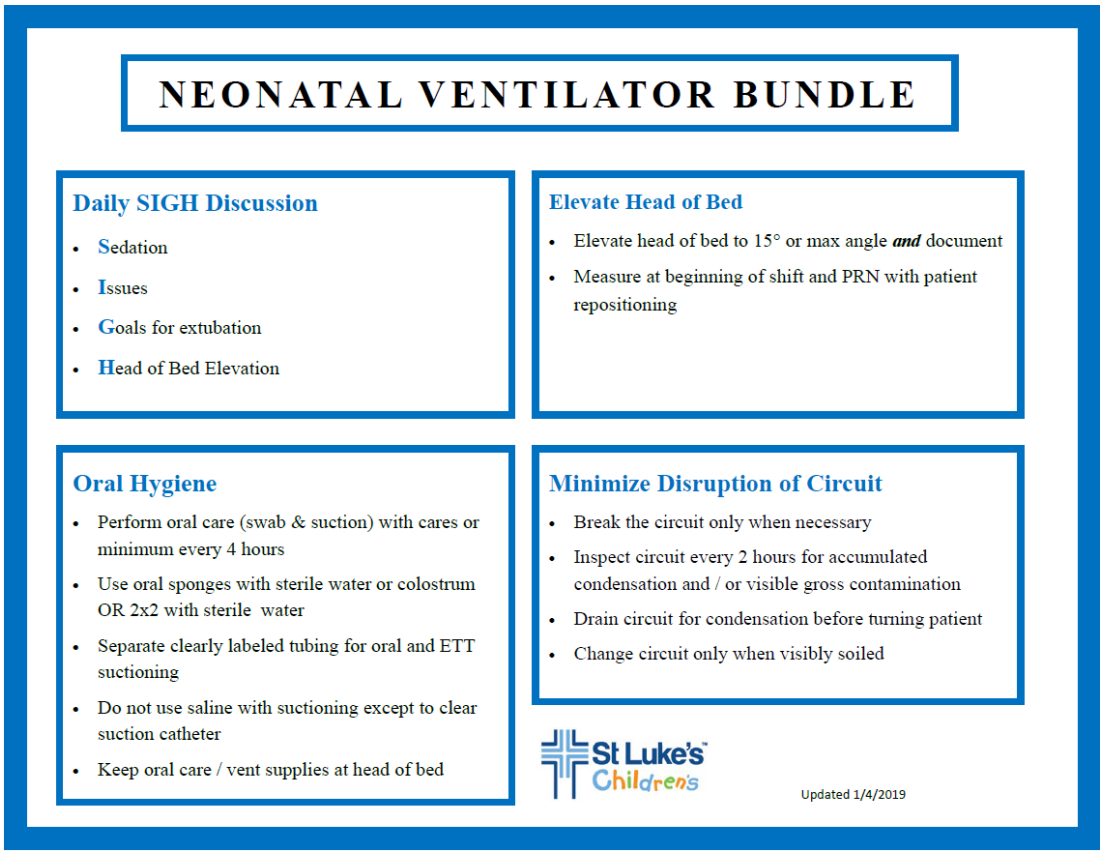
- Do not rest urimeter on floor
- Keep bag below level of bladder even when transporting patient

Secure Catheter

- Secure to inner thigh, ensuring legs can move without pulling on catheter

St Luke's Children's

Updated 1/24/2019



NEONATAL VENTILATOR BUNDLE

Daily SIGH Discussion

- **S**edation
- **I**ssues
- **G**oals for extubation
- **H**ead of Bed Elevation

Elevate Head of Bed

- Elevate head of bed to 15° or max angle ***and*** document
- Measure at beginning of shift and PRN with patient repositioning

Oral Hygiene

- Perform oral care (swab & suction) with cares or minimum every 4 hours
- Use oral sponges with sterile water or colostrum OR 2x2 with sterile water
- Separate clearly labeled tubing for oral and ETT suctioning
- Do not use saline with suctioning except to clear suction catheter
- Keep oral care / vent supplies at head of bed

Minimize Disruption of Circuit

- Break the circuit only when necessary
- Inspect circuit every 2 hours for accumulated condensation and / or visible gross contamination
- Drain circuit for condensation before turning patient
- Change circuit only when visibly soiled

St Luke's Children's

Updated 1/4/2019

Hematology

Delayed Cord Clamping vs. Umbilical Cord Milking in Delivery Room:

Umbilical cord milking (UCM) and delayed cord clamping (DCC) in premature infants have been shown to improve short term outcomes including blood pressure, reduction in need for blood transfusions, NEC, IVH, and sepsis (Fogarty 2018). UCM has the advantage of being faster and therefore not delaying resuscitation compared to DCC. However, in a recent RCT by Katheria (2019) comparing UCM and DCC, with cohorts separated into 23-27 weeks and 28-31 weeks, the trial was stopped in the 23-27-week age group due to a statistically significant increase in severe IVH in the group receiving UCM. There was no significant difference in death between the two age groups receiving UCM or DCC. Based on this study, the recommended approach for SLN is to perform DCC, but not UCM, in the small baby population.

Table 2 Delivery Room and Neonatal Outcomes (infants: 23-27 wks GA)	DCC (N=89)	UCM (N=93)	*p*-value
Time of cord clamp, seconds	56.7 (16.4)	21.1 (13.8)	<0.0001
Crying or breathing before cord clamping	68 (76%)	48 (52%)	0.0007
Admission temperature, °C	36.8 (0.7)	36.8 (0.6)	0.998
Apgar score, 1 min: Median (Q_1-Q_3)	5.0 (2, 6)	4.0 (3, 7)	0.47
Apgar score, 5 min: Median (Q_1-Q_3)	7.0 (6, 8)	7.0 (5, 8)	0.91
Needed Positive Pressure Ventilation	77 (87%)	79 (85%)	0.899
Intubation in delivery room	54 (61%)	53 (57%)	0.67
Hemoglobin at 4 hours of life, g/dL	15 (2.4)	15 (2.8)	0.86
Urine output first 24h, mL/kg per h	4.0 (1.5)	4.5 (1.3)	0.025
Peak bilirubin, mg/dL	7.1 (1.9)	7.3 (2.0)	0.70
Retinopathy necessitating surgery	16 (18%)	6 (6%)	0.045
Necrotizing enterocolitis	6 (7%)	4 (4%)	0.75
Spontaneous intestinal perforation	4 (4%)	1 (1%)	0.37
Oxygen at 36 wk corrected	23 (26%)	20 (22%)	0.97
Any IVH	27(30%)	25 (27%)	0.61
Severe IVH	4 (4%)	20 (22%)	0.0007
Death	12 (13%)	14 (15%)	0.76
Severe IVH or Death	16/89 (18%)	26/93 (28%)	0.11

Data are presented as mean (SD) or count (percentage) unless otherwise stated. UCM, umbilical cord milking. DCC, delayed cord clamping. IVH, intraventricular hemorrhage.

Source: Katheria, 2019. OJOG, Vol 220, Issue 1, Suppl, pS682

Anemia of Prematurity:

Anemia of prematurity is nearly ubiquitous in the extremely preterm newborn. The reasons are multifactorial, and include the following:

1. Rapid growth rate. The extremely accelerated growth rate in the third trimester causes difficulty for the preterm infant to keep up with red cell production.
2. Low iron reserves. 80% of iron present in the healthy term newborn is accreted during the 3rd trimester of pregnancy. ELBW infants miss the majority of this accretion period.
3. Phlebotomy losses. ELBW infants have a total circulating blood volume of about 90ml/kg. Therefore a 0.5kg infant has a blood volume of only ~45ml. We can (and unfortunately do) sometimes draw upwards of 10ml of blood in the first week of life. This translates to nearly 22% of total blood volume.
4. Inadequate erythropoietin (epo) response to anemia. In fetal life and in preterm infants, epo is produced in the liver prior to transitioning to renal production at full term and beyond. The liver is 10 times less sensitive to hypoxemia than the kidney, resulting in far less epo production overall.

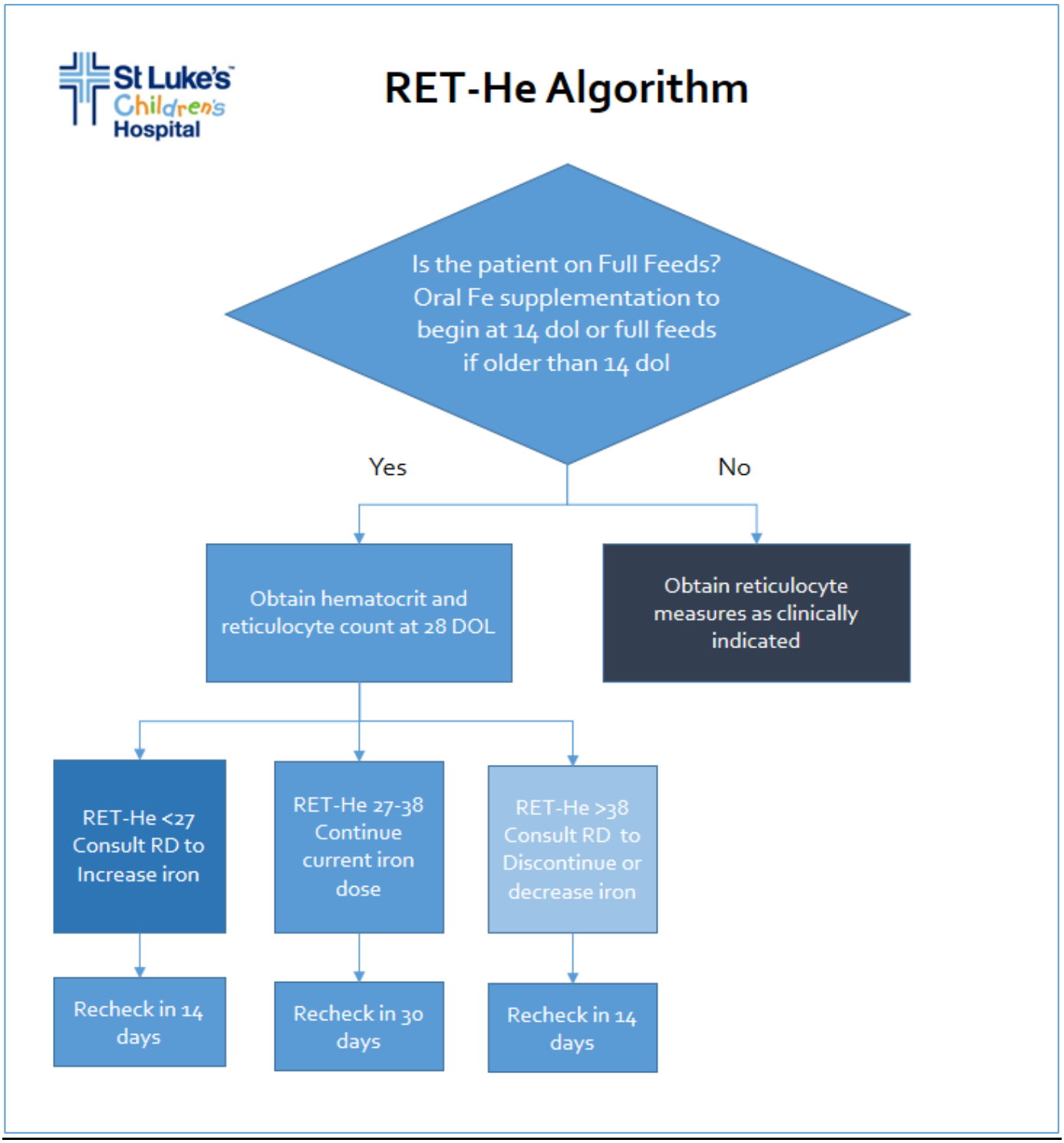
Iron Deficiency:

Iron deficiency (ID) is the most common childhood single nutrient deficiency in the US and other industrialized nations. Fourteen percent of preterm infants develop ID between 4-8 months of age, despite iron containing formulas and fortification. Iron during infancy is felt to be essential for normal neurodevelopment, and impacts neurotransmitter metabolism, myelination of neurons, and likely plays a part in behavior and memory development.

Diagnosis of ID can be done using several biochemical parameter tests, most commonly ferritin and serum iron levels. These tests require significant blood volumes and are only done in regional laboratories, making them impractical. The reticulocyte percentage (retic count) is a measure of the percentage of RBCs that are immature and recently formed. A high retic count is a good indicator of active erythropoiesis and red cell production. While it may sometimes be necessary, transfusing an infant with a high retic count will have the unfortunate consequence of suppressing endogenous epo production and decreasing the volume of new RBCs produced, therefore transfusions should be used very judiciously.

The reticulocyte hemoglobin level (RET-He) is a measure of iron availability to newly produced red cells. Both the retic count and the RET-He are performed routinely as part of a CBC, requiring no additional blood to be drawn. A RET-He <27 pg/cell indicates iron deficiency. A RET-He 27-38 pg/cell indicates iron sufficiency. A RET-He >38 pg/cell may indicate iron overload. The following algorithm can help guide decision making when assessing overall infant iron status.

RET-He Algorithm:



Small Baby Lab Draw Recommendations and Phlebotomy Losses:

DOL	AM lab/volume	Blood Gas *Ical if not getting BMP	Special consideration	Phototherapy/NB	Heme	Daily & (Total) Blood out
DOB	**TG level at 1, 2 & 3 gms** **BMP DOL1 and when mg or phos is needed**	**22-24 wks:** Gas with UAC, q2 hr then q 4 x 24 hrs. Q 6 25-48 hrs Q 8 49-72 hrs **25-27 wks:** Q 4 hrs and PRN if intubated **NIPPV/CPAP/HHHFNC:** 1 hr post initiation/PRN	**Phos and mg can be added on to already obtained sample for BMP**	**NB can be added on to already obtained sample** Once NB is stable or coming down follow every 2-3 days	CBC 0.3 bld cx 1.0 if not obtained from cord blood	1.3 (1.3) + gases
1 **24hrs of age**	BMP 0.6 IL 0.5 gm/kg	POCT gas 0.2	IUGR/SGA phos 0.3	NB 0.3 phototherapy as needed		1.1-1.4 (2.4-2.7) +gases
2	Chem 8 0.2 IL inc to 1 gm/kg	POCT gas 0.2	If high Ca add phos 0.3	NB 0.3		0.7-1 (3.1-3.7) +gases
3	BMP 0.6 Mg 0.3 IL inc to 1.5 gm/kg TG level 0.3 on 1 gm/kg	POCT gas 0.2	BMP if need BUN and Cr instead of istat lytes at any time		CBC 0.3 if neutropenia Plt count 0.3 if thrombo-cytopenia	1.1-1.4 (4.2-5.1) +gases
4	Chem 8 0.2 IL inc to 2 gm/kg	POCT gas 0.2	Phos 0.3 if hyperglycemia	NB 0.3		0.7-1 (4.9-6.1)
5	BMP 0.6 Phos 0.3 IL inc to 2.5 gm/kg TG level 0.3 on 2 gm/kg	POCT gas 0.2				1.1 (6-7.2)
6	Chem 8 0.2 IL inc to 3 gm/kg	POCT gas 0.2				0.4 (7.1-7.6)
7	Chem 8 0.2 IL 3gm/kg TG level 0.3 on 3 gm/kg	POCT gas 0.2		NB 0.3	CBC 0.3 if neutropenia Plt count 0.3 if thrombo-cytopenia	1-1.3 (8.1-8.9)
8	Chem 8 0.2 Phos 0.3					0.5 (8.6-9.4)
9	Chem 8 0.2	POCT gas 0.2				0.4 (9-9.8)
10	ISTAT/BMP PRN BMP 0.6 5-7 days off PN Phos 0.3 5-7 days off PN					0.9 (9.9-10.7) Save 1.4 by adding on mg and phos

v.10-14-19

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Erythropoietin Use in Preterm Infants:

Erythropoietin (epo) has been extensively studied in neonatology to assess its impacts on not only red cell production, but also neuroprotection, ROP, HIE, and other potential benefits. Thus far, the data has been conflicting. Studies are ongoing that may enlighten our use in the future, however as of this writing, the current recommendations regarding epo use are as follows.

- **Neuroprotection: Not indicated based on current data.**
  Smaller trials preceding PENUT trial were mixed but overall appeared promising. The PENUT trial (24-27 6/7 weeks multicenter) data is not currently published but is reported to have demonstrated no improvement in primary outcome of death or NDI at age 2.
- **Anemia/avoidance of transfusion**: Epo may be considered on a case by case basis (i.e. Jehovah witness, infant with increased/extraordinary ongoing lab draws) but is not recommended as part of our routine practice at the present time.
- **When used:** Follow Neofax dosing regimen (400 units/kg/dose SQ qMWF with enteral iron supplementation at 6 mg/kg/day and possibly folate and vitamin E supplementation working closely with registered dietitians). Length of treatment to be determined by individual scenario and response.

ELBW Infants born to Jehovah's Witness Families:

Ninety percent of ELBW and 60% of VLBW infants are estimated to receive at least 1 red blood cell (RBC) transfusion during their NICU stay (Kim 2018).

One case study presenting a 23 week infant born to a Jehovah's Witness family concluded that, "Currently, it is nearly impossible to honor the beliefs of Jehovah's Witnesses to provide lifesaving treatments without blood transfusions for infants born at the border of viability" (Sauer 2016). While it is our goal to mindfully preserve any infant's blood as much as possible, we may have to deviate from ideal practice in the case of JW infants.

As caregivers and providers, we must remember that these parents love their baby and want the best for them despite what seems "reasonable" to us in the medical community. Our best care of the baby includes embracing the family and working with them within the confines of their faith.

Medical Strategies:

- Avoid iatrogenic losses as much as possible.
- Perform delayed cord clamping at delivery.
- Use cord blood for initial labs: CBC, BCx
- Consider erythro- or darbepoetin (Ohls, Roohi, Peceny, Schrader, & Bierer, 2012)
- Provide iron supplementation and excellent nutrition (supportive measures).
- Use fractional products as able such as Hgb, albumin, clotting factors, and immuno-globulins which may be accepted on an individual basis and in life-threatening situations (Campbell 2016).

Supportive and Educational Strategies:

- Complete an antenatal consult when possible explaining our intent to honor their wishes as much as possible, the efforts we will make to avoid need for transfusion, the parameters that will require a transfusion for survival, and honest discussion about our ability to avoid transfusion in ELBWs (probably can't).
- Maintain open dialogue, be sure we understand their position and expectations.
- Have conversations privately with parents away from friends and family (may refuse transfusions in front of others to avoid being judged, coerced, and shunned by their church).
- Respect their autonomy and beliefs—no one is won over by contempt.
- Confidentiality is essential as parental decisions to transfuse may affect their standing in their community (Cervantes 2018).
- Be sure parents understand that we may need to deviate from ideal practice to respect their wishes, such as using educated guesses rather than lab data to manage treatments such as phototherapy or management of FEN. Ensure that parents are aware that this deviation may result in negative outcomes. We may need to consider legal consent/coverage here. At the very least, clearly document all discussions with the family in the medical record.

Resources:

- Jehovah's Witness Hospital Liaison Committee: Community-based ministers, who assist providers and hospital personnel with evidence-based alternative treatments, facilitate communication among health care providers, clarify ethical issues, and arrange for pastoral care. They also provide support and counseling to families whose infant has received a transfusion by either court order or parental consent.

Transfusion Threshold Considerations:

Several trials have been conducted in the NICU population assessing the benefits and risks of "liberal" versus "conservative" transfusion limits. In one randomized, multicenter study enrolling 451 ELBW it was concluded that "liberal" transfusion limits resulted in higher hemoglobin levels, but conferred no benefit on survival, severe ROP, BPD, or brain injury. The lack of any clear benefit came at the cost of increased resource utilization. An earlier randomized trial enrolling 100 infants <1300 grams found that "liberal" transfusion guidelines resulted in lower adverse neurologic events (combined outcomes of IVH or PVL) when compared to "conservative" transfusion limits. Given these diverging outcomes the NRN set out with a third study, the Transfusion of Prematures (TOP) Trial, to identify ideal transfusion thresholds in the ELBW population. The TOP Trial has finished enrollment and is currently gathering long-term follow up data.

Given the lack of consensus based on current available evidence, it is recommended that we continue to utilize our current transfusion guidelines, which fortunately fall between both the "liberal" and "conservative" limits set forth in the aforementioned trials, until the data from the

TOP Trial is available for review. Note that there is a significant body of adult data that clearly demonstrates a linear dose-response curve between transfusion volume and adverse outcomes such as Transfusion Related (TR) Acute Gut Injury, TR Acute Lung Injury, and TR Acute Kidney Injury. Therefore, the minimum transfusion volume to achieve the desired improvement should be used. "Topping off" since "we are giving blood anyway" should not be performed. SLN has previously agreed that we would use 15ml/kg for all pRBC transfusions, unless extraneous circumstances (such as high-volume, active hemorrhage) were present.

pRBC Transfusion Guidelines:

Hematocrit	Associated Clinical Variables
<35%	PDA, PPHN, FiO2 >40%, or ventilated
<28%	NIPPV, SiPAP, CPAP, HHHFNC
<25%	Supplemental O2 and symptomatic (i.e. apnea, multiple spells with intervention, poor weight gain, HR >165 for >48 hours, unexplained lethargy
<20%	Asymptomatic and in RA

Platelet Transfusion Thresholds:

Normal reference range platelet levels for neonates were published in 2016 based on data gathered from the IHC database (SLC, UT) using >350,000 CBCs from 100,000 neonates between the years of 2005-2014.

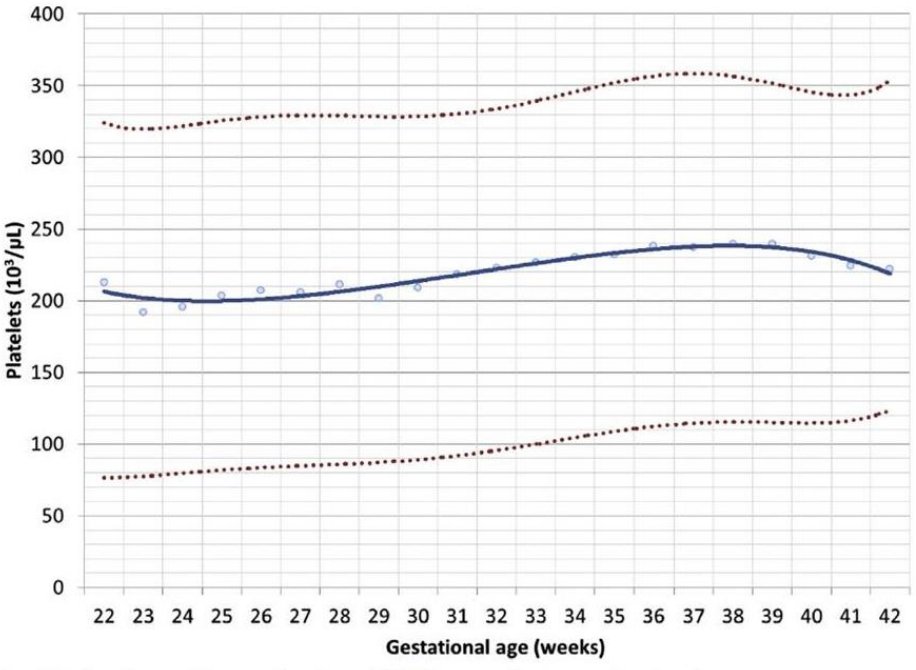


Fig. 11. Platelet counts on the day of birth, according to gestational age.

5th percentile, 95th percentile, and average. Henry, Christensen. Clin Perinatology. Vol 42:3. 2015

There are risks associated with platelet transfusions. Platelets have increased amounts of cytokines and can synthesize proteins, many of which are involved in the inflammatory cascade. The inflammatory mediators in stored supernatant increase with length of storage time. Platelets also have increased amounts of pro-thrombotic mediators and lipids that have been implicated in transfusion-related acute lung injury following transfusion. The preterm lung is at increased risk to injury from these factors as it has a large capillary bed and abundant immune cells. Because platelet transfusions are not necessarily benign and because they are a scarce resource, research has tried to determine the threshold below which there is an increased risk of bleeding in the premature infant.

There are currently 2 RCTs that are informing the practice of prophylactic platelet transfusion in the premature infant. The first study examined platelet transfusions given to VLBW infants (without active bleeding) in the first week of life using the thresholds of 150k or 50k (Andrew, 1993). This study showed no significant difference in the incidence of the primary composite outcome of new intracranial hemorrhages or worsening of existing intracranial hemorrhages. A non-RCT study done by Sparger (2016) looking at transfusion practices in VLBW infants in the first 7 days of life also found that platelet transfusions did not have a significant effect on the incidence of IVH.

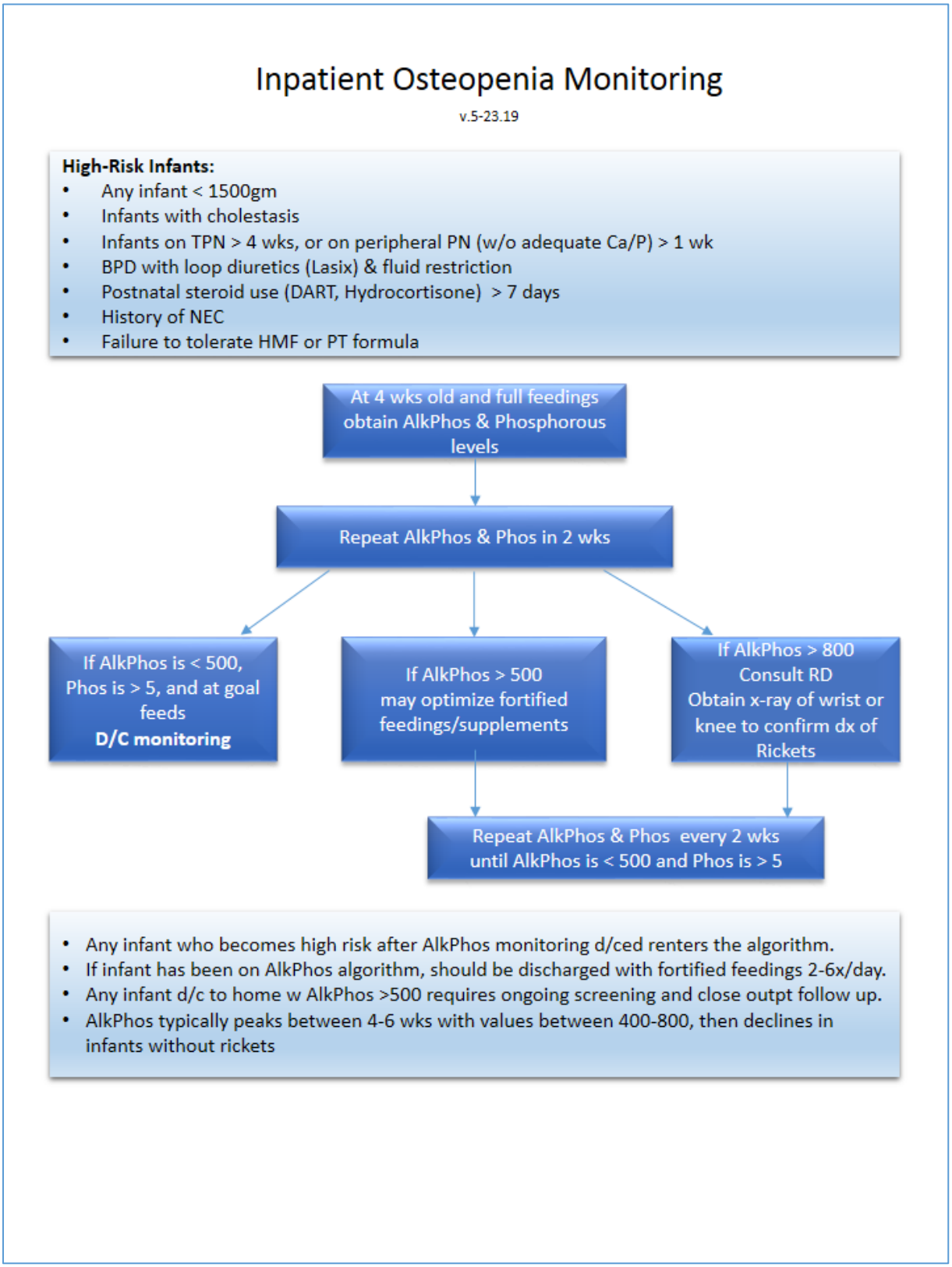
The second RCT (Curley 2019) looked at infants born <34 wks (median GA 26.6 wks (22.7wk – 33.9 wk), median BW 740gm (360gm-2490gm)) who were randomly assigned to receive a *prophylactic* platelet transfusion at thresholds of 50k or 25k. Many patients were clinically unwell at the time of randomization. Only 37% of infants were recruited before DOL 5. Those with defined bleeding were not included in the study. The primary outcome was a composite of death or new major bleeding (quantified using a validated neonatal bleeding assessment tool) within 28 days after randomization. Infants in the high-threshold group had a significantly higher rate of death or major bleeding within 28 days after randomization than those in the low-threshold group.

Platelet Transfusion Recommendations:

- May consider platelet threshold of 50k for prophylactic platelet transfusion in premature infants <72 hrs of life (freshest available).
- May consider lower threshold of 25k for prophylactic platelet transfusion in premature infants >72 hrs of life (freshest available).
- Transfuse volume of 20ml/kg. "Volume reduced" transfusions are not recommended.
- Avoid enemas in patients with platelet count <50k.
- These guidelines are NOT meant for:
  - Grade 2 or greater IVH within 72 hrs of life, or fetal intracranial hemorrhage
  - Immune mediated thrombocytopenia
  - Infants with shock/hemodynamic instability requiring pRBCs/volume
  - Life-threatening bleeding or Disseminated Intravascular Coagulation
  - Life-threatening congenital malformation
  - Patients who did not receive Vitamin K
  - Surgical patients

Endocrine and Metabolic

Inpatient Osteopenia Monitoring:



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Developmental

In the past several years there has been a significant reduction in mortality and morbidity among children born extremely preterm. However, there has been no change in the rate of severe neurodisability in this patient population. Additionally, because of the increase in survival, there has been an increase in the overall number of children with neurodisabilities (Lea 2017). Neurodevelopmental sequelae are inversely related to gestational age at birth (Poggi Davis 2011, Pugliese 2013).

VLBW infants are at the highest risk for the development of:

- Cerebral palsy
- Coordination disorders including motor delays, altered muscle tone, abnormal movement patterns and difficulties with balance and visual-motor coordination.
- Hearing and visual impairment
- Speech-language delays
- Sensory processing issues
- Learning disabilities
- Behavioral problems
- Social-emotional and mental-health issues including schizophrenia, autism spectrum disorder, and attention deficit/hyperactivity disorder

(Askshoomoff 2017, Hutchinson 2013, Altimier 2013, Pugliese 2013, Shah 2016).

To better understand why this occurs one must understand fetal brain and central nervous system (CNS) growth and development. There are overlapping but distinct stages of fetal neurologic development: proliferation, migration, circuit formation, and pruning (Stiles 2010)

The third trimester of pregnancy is a period of considerable growth and evolution for the fetal brain and central nervous system (Altimier 2013). The most critical time for circuit formation and pruning starts just prior to the beginning of the third trimester of pregnancy. Circuit formation is regulated by chemical & molecular signals that promote neuronal growth toward specific target cells and form connections. Pruning, also known as neuroplasticity, includes removing unnecessary neurons and synapses as well as organizing synaptic connections. Pruning changes brain function and is determined by experiences (DeMaster 2018)

The brain of a child born <28 weeks gestation has a reduced cerebral and cerebellar mass with abnormal structural organization and function, even in the absence of injury (Kapellou 2006)

Brain structure and development, which determines function, is influenced by four main factors: genetic endowment, endogenous stimulation and sleep, external experiences, and stimulation from the physical, chemical, sensory, and social/emotional environments (Graven 2008). The preterm infant is deprived of the normal stimuli of the womb while being exposed to noxious stimuli in the NICU. Therefore, neurological development is altered by premature delivery and the NICU experience (Buss 2014, Liu 2007, McGrath 2011). Medical professionals

and families can work together to minimize the negative impact of the NICU experience with the goal of reducing subsequent impairment and disability.

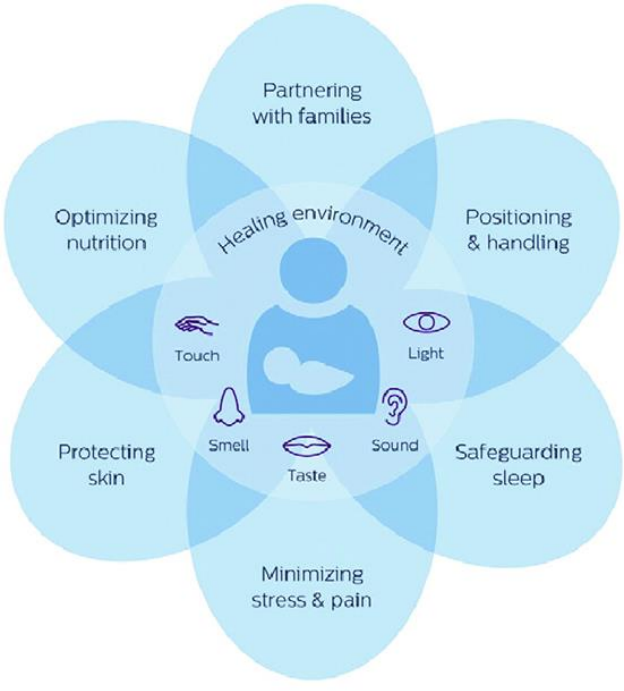
The objective of neuroprotective care is to support normal brain growth and maturation by minimizing neuronal cell death, supporting healing, and promoting normal synaptic development and function (Montirosso 2012). High-quality, family-centered developmental supportive care is associated with improved physical, cognitive, behavioral, and emotional outcomes (Coughlin 2009, DeMaster 2018). For optimal neurodevelopmental outcomes, NICU staff should be experts in providing consistent clinical developmentally supportive care as well as psychosocial support to families.

The following neuroprotective guidelines are primarily the integration of Trauma-Informed Care (TIC) in the NICU, using the framework of The Neonatal Integrative Developmental Care Model.

Trauma-Informed Care (TIC) in the NICU: Evidence-Based Practice Guidelines for Neonatal Clinicians. This book is an evidence based clinical practice guideline for providing age-appropriate care in the NICU. The model integrates the theory of trauma-informed care in addressing five core measures: Healing Environment, Pain and Stress, Protected Sleep, Activities of Daily Living, and Family Collaborative Care (Coughlin 2017).

The Neonatal Integrative Developmental Care Model. This article is a clinical guide for providing family-centered, evidence-based neuroprotective care for preterm infants in the NICU. The care model identifies seven core measures: Healing Environment, Partnering with Families, Positioning and Handling, Safeguarding Sleep, Minimizing Pain and Stress, Protecting Skin, and Optimizing Nutrition (Altimier 2016).

The Neonatal Integrative Developmental Care Model



The Healing Environment - Core Measure 1:

The healing environment includes the physical environment. This includes everything the family and baby is exposed to or can perceive. The infant's microenvironment is the area immediately surrounding the baby (Altimier 2016).

Light

The visual system is complex and susceptible to pre- and postnatal nutrition as well as postnatal visual stimulation. The NICU can negatively interfere with visual development and brain activity, and cause sleep deprivation and fragmented sleep as well as exposing the ocular structures to intense light. Protective sleep strategies that support sleep such as cycled lighting, maintaining ambient light, and controlling sound levels can minimize the effect in the NICU environment on the developing system (Coughlin 2017).

Brandon et al (2017) found that the initiation of early (28 weeks CGA) day-night cycled lighting versus late (36 weeks CGA) day-night cycled lighting resulted in a shorter length of stay as well as improved weight gain. Although in this study the results were not statistically significant, there is potential for improved clinical outcomes with a relatively innocuous intervention. Cycled lighting was provided by allowing light in from 4 sides of the incubator during "daylight" hours and an incubator cover was used during "night hours" (Brandon 2017). Light was used as needed during cares and procedures with care to cover the baby's eyes from direct overhead light. It is possible that cycled lighting may aid in the development of circadian rhythms and sleep patterns (Coughlin 2017, Brandon 2017).

Olfactory and Taste

Taste and smell develop early in gestation and the sense of taste is important for swallowing in intrauterine life. Taste buds develop by 7 weeks gestation and are mature by 17 weeks. By 24 weeks the olfactory receptors are functioning. Research shows that sweet tastes stimulate swallowing while bitter/sour tastes decrease swallowing. Amniotic fluid has a distinct flavor and odor that bathes the taste and olfactory senses of the developing fetus. By 6 months gestation the individually distinct flavor of amniotic fluid is completely experienced by the fetus as the epithelial plugs in the nasal passage dissolve. These same odor and flavors are evident in maternal breast milk and recognized by the neonate (Coughlin 2017).

Neonatal exposure to maternal odor and flavors decreases crying and increases soothing. Early exposure to maternal breast scent and taste promotes positive developmental behaviors and stimulates rooting and sucking, promoting early feeding cues in preterm infants. Exposure to maternal breast milk odors and tastes results in faster oral feedings in preterm infants. (Coughlin 2017).

Sound

Fetal hearing and vestibular function develop simultaneously with the structures of the inner ear. The cochlea and auditory system is functional between 22 and 25 weeks gestation. The development of these structures continues through the first decade of a child's life. The low

frequency (<500hz) sounds of the intrauterine environment, maternal heart and blood vessels, muted maternal speech, and bowel tones are the ideal stimulus for the developing cochlea. Bone conduction with fluid transmission is the primary mode of hearing in the developing fetus. The prematurely born infant is abruptly exposed to air conduction of sound. These sounds are broad spectrum in frequency, electronic, non-biologic, unpredictable and direct from source rather than being attenuated by maternal fluid and tissue (Coughlin 2017).

Premature infants do not habituate to sounds as readily as term infants, though babies of all gestations can be stressed by noise. Infants with CNS injury are especially vulnerable to and affected by increased noise levels. The most common loud noise in the NICU is staff conversation (Gardener 2011). Infants in the NICU are continually exposed to inconsistent poor-quality language referred to as "multi-talker babble," rather than their mother's exclusive voice (Coughlin 2017).

The negative effects of noxious sound exposure for an infant in the NICU include increased stress responses, increased agitation, hypoxemia, blood pressure and heart rate fluctuations, increased risk of IVH due to increased cerebral blood flow, mottling, apnea, feeding intolerance, poor state modulation, impaired sleep and the development of abnormal sleep wake cycles (Gardener, 2011). Among NICU graduates, the incidence of hearing impairment is estimated to be 10-fold greater than in term infants (Coughlin 2017).

Touch

Touch is the first sensory system to develop in the fetus and occurs during the eighth week of gestation (Coughlin 2017). In the ELBW, excessive stimulation causes repetitive activation of the infant's stress response, leading to maladaptive neurological patterns in the developing infant. Babies in the NICU are often subjected to repeated painful tactile experiences that can cause toxic stress, which may lead to trauma in the ongoing neurological development of the infant. The main areas that touch can be influenced in care of the ELBW infant are pain and stress. Pain and stress events include procedures, disruption of sleep states, completion of activities of daily living like diaper changes, and skin care (Coughlin 2017).

Infants rely on their caregivers to manage painful and stressful events in order to help the developing brain process these stressors and convert them into tolerable stress verses toxic stress. There is evidence to show that there are inconsistencies in treatment and management of neonatal pain, specifically that it is typically undermanaged. The occurrence of under-management of neonatal pain should be a "never event" (Coughlin 2017). By this, we mean that if interventions are used consistently for pain and stressful events, positive stressors and tolerable stressors shouldn't increase the likelihood of trauma to the neonatal brain. Examples of pain stressors include feeding tube insertion, needlesticks/heel sticks, and dressing changes (Coughlin 2017). Other stressors can include diaper changes, repositioning, and increased access into the infant's isolette. In order to best elicit positive responses and decrease negative responses to painful or stressful experiences, consistent interventions need to be performed to effectively manage stress.

Skin-to-skin care (SSC) has been well-studied and proven to improve a multitude of outcomes. Benefits of SSC include longer and more successful breastfeeding, less parental stress and improved satisfaction with the NICU, and improved parental responsiveness to their baby's cues (Baley 2015). Additionally, it has been suggested that there are improved neurobehavioral outcomes, more mature sleep organization, more alertness, and less time spent crying (Baley 2015). Buss et al (2012) found that there can be a reversal of the effects of prenatal stress when there is strong parental attachment/bonding. Knowing this, we should encourage a secure attachment between mom/dad and baby whenever possible. It is important to note that despite these benefits, the risks of IVH and line dislodgement outweigh these benefits, and therefore ELBW infants should not do SSC for the first 72h of life or while umbilical lines remain in place.

Partnering with Families - Core Measure 2:

Collaborating with families is imperative in providing care that will optimize developmental outcomes in the NICU (Altimier 2016). Studies show that integrating and empowering families in the care of their infant reduces morbidities and length of stay, thus decreasing hospital costs, monetary costs to society, as well as human costs to the family which are associated with NICU hospitalization (Altimier 2016, Coughlin 2017).

Principles involved in partnering with families include: parents are part of the care team in the NICU caring for their infant; parents need to be provided with education and tools to help them understand the care their infant requires; parents need to be engaged in all aspects of the care their infant receives in the NICU; and the entire care team needs to support this model of care (Banerjee 2017, Coughlin 2016).

Partnering with families/Family Integrated Care will be discussed at length in the Social portion of the Small Baby Guidelines.

Resources for parents:

- handtohold.org/support/nicu-support
- marchofdimes.org/complications/the-nicu.aspx
- Babystepstohome.com
- familynursing.ucsf.edu/resources-parents

Positioning and Handling - Core Measure 3:

Fluctuations in blood pressure and cerebral blood flow are central in the pathogenesis of intraventricular hemorrhage (IVH). Studies have shown that turning the head to the side effects jugular venous return and may affect intracranial pressure and cerebral blood flow (Coughlin 2017). Maximizing comfort and avoiding noxious stimuli is ideal when providing care for this vulnerable population. Therapeutic positioning provides support and boundaries. A nest-like environment helps support positions that mimic flexible and consistent womb-like boundaries (Coughlin 2017). Gentle flexion and midline orientation of the extremities along with head and trunk midline or neutral alignment promote positive growth and development of the neuromotor and muscular systems. Regular changes in posture and position, as well as use of positioning aids to support hip and shoulder posture (including appropriately sized diapers to

allow adequate hip adduction), can reduce pain and stress behaviors during routine caregiving and support normal neuromuscular and osteoarticular function (Coughlin 2017). Therapeutic positioning can also positively impact physiologic stability, facilitation of optimal early sensory-system, and brain development.

Safeguarding Sleep - Core Measure 4:

Providing for adequate rest and sleep may be the single most important contribution that NICU caregivers can make to a preterm infant's long-term outcome (Lockridge 2018). The benefits of protecting sleep include a decrease in infant's length of stay, decrease in morbidity and mortality, improved neurodevelopmental outcomes, easier to transition home, and decrease in hospital readmissions after discharge (Coughlin 2017). Preterm infants can spend up to 20 hours a day in a sleep state. As the preemie's brain matures and becomes more organized, less sleep is required, and the preemie will begin to have longer periods of wakefulness (Coughlin 2017). Sleep is essential for the growth, healing and healthy development of the premature infant. Quiet sleep is important for restoring the infant's energy and maintaining homeostasis.

The predominant sleep state for a preemie is the active sleep state. This is when meaningful input experienced by the infant is prepared to be transferred into long-term memories. Active sleep is important for making memories, processing sensory input, consolidating information and learning (Coughlin 2017, Altimier 2016).

AAP recommendations regarding back to sleep are to place infants on their backs starting at 32 weeks gestation up to 12 months of age (Coughlin 2017). It is important to help parents establish a consistent and healthy sleep routine with their baby. Modeling safe sleep practices and encouraging parents builds confidence in their ability to recognize the infant's cues, state, and uniqueness (Coughlin 2017).

Minimizing Stress and Pain - Core Measure 5:

Physiologic or stress defense mechanisms are mediated through the hypothalamic-pituitary-adrenal (HPA) axis and the social engagement system. The three neural circuits that regulate the reaction to perceived threats include: immobilization, mobilization, and social engagement (Coughlin 2017). Immobilization is the most primitive defense mechanism, it manifests as *feigning death* or *playing possum*. This is seen when there is an inability to express normal stress behaviors and manifests as clinical decompensation, loss of tone, loss of consciousness or responsiveness (Coughlin 2017). Mobilization, also known as *fight* or *flight*, stimulates the sympathetic nervous system and results in increased metabolic activity, swatting, kicking, crying, etc. If mobilization is not effectively managed by caregivers, the baby will revert to immobilization or disengagement. Social engagement supports a sense of calm and inhibits sympathetic activity. Relaxed facial expressions or a quiet alert state are signs of healthy social engagement (Coughlin 2017).

Protecting Skin - Core Measure 6:

Refer to Thermoregulation/Integumentary chapter of the Small Baby Guidelines.

Optimizing Nutrition - Core Measure 7:

Refer to the Fluids, Electrolytes, and Nutrition chapter of the Small Baby Guidelines.

There is overwhelming evidence to suggest that the use of breast milk positively influences health outcomes throughout life (Coughlin 2017). Lactation support has been proven to reduce maternal anxiety and increase and prolong breast milk feeding (Coughlin 2017).

Recommendations to Maximize Normal Development:

Recommendations to Maximize Normal Development
#1 Healing Environment: Maintain an environment of teamwork and mindfulness that promotes healing by minimizing the impact of the NICU environment on the developing infant's brain. • Impress the importance of the healing environment in an effort to protect the developing sensory systems and emphasize the parents' central role in this effort • Educate parents on sensory exposures and how to manage them in order to maintain a healing environment • Maintain an organized, non-cluttered, pleasant space for the family to care for their baby with as much privacy as possible • Encourage and facilitate parental contact, presence, and care involvement as often as possible – reduce separation • Consider all sensory sources that a baby is exposed to during cares and eliminate inappropriate or unnecessary sources Light: • Shield eyes from direct overhead light during all interventions • Keep incubator covered until 28 weeks with goal of near darkness • Initiate cycled lighting at 28 weeks until in open crib - allow light into incubator from 4 sides during daytime hours, provide near darkness at night • Minimize purposeful visual stimulation until 37 weeks (avoid toys, photos, etc.) Taste and Smell: • Maintain a scent and fragrance free unit • Minimize exposure to noxious odors including hand sanitizer, perfume/cologne, alcohol prep pads, Cavilon No-Sting Barrier (consider adequacy of ventilation with these items in an incubator/the baby's microenvironment) • Expose the baby to parents' scents by placing breast pads or soft clothes near the baby's face. • Facilitate positioning that promotes the baby's hands near the mouth. • Utilize colostrum or breast milk for oral cares. Sound: • Monitor periodic decibel levels in patient care areas. Goal decibel level is 45dB with intermittent maximum of 65dB • Limit "multi-talker babble" (including family) and staff conversations (report or rounds) in the baby's microenvironment • Encourage soft parental conversation with the baby (reading books, singing lullabies, etc.) • Utilize the newest equipment and ensure proper functionality to avoid extraneous hardware noises (for instance fans or motors running • Silence alarms as soon as possible • Do not allow water to settle in respiratory equipment to prevent extraneous noise from turbulent flow • Use incubator covers to insulate external noise • Ensure careful, quiet closure of porthole covers and drawers • Do not place equipment on top of incubator • Limit cell phone use in the baby's microenvironment

Touch:
- Refer to chart with suggested pain management interventions
- Promote, early, frequent, and prolonged skin-to-skin with parents (after 72h of age)
- Demonstrate therapeutic touch to parents for their baby using gentle pressure, facilitated tuck, containment or hands to midline. Discourage stroking skin or excessive patting.
- Provide a neutral thermal environment
- Avoid rough surfaces such as lying on seams or piling of fabrics on line

#2 Partnering with Families: Provide family-centered care from birth. Infant will develop emotional connection & secure attachment with parents.
- Parents are recognized as primary caregivers for their baby, involve parents in decision making and care planning
- Support zero-separation whenever possible
- Discuss the baby in a culturally appropriate and understandable way, avoiding acronyms and medical jargon
- Utilize Social Work early to identify and support family needs especially regarding grieving, postpartum depression, and post-traumatic stress

#3 Positioning and Handling: Maintain clinical stability throughout positioning changes and handling activities. Prevent positional deformities by maintaining a midline, flexed, contained, and comfortable position.
- Change the baby's position slowly, avoid sudden movements
- First 72 hours:
  - Refer to Philips recommendations for *softly supine* in order to properly utilize available positioning aids. https://usermanual.wiki/Philips/PositioningPoster.3510728089.pdf
  - Neutral (midline) head positioning should be initiated and maintained from time of delivery and regardless of required respiratory support
  - Elevate the head of bed 30 degrees, do not place in Trendelenburg
  - Use caution when adjusting head of bed or repositioning bed for radiographic imaging, move slowly and account for linen under the infant, level the baby not the surface of the bed
  - Supine positioning is preferred with additional supports to maintain midline head positioning
  - Partial side-lying position is acceptable with additional supports to maintain midline head positioning
  - All cares require at least 2 caregivers present and should be coordinated with the entire care team whenever possible
  - Cares should be done with cues whenever possible but at least every 6 hours
  - Change diaper by supporting hips and shifting lower body to the side and sliding diaper beneath infant while maintaining neutral head positioning. Hips should not be lifted above the shoulder
  - Maintain midline head position and flexion and support of extremities throughout cares
- After 72 hours:
  - Refer to Philips recommendations for *properly prone, side-lying support,* in addition to previously used *softly supine* positioning
  - Do not swaddle until no longer requiring humidity

- OT/PT for routine positioning, range of motion, oral/motor skills progression, sensory development, and parent education. Follow for individual recommendations from OT/PT.
- Initiate regular skin-to-skin as tolerated
- After 32 weeks - may swaddle
- After 36 weeks - remove nest/boundaries, swaddle lightly (may require warmer clothes)

#4 Safeguarding Sleep: Protect prolonged periods of uninterrupted sleep.

- Cares and interventions by cues whenever possible
- Protect all aspects of the healing environment to promote healthy sleep-wake cycles
- Arouse gently using soft voice and touch
- Promote smooth transition back to sleep after interventions
- AAP recommendations for back to sleep implemented at 32 weeks per Safe Sleep Guideline.

#5 Minimizing Stress and Pain: promote self-regulation and neurodevelopmental organization, minimize excessive stress and pain.

- Facilitate skin-to-skin contact
- Educate parents on their baby's cues related to stress and pain and how to provide nonpharmacologic support
- Anticipate, prioritize, and support the needs of the baby to minimize stress and pain
- Utilize and document PIPPs score, interventions, and response
- If physical pain is ruled out caregiver should respond to emotional distress by consoling the infant, holding or rocking (cuddler, parent, staff, etc.), provide swing, or other movement
- Continually evaluate need for labs and procedures

The following is a list of interventions to minimize the stress response to painful stimuli. This list is not exhaustive, and caregivers should always consider the possibility that any intervention may cause stress.

- Sucrose should be administered 1-2 minutes prior to the initiation of painful or stressful procedures with non-nutritive sucking offered when appropriate
- Breast milk may also be used in small quantities with non-nutritive sucking to promote comfort
- Parents should be present during the procedure whenever appropriate and should be allowed to perform the suggested interventions when appropriate

Stressor	Technique
Heel stick, venipuncture, arterial stick	Facilitated tucking Skin-to-skin holding as appropriate Breastfeeding or Breast milk as appropriate Rocking/holding as appropriate
Feeding tube insertion	Facilitated tucking Slow, gentle technique w/lubrication
Endotracheal suctioning	Facilitated tucking, swaddling and containment Two caregivers

ETT placement	Employ rapid sequence induction for ALL non-emergent endotracheal intubations
Vaccinations	Facilitated tucking Skin-to-skin holding as appropriate Breastfeeding or Breast milk as appropriate Rocking/holding as appropriate
Lumbar puncture	EMLA cream Local anesthesia
Eye exam	Local anesthetic drops
Tape Removal	Non-nutritive sucking with or without sucrose Utilize silicone-based adhesive remover
Diaper changes	Skin-to-skin Postural support
Umbilical cord catheterization	Positioning and containment Gentle technique
PICC placement, arterial line placement, central venous line insertion	Positioning and containment Gentle technique Consider opioid analgesia
Chest tube placement	Consider local anesthetic Consider opioid analgesia Consider the use of short-acting anesthetic/analgesic agents

#7 **Optimizing Nutrition:** Feeding will be safe, functional, nurturing, and developmentally appropriate.

- Immediate and on-going lactation support
- Utilize Occupational Therapy as appropriate to support oral feeding skills
- Follow Breast and Bottle Feeding Algorithm as ordered
- First oral feeds will be at the breast for babies whose mothers are pumping their milk
- Minimize negative perioral stimulation (adhesives, suctioning, etc.)
- Promote non-nutritive sucking during gavage feedings
- Educate parents about positive oral stimulation, infant feeding cues, and feeding techniques

Occupational Therapy/Physical Therapy (OT/PT):

All infants born less than 28 weeks will receive an order for an OT/PT consult. OT/PT staff will collaborate with the medical and nursing team regarding the timing of assessments and interventions.

The primary goal of OT/PT assessments are to detect early central nervous system dysfunction. Evaluation provides earlier diagnosis, prognostic discussions with families, establishment of realistic goals for family centered interventions to improve outcomes.

Additional roles of OT/PT are to assess for aspiration risk/prevention/intervention, oral motor/feeding progression, developmental progression, tone management, positioning, family education, etc.

An individualized developmental plan and educational materials will be given to each family that will include:

- Description of the Role of Rehabilitation (OT/PT/SLP)
- Week by week description of neonatal neurodevelopment/sensory development with recommendations
- Week by week description of neonatal pre-feeding/feeding development/recommendations
- Infant stress/stability cues, calming interventions, and sleep/wake cycles
- Week by week Kangaroo/positioning guidelines/recommendations (visuals will be provided)
- Handout - pacifiers (wee thumbie, wee soothie, soothie), nipples
- Developmental/feeding home program
- List of appropriate toys for purchase to progress infant development
- Developmental milestones post discharge corrected through term-3 months
- Feeding milestones post discharge corrected to term through 3 months
- Appropriate recommendations for seating device/positioning device handout
- Safe sleep practices handout
- Neurodevelopmental Discharge Plan
- Review therapies post discharge
    - OT/PT/SLP
    - Infant Toddler Program (ITP)
    - NICU Follow up Clinic: All babies under 28 weeks should have follow up standardized assessment until 3 years of age.

OT/PT will complete 3 evaluations prior to discharge:

- Hammersmith Infant Neurological Examination (HINE)
- Test of Infant Motor Performance (TIMP)
- General Motors Assessment (GM). One inpatient OT and one inpatient/outpatient NICU follow up PT to attend training next year (2020).

- Results of OT/PT evaluations may yield need for Pediatric Medicine and Rehabilitation (PM&R) consult/management (Dr. Conlee). Criteria includes low scores on motor assessments completed by OT/PT and of the following diagnoses:
  - Periventricular leukomalacia (PVL)
  - Neonatal posthemorrhagic hydrocephalus (PHH)
  - Intraventricular hemorrhage (IVH) grade 3 and 4
  - Asphyxia
  - Encephalopathy
  - Seizures
  - Ventriculoperitoneal (VP) shunt
  - Other Neurological deficit

Follow-Up Clinic:

The St. Luke's Children's Hospital NICU Follow–Up Clinic provides ongoing developmental assessment for infants meeting high risk criteria after discharge from level 3 or higher NICU per Guidelines for Perinatal Care 8th edition.

Criteria for clinic referral:

- Less than or equal to 30 6/7 weeks gestation
- Less than or equal to 1500 grams
- Twin or triplet of a sibling that qualifies by weight (not mandatory)
- Length of stay greater than 60 days (regardless of BW/GA)
- Grade III-IV IVH, hydrocephalus (regardless of birth weight/GA)
- PVL on MRI or head ultrasound (regardless of birth weight/GA)
- IUGR/SGA <10% standard NICU curve at birth (regardless of gestational age)
- Hypoxic ischemic encephalopathy (HIE) moderate & severe (Sarnat 2 or 3)
- Therapeutic Hypothermia
- Seizures (unless part of known syndrome)
- Persistent pulmonary hypertension of the newborn (PPHN) requiring iNO
- Congenital Diaphragmatic Hernia
- Gastroschisis and short bowel
- Sensory impairment: Grade 3-4 ROP
- ECMO
- Hearing impaired requiring intervention
- CNS or congenital infections: (meningitis, TORCH)
- Referred by Neonatology (abnl tone, feeding problems, prolonged NG/NJ/GT support)
- Suspected syndrome without identified diagnosis

Methods/action:

1. Provide serial multi-disciplinary assessments of development, growth, nutrition, health and wellbeing for the first 3 years of life to high risk infants previously managed in the NICU in service to the patient, the family, and the primary care provider with the goal of optimized long-term neurodevelopmental and health outcomes.

a. Screening of nutrition and feeding status (RD and OT/SLP) with recommendations and referrals *(Established – RD, MD)*

- GI, WIN, RD, feeding therapy

b. Diagnose cerebral palsy early (before 5-6 months) in accordance to guidelines established in 2017 to optimize infant neuroplasticity, prevent complications and enhance parents and caregiver wellbeing using standardized motor assessment tools (GMs, HINE). *(Developing - OT/PT/MD)*

- PM&R, PT/OT - child-initiated movement, task-specific practice and environmental adaptations that stimulate independent task performance (*Learning Games Curriculum* (diplegia); *CIMT* or bimanual (hemiplegia) and *GAME* (all subtypes)) by inducing neuroplasticity and producing functional gains.

c. Assess communication skills and refer for SLP interventions to promote parent-infant transactions and to provide compensation when speech is not possible or inadequate. *(Established – using Bayley 3)*

- SLP, *It Takes Two to Talk* and *More Than Words* programs and alternative and augmentative communication.

d. Assess cognition and refer for intervention (includes OT, dev therapy and/or other therapies) as indicated. (E*stablished – using Bayley 3)*

e. Screen for autism spectrum disorder and other behavioral disorders using established screening tools (MCHAT; CBCL) with appropriate recommendations and referrals as indicated. *(Developing – plan for MCHAT at 1-3 year visits)*

- Dev peds, Center for Autism and Neurodevelopmental Disabilities

f. Place referrals for definitive diagnoses and/or treatment including medical subspecialties, therapies, counseling and care coordination as indicated. *(Established)*

g. Establish developmental transition care plan for patients at age 3. *(Established; but need comprehensive list of available programs in geographic regions to provide better information to families)*

h. Provide PCP with comprehensive documentation of assessment and recommendations *(Established)*

i. Establish and maintain a database or registry to track outcomes for ELBW infants (<1000gm) through VON ELBW Follow Up in order to allow comparison to national benchmarks for outcomes in this population. *(Developing – reviewing with IRB currently)*

j. Establish and maintain a database or registry to track outcomes for high risk groups (VLBW, SGA, HIE) in order to allow comparison to national benchmarks for outcomes in these populations. (*Not yet established*.)

Thermoregulation/Integumentary

One of the most challenging initial aspects of care from the first moments of an ELBW infant's birth is the maintenance of normothermia and the avoidance of hypothermia. Hypothermia can lead to perturbations in perfusion and blood pressure, impact clotting times, and increase metabolic demand. These and other side effects of poor temperature management may contribute to increased risk of intraventricular hemorrhage and even death. One of the reasons for poor thermoregulation in tiny infants is immaturity of the natural integumentary barriers to fluid and heat loss, hence we have chosen to combine these inextricably intertwined components of our Small Baby Guidelines.

Thermoregulation:

Preterm infants can only maintain core temperatures in a narrow range of environmental temperatures. Extremely preterm infants are at higher risk for hypothermia, compared with term infants, because of several characteristics, including:

- Large head and greater ratio of skin surface to body weight, almost 4x that of an adult
- Minimal subcutaneous fat and thinner skin with more transepidermal water losses
- Decreased ability to maintain a flexed position
- Inability to shiver
- Minimal amount of brown fat and glycogen stores
- Inefficient vasoconstriction due to underdeveloped vessel musculature
- Low levels of thermogen and 5'3' monodeindinase
- Lower surge of thyrotropin

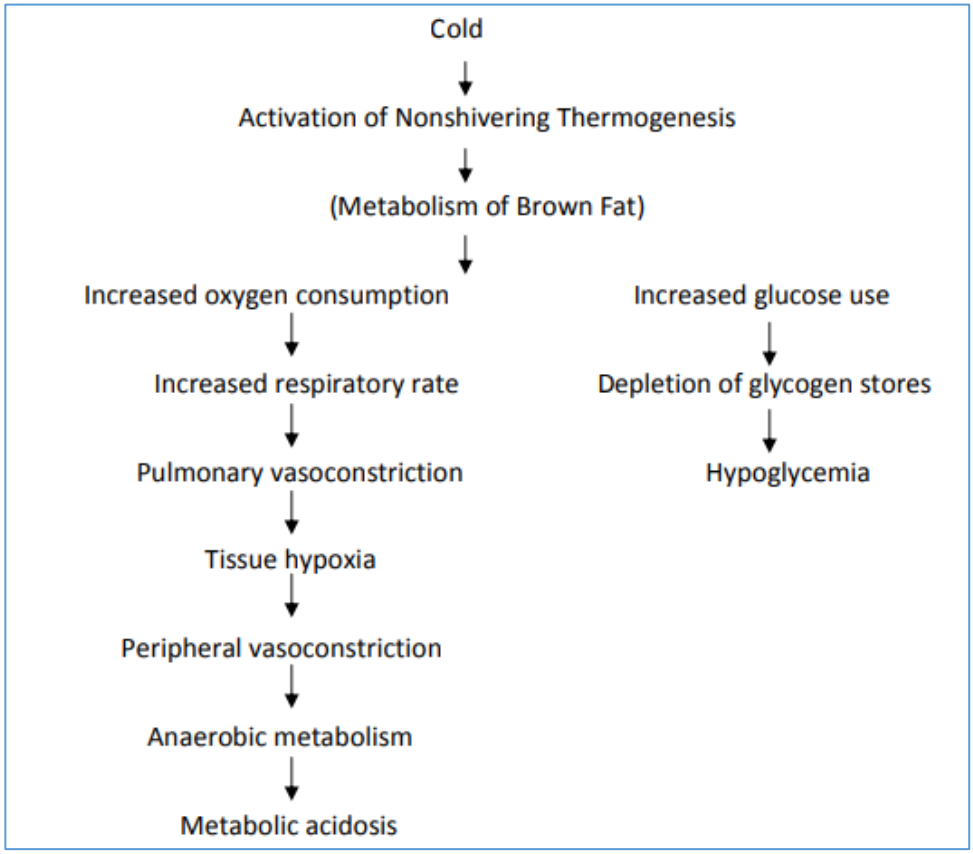
The Four Sources of Heat Loss or Gain:

- **Radiation** is loss from the infant to the surrounding objects.
- **Convection** is heat loss from the skin to moving air.
- **Evaporation** is insensible water loss from the skin's surface.
- **Conduction** is when heat transfers from one object to another

Cold Stress:

The World Health Organization (WHO) defines cold stress as a temperature <36.5°C. Cold stress effects oxygenation and inhibits normal perfusion. Poor perfusion causes an increase in anaerobic metabolism causing acidosis. Acidosis increases pulmonary artery pressure which decreases the amount of blood flow through the lungs leading to further hypoxia. Cold stress also reduces surfactant production, and the ability of surfactant to decrease surface tension is impaired if the temperature drops below 35.0°C. Cold stress increases the metabolic rate and the utilization of glucose which can lead to hypoglycemia.

Prolonged or profound hypothermia leads to a cascade of acidosis, hypoxia, clotting disorders, poor cardiac output, impaired intestinal blood flow, and decreased blood flow to the central nervous system increasing the risk for intraventricular hemorrhage, and can ultimately lead to death.



Hyperthermia:

Hyperthermia is most frequently a result of environmental factors. Hyperthermia is less likely to be a sign of sepsis in the newborn compared to the older child or adult. Causes of hyperthermia include maternal fever, maternal epidural anesthesia, overheating from incubators and radiant warmers, phototherapy lights, sunlight, excessive swaddling, infection, CNS disorders, and dehydration.

Hyperthermia can have detrimental consequences including hypotension, dehydration, hyponatremia, apnea, and seizures.

Neutral Thermal Environment (NTE):

ELBW infants should be maintained in a neutral thermal environment (NTE). The NTE is the environmental temperature at which the infant's metabolic demands and oxygen consumption are minimized. NTE depends on birthweight, postnatal age, and the presence of clothing or swaddling. Strategies for maintaining thermal stability in the ELBW beyond the first two weeks of life change due to the rapid maturation of the stratum corneum in the first 10-14 days (Jurica 2016).

Integument:

The skin provides many functions essential for survival, including:

- Thermoregulation and minimization of caloric losses
- Antimicrobial defense
- Protection from environmental toxins
- Protection from trauma
- Protection from ultraviolet radiation
- Tactile sensation
- Maintaining electrolyte and fluid homeostasis

The epidermal permeability barrier is in the stratum corneum, the outermost layer of the skin. This barrier typically forms in utero during the third trimester. Infants born <28 weeks have minimal anchoring fibrils, anchoring filaments, and hemidesmosomes compared to the term infant. This leads to decreased anchoring of the epidermis and increased susceptibility to shear forces[2].

The stratum corneum epidermal permeability barrier is significantly underdeveloped, leading to increased transepidermal water loss (TEWL) as much as 15 times more water per kilogram of body weight compared with term neonates, loss of heat, increased caloric demands, increased potential for absorption of environmental toxins, and compromised antimicrobial defense[2].

Postnatal age and gestational age are important considerations in assessing skin maturity and in determining skin-care practices. Exposure of premature skin following birth to the dry extrauterine environment accelerates development of an effective epidermal barrier. Barrier maturation following birth typically takes 2-4 weeks but can take up to 9 weeks in extremely premature infants.

Almost 80% of ELBW newborns develop a skin problem during the first month of life. Unfortunately there is limited information available on effective and safe skin care treatments for this population. Based on current knowledge about the characteristics and limitations of the ELBW skin, however, we propose several strategies below.

Wound Care:

Due to the fragile nature of the ELBW's skin, they are at the highest risk for skin breakdown and development of wounds. Medihoney contains active Manuka honey (species Leptospermum or Tea Tree) from New Zealand. Medihoney received FDA approval in 2008 and, although still being studied in the neonatal population, has been safely and effectively used on neonates as young as 22 weeks gestation. It is gaining popularity as the standard of care for skin injuries in the NICU. Medihoney is a medical grade honey which maintains its effectiveness after rigorous manufacturing to ensure that it is sterilized against contaminants and contains no bee venom or botulism spores. Honey increases antibody production, is anti-inflammatory, and has anti-oxidant properties as well as antibacterial, antiviral, and anti-fungal characteristics. It is used on minor and difficult to treat wounds. Two key mechanisms of Medihoney create an

optimal environment for wound healing. First, it has a high osmolarity which draws fluid from deep tissues, aiding in the removal of debris, and leaves microorganisms insufficient water for growth. Second, it has a low pH (3.2-4.5) which provides an acidic environment that is unfavorable for pathogens. Medihoney facilitates all stages of wound healing from debridement to granulation to wound closure. Healing time with Medihoney is of shorter duration with reduced odor, edema, pain, scarring and pulling on tissue than with conventional dressings. It is classified as a non-irritant, however there may be transient stinging due to its acidic nature. No other adverse effects have been noted. It does not have a significant impact on white blood cell counts or glucose levels. Medihoney may offer expanded uses beyond what we are accustomed to which we will continually explore. The method and frequency of application may be based on wound care recommendations as well as provider discretion.

Management Strategies - Delivery Room and Following Admission:

GOAL: Giraffe top down 1 hour from admission to the NICU

Equipment:

- Mepitac silicone tape
- Cavilon No-Sting Barrier
- Preemie Pack
- Prewarmed: betadine, saline wipes, sterile towels, Giraffe incubator, and IV fluids (IV fluids cannot be maintained long-term at prewarmed temperatures, therefore D10SPN should be pulled as soon as delivery is anticipated so that it can be warmed just prior to use).

Thermoregulation:

- DR/OR and NICU room temps to at least 76°F.
- Place infant in bowel bag immediately, maintain throughout stabilization.
- Utilize a chemical mattress, bowel bag, insulated hat.
- Admit on prewarmed Giraffe incubator with exam light.
- Obtain axillary temperature at admission. No *routine* rectal temperatures, however axillary temp less than 36.2°C can be confirmed with rectal temperature.
- Place new chemical mattress if temp <36.5°C immediately after umbilical line placement x-ray.
- When possible, do not admit to a window bed space.
- Initiate humidity protocol.
- Remove bowel bag and chemical mattress once Giraffe top is down, infant temp >36.5°C, and humidity is >40%.
- Place KPad/heated blanket if unable to normalize temp by 4 hours after admission.
- Use Air Curtain feature with Giraffe whenever portholes are opened.

Integument:

- Use Cavilon no sting barrier under all adhesives (Brandon 2010).
- Secure temp probe in this order: skin – Cavilon – probe wire – Mepitac – reflective probe cover.

- Use Cavilon under micro leads and place leads mid-axillary or laterally to avoid interference with X-ray images.
- Use minimal betadine, dab the product, do not rub, to prevent shearing the skin and absorption of the product. Remove all product with warm Saliwipe after procedure.
- Always use adhesive remover when removing adhesive securement devices including umbilical catheter anchor devices.
- Secure umbilical catheters with umbilical catheter stabilizing device.

Management Strategies – First Week:

Thermoregulation

- Follow humidity guidelines.
- Prewarm all items prior to contact with infant.
- Use air curtain feature on Giraffe for all interventions through portholes.
- Place on servo control with temp probe over the liver or flanks.
- Infant should *not* be swaddled or clothed while in servo-controlled incubator.
- Offer containment with boundaries and positioning aids.

Integument

- First bath should be no earlier than 72 hours of life and then every 4 days until DOL 30.
- Bathing in the first 2 weeks of life should consist of the removal of visible debris from creases with warmed Saliwipe or warm damp soft gauze and patting dry, no rubbing.
- Bathe with sterile water only if skin breakdown is present.
- Infant soap may be used after 28 weeks CGA or 14 DOL, whichever is later.
- Diapers should fit carefully to maximize removal of moisture from the perineal area while using caution not to fit the diaper too tightly.
- Use Cavilon No-Sting Barrier every 12-24 hours over diaper area for prevention of diaper dermatitis.
- Hydrogel dressing over high risk areas or for mild excoriations.
- Only utilize Medihoney gel or paste *per WOC RN recommendations*.
- Hollister silicone adhesive remover or Cavilon No-Sting Barrier or should be used when removing adhesives.
- Cue based cares at least every 6 hours for the first 72 hours then at least every 4 hours.

Management Strategies – Second Week Until Discharge:

Thermoregulation:

- Continue humidity protocol until 32 weeks CGA.
- NTE: Remain in double walled incubator using servo control with goal axillary temperature 36.7°C-37.5°C (Knobel-Dali 2014; Agren 2015).
    - Remain on servo control until >1200 grams and stable off humidity.
    - Once able to move to air control utilize Elsevier guidelines for set temperature.
    - Adjust set air temperatures slowly, increase or decrease by 0.5-1°C with each set of cares, no more than 1 degree in 12 hours.

- Infants with challenging growth may benefit from enhanced thermoregulation such as higher set air temperatures or remaining in an incubator for longer to minimize caloric expenditure as "thermal stress can substantially increase energy expenditure" (Poindexter & Ehrenkranz 2015).
    - If infant is in an incubator, increase set air temperature by 0.5-1°C and monitor VS closely.
    - If infant is in an open crib, place the baby back in an incubator at 27.5°C-28°C and adjust set air temperature as needed while monitoring VS closely.

Integument:

- Infant soap may be used after 28 weeks CGA or 14 DOL, whichever is later, on nonexcoriated skin.
- Utilize sterile water to cleanse areas of excoriation (no soap) after 28 weeks CGA or 14 DOL, whichever is later.
- Use Betadine aseptic cleanser until 30 days of life or 28 weeks CGA (whichever occurs later) then change to Chlorhexadine.
- Use AWHONN Neonatal Skin Care Condition Score Tool and treatment when infant is >32 weeks CGA.
- For infants less than 32 weeks CGA:
    - Cavilon No Sting Barrier every 12-24 hours over diaper area for prevention of diaper dermatitis. Allow product to dry completely before replacing diaper.
    - For broken skin in diaper area, follow wound care recommendations.
- After 32 weeks CGA utilize Diaper Dermatitis Guidelines:
    - Prophylactic treatment (barrier ointment) of every baby, every diaper, every time.
    - Consider leaving buttocks open to air several times a day.
    - If erythema is present at all, use Peri-bottle instead of rubbing with wipe. If redness is visible, breakdown is already occurring.
    - Use infant soap to help remove meconium and reduce rubbing.
    - **IF EXCORIATION OCCURS:**
        - Involve wound care early!
        - Discuss plan of care with medical team.
        - Consider use of stoma powder and Cavilon (3M)
        - **DO NOT** use products other than Cavilon (3M) and stoma powder without the involvement of wound care.
- Humidity protocol:

DOL	22-24 weeks at birth	25-27 weeks at birth
1-7	90%	70%
8	80%	60%
9	70%	50%
10	60%	50%
11	50%	50%
	D/C at 32 weeks CGA*	
*Provider may use discretion to discontinue sooner		

Social

Delivery of the extremely small baby is usually unexpected, leaving the family unprepared for the crisis of having their tiny newborn in the alien environment of the NICU. After the admission to the NICU, the family may be separated from their personal support system at a time when they are most critical for their mental and emotional well-being. There is a wealth of evidence demonstrating that parents of NICU babies experience greater emotional stress, depression, anxiety, financial stress, and even post-traumatic stress disorder (PTSD) compared to parents of healthy term babies. It is important to recognize that this experience and each family's response will be different.

Normal parent-infant bonding is forever altered with an admission to the NICU. The family's preconceived "Gerber" baby is gone once their baby is born premature and admitted to the NICU. The NICU experience impacts not only the developing vulnerable baby and the family's mental/emotional and physical health, but also the developing bond between the baby and parents. This experience impacts not only the family dynamics during the hospital stay, but also affects those dynamics for months and years following the NICU experience. That first experience in the NICU can set the trajectory for the long-term parent-child relationship and the parents' perspective of their parental role. Many parents learn their first lessons about parenting in the NICU environment which may be helpful or potentially damaging for their future role as a parent. The baby, on the other hand, will experience many threats to the successful establishment of secure and nurturing relationships. Evidence suggests that exposure to medical procedures and practices result in altered social interactions and emotional resilience. The importance of experiencing early relationships as warm, caring and stable is clear because this results in the baby's ability to develop appropriate social-emotional development and long-term mental health.

The priority for NICU staff needs to be assisting families to achieve a positive outcome from their NICU experience. Families are the constant in the infant's environment and hopefully throughout the rest of their life. Respect among all members of the care team will promote optimal patient care, enhance family satisfaction, and engage the healthcare team in ways that improve job satisfaction and a sense of fulfillment.

Parents should have unlimited access to their infant to ensure early positive bonding as well as optimal neurodevelopment of the infant. The NICU can become a comforting and inviting environment for the parents with attentive and compassionate caregivers who enable parents to be at the bedside of their vulnerable infant, coach them how to understand their baby's behavioral cues, and teach them how to appropriately care for their infant. Skin-to-skin is a very important part of the VLBW infant's growth and development. Studies have shown that skin-to-skin improves infant's weight gain, leads to earlier full enteral feeds, increases exclusive breast milk feeding at discharge, decreases parental stress/anxiety and decreases length of stay. Frequent holding has been related to improved neurobehavior at discharge and frequent skin-to-skin was related to better gross and fine motor skills at 4-5 years of age.

Creating an effective partnership between the families and healthcare professionals has been shown to decrease length of stay, increase satisfaction for families as well as increase job satisfaction for staff, and enhance neurodevelopmental outcomes for infants.

Medical staff discussed using the FARM pneumonic:

F: from, family members, names
A: affiliations, work, church
R: requirements, related concerns
M: me – share as you like

Plant seeds of trust:

Personal: using FARM, create a connection, establish trust
Like it is: update on current condition
Action: what are the changes to the plan, labs, upcoming tests, etc.
Need: further explanation, questions, other needs
Trust

Care Conferences:

Small baby families should have a prenatal conference and at least two care conferences during their infant's stay, more if clinical course dictates. These conferences, scheduled and coordinated by the PCCs, should clarify the parent's understanding of the past, discuss the current plan, and look at the potential future plan. The medical team takes the initiative in providing reassurance to the parents that their presence, opinions, and insights about their baby, as well as their active participation in their baby's care, are essential to achieving the best possible outcomes. Either Neos or NNPs may perform care conferences. For optimal time efficiency, conferences may be structured such that supporting disciplines (i.e., lactation, OT, RDs) rotate through the session allowing others to break away. PCCs may take brief notes for family during the session.

Prenatal Care Conference

- Occurs prior to delivery, hopefully not emergently
- Neonatology provider to discuss information related to gestation, survivability, morbidities, and likely clinical course
- Focus on the importance of parental involvement, how skin-to-skin and EBM are contributions they can make

Acute Care Conference (as needed only)

- Only indicated if routine bedside updates are inadequate or for significant and complex change in condition and/or plan of care

Chronic Care Conference (typically ~32-34wks CGA)

- Scheduled when the infant has stabilized and is free of acute illness
- Review full problem list with family
- Discuss chronic issues (BPD, ROP, growth)
- Make a plan for introduction to oral feeds and the role that the family wishes to play
- Identify PCP

Discharge Care Conference (1-2wks prior to discharge)

- Discuss what infant must do to qualify for discharge
- Review full problem list with family
- Confirm PCP
- Counsel parents/family to obtain necessary baby items including car seat, vitamins, outpatient medications if Rx and discharge dosing is available
- Discuss teaching that may be appropriate prior to discharge (home medical equipment, fortification, CPR, etc.)
- Discuss follow up support team and the importance of keeping all appointments (PCP, specialists, Follow Up Clinic, etc.)

Guidelines for Family Centered Care:

Attributes	Criteria	SLHS
Parents are integral to the comprehensive care of their infant	*Parents have unrestricted access to their infant *Parents are invited and encouraged to be present and participate in bedside rounds *Supportive spaces and resources are readily available for parents (comfortable bathrooms, comfortable seating, space for personal belongings, etc.)	* Parents are not considered visitors *Parents are invited to daily bedside rounds
Assessing and supporting the emotional well-being of parents is an expressed priority	*The unit has appropriate staffing ratios of licensed mental health professionals *Parents are assessed/reassessed routinely for postpartum depression and acute stress disorder; all staff are competent and responsible for this assessment *Appropriate, effective therapeutic interventions and additional crisis support resources are available (family support groups, a peer-to-peer support network, financial, spiritual)	*All units have SW available and all parents/families meet with SW/PCCs as needed.
Competence and confidence in parenting skills are mentored, supported and validated over the hospital stay	*Competency-based education is provided to all parents across all facets of the core measures for age-appropriate care to include (but not limited to) breastfeeding/feeding skills, skin-to-skin care, safe sleep, bathing and hygiene practices, infant communication cues, nonpharmacologic pain and stress strategies, etc. *All staff are culturally competent to support the parenting needs of their unique patient demographics *Parents are empowered and supported in relationship building and role validating activities with their infant such as the provision of routine infant caregiving, feeding activities, supporting their infant during painful/stressful procedures, etc.	*Neo team chose to use March of Dimes educational information which RNs can access online. PCCs continue to update NICU information booklet and provide this information to parents/families. Three NICU apps are also available for parents/families. **-My Preemie App, Graham's Foundation** **-My NICU Baby – March of Dimes** **-Peekaboo ICU** *Staff receive education about cultural differences during orientation *Staff are educated in orientation concerning family centered care. Group needs to meet with PCCs/RN champions to improve this process.

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References

FEN:

1. AAP Policy Statement. SIDS and Other Sleep-Related Infant Deaths: Updated 2016 Recommendations for a Safe Infant Sleeping Environment.
2. Adamkin DH, Radmacher PG. Current trends and future challenges in neonatal parenteral nutrition. *J Neonatal Perinatal Med*. 2014 Jan 1; 7(3):157-64. doi: 10.3233/NPM-14814008.
3. Alba Salguero-Olid et al. A Systematic Review About Prophylactic L-carnitine Administration in Parenteral Nutrition of Extremely Preterm Infants. *Farm Hosp*. 2018 Jul 1;42(4):168-173. doi: 10.7399/fh.10976.
4. Angelidou et al. Implementation of a Guideline to Decrease Use of Acid-Suppressing Medications in the NICU. Pediatrics, 140 (6). December 2017.
5. Arave, S. Capstone Project, 2018.
6. Aschner JL et al. Neuroimaging identifies increased manganese deposition in infants receiving parenteral nutrition. *Am J Clin Nutr*. 2015 Dec; 102(6):1482-9. doi: 10.3945/ajcn.115.116285. Epub 2015 Nov 11.
7. Barlow, S.M. (2009). Oral and respiratory control for pre-term feeding. Current Opinion in Otolaryngology & Head and Neck Surgery. 17, 179-186.
8. Berger, I. et al. (2009). Energy expenditure for breast feeding and bottle feeding pre-term infants. Pediatrics. 124(6). E1149-e1152.
9. Bhatia J. Fluid and electrolyte management in the very low birth weight neonate. *J Perinatol*. 2006 May;26 Suppl 1:S19-21. DOI: 10.1038/sj.jp.7211466.
10. Bingham, P.M, Ashikaga, T. and Abbasi, S. (2012). Relationship of Neonatal Oral Motor Assessment Scale to feeding performance of premature infants. Journal of Neonatal Nursing. 18, 30-36.
11. Blaymore Bier, J. et al. (1993). Breast-feeding of very low birth weight. The Journal of Pediatrics. 123 (5) 774-778.
12. Bonsate F et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants--It is time to change the composition of the early parenteral nutrition. *PLoS ONE*. 2013 Aug 15; 8(8):e72880. doi: 10.1371/journal.pone.0072880. eCollection 2013.
13. Bozzetti et al. Impact of Continuous vs Bolus Feeding on Splanchnic Perfusion in Very Low Birth Weight Infants: A Randomized Trial. J Peds, Vol 176, 85-92. Sept 2016.
14. Briere, C. E. et al. (2014). A contemporary review of feeding readiness in the preterm infant. Journal of Perinatal and Neonatal Nursing. 28(1) 51-58.
15. Browne, J. V. and Ross, E. S. (2011) Eating as a Neurodevelopmental Process for High-Risk Newborns. Clinics in Perinatology. 38(4), 731-743.
16. Burklow, K. A., McGrath, A. M. and Kaul, A. (2002). Management and prevention of feeding problems in young children with prematurity and very low birth weight. Infants and Young Children. 14(4), 19-30.
17. Chen, C. H. et al. (2000). The effect of breast and bottle feeding on oxygen saturation and body temperature in pre-term infants. Journal of Human Lactation. 16(1). 21-27.
18. Cormack BE, Bloomfield FH. Increased protein intake decreases postnatal growth faltering in ELBW babies. *Arch Dis Child Fetal Neonatal Ed*. 2013 Sep; 98(5):F399-404. doi: 10. 1136/ archdischild-2012-302868. Epub 2013 Mar 13.
19. Cormier, D. M. (2015). A Review of the Principles and Benefits of Cue-Based Feeding. Nursing Commons. 1(1). 1-6. http://fisherpub.sjfc.edu/mwg-internal/de5fs23hu73ds/progress?id=7YzCjMTrH-d_KdC_lfdHPjKCjW8ePDvW8faVhQPYZEs,&dl
20. Cunha, M. et al. (2009). Nutritive sucking pattern-From very low birth weight preterm to term newborn. Early Human Development. 85, 125-230.
21. da Costa, S. P. et al. (2010). The development of sucking patterns in pre-term small for gestational infants. The journal of Pediatrics. 157(4). 603-609.

22. da Costa, Saajke P., et al. (2010). Development of sucking patterns in pre-term infants with bronchopulmonary dysplasia. Neonatology. 98, 268-277.
23. Dreyfus L et al. Low phosphatemia in extremely low birth weight neonates: a risk factor for hyperglycemia? *Clin Nutr*. 2016 Oct; 35(5):1059-65. doi: 10.1016/j.clnu.2015.07.019. Epub 2015 Aug 10.
24. Eichenwald and Committee on Fetus and Newborn (COFN). Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants, Pediatrics, 142 (1), 1-9. July 2018.
25. Finch CW. Review of trace mineral requirements for preterm infants: what are the current recommendations for clinical practice? *Nutr Clin Pract*. 2015 Feb; 30(1):44-58. doi: 10.1177/0884533614563353. Epub 2014 Dec 19.
26. Fischer CJ et al. Early parenteral lipids and growth velocity in extremely low birth weight infants. *Clin Nutr*. 2014 Jun; 33(3):502-8. doi: 10.1016/j.clnu.2013.07.007. Epub 2013 Jul 18.
27. Gelfer, P., McCarthy, A. and Turnage Spruill, C. (2015). Infant driven feeding for preterm infants: Learning through experience. Newborn & Infant Nursing Reviews. 15, 64-67.
28. Graven, S. N. and Browne, J. V. (2008). Sensory development in the fetus, neonate, and infant: Introduction and overview. Newborn Infant Nursing Reviews. 8(4), 169-172.
29. Guthrie G, Premkumar M, Burrin DG. Emerging Clinical Benefits of New-Generation Fat Emulsions in Preterm Neonates. *Nutr Clin Pract*. 2017 Jun; 32(3):326-336. doi: 10.1177/0884533616687500. Epub 2017 Jan 27. Review.
30. Hair AB et al. Delayed introduction of parenteral phosphorus is associated with hypercalcemia in extremely preterm infants. *J Nutr*. 2016 Jun; 146(6):1212-6. doi: 10.3945/jn.115.228254. Epub 2016 May 4.
31. Hemachandra A, Cowett R. Neonatal hyperglycemia. Peds in Review. 1999. Vol 20, issue 7
32. Hillman NH, Kallapur SG, Jobe AH. Physiology of transition from intrauterine to extrauterine life. Clin Perinatol. 2012 Dec; 39(4):769-83. doi: 10.1016/j.clp.2012.09.009.
33. Horner, S. et al. (2014). Setting the stage for successful oral feeding: the impact of implementing the SOFFI feeding program with medically fragile NICU infants. The Journal of Perinatal & Neonatal Nursing. 28(1) 59-68.
34. Kish, M.Z. (2013). Oral feeding readiness in pre-term infants: A concept analaysis. Advances in Neonatal Care. 13(4), 230-237
35. Lima, A.H. et al. Preterm newborn readiness for oral feeding: Systematic review and meta-analysis. CoDAS. 2015, 27(1). 101-107.
36. Ludwig, S. M. (2007). Oral Feeding and the Late Preterm Infant. Newborn & Infant Nursing Reviews. 7(2) 72-74.
37. Ludwig, S. M. and Waitzman K. A. (2007). Changing feeding documentation to reflect infant-driven feeding practice. Newborn & Infant Nursing Reviews. 7(3), 155-160.
38. Maastrup, R. et al. (2014). Factors associated with exclusive breast feeding of preterm infants. Results from a prospective national cohort study. PLOS One. 9(2).
39. Malcolm et al. Transpyloric Tube Feeding in Very Low Birthweight Infants with Suspected Gastroesophageal Reflux: Impact on Apnea and Bradycardia. J Perinatol, 29 (5), 372-375. May 2009.
40. Malcolm, et al. Transpyloric Tube Feeding in Very Low Birthweight Infants with Suspected Gastroesophageal Reflux: Impact on Apnea and Bradycardia. J Perinatol, 29(5), 372-372. May 2009.
41. Manea A et al. Benefits of early enteral nutrition in extremely low birth weight infants.
42. McGrath, J.M. (2014). What are best practices for beginning oral feedings for high-risk infants? Journal of Perinatal and Neonatal Nursing. 28(1), 6-8.
43. Meier, P. P. (1988). Bottle and breast feeding effects on transcutaneous oxygen pressure and temperature in pre-term infants. Nursing Research. 37(1), 36-41.
44. Meier, P. P. et al. (2013). Supporting breastfeeding in the neonatal intensive care unit: Rush mother's milk club as a case study of evidence-based care. Pediatric Clinics of North America. 60(1). 209-226
45. Moltu SJ et al. Enhanced feeding in very-low-birth-weight infants may cause electrolyte disturbances and septicemia – a randomized, controlled trial. *Clin Nutr*. 2013 Apr; 32(2):207-12. doi: 10.1016/j.clnu.2012.09.004. Epub 2012 Sep 21.

46. Ng DV et al. How Close Are We to Achieving Energy and Nutrient Goals for Very Low Birth Weight Infants in the First Week? *JPEN J Parenter Enteral Nutr*. 2017 Mar; 41(3):500-506. doi: 10.1177/0148607115594674. Epub 2016 Jul 11.
47. Nyqvist, K. H. (2013). Lack of knowledge persists about early breast feeding competence in preterm infants. Journal of Human Lactation. 29(3). 296-299
48. O'Brien F, Walker IA. Fluid Homeostasis in the neonate. *Paediatr Anaesth*. 2014 Jan; 24(1):49-59. doi: 10.1111/pan.12326. Epub 2013 Dec 4. Review.
49. Ohnishi S et al. Early and intensive nutritional strategy combining parenteral and enteral feeding promotes neurodevelopment and growth at 18months of corrected age and 3years of age in extremely low birth weight infants. *Early Hum Dev*. 2016 Sep; 100:35-41. doi: 10.1016/j.earlhumdev.2016.03.014. Epub 2016 Jul 5.
50. Park, J. et al. (2015). Factors associated with feeding progression in extremely preterm infants. Nursing Research. 64(3), 159-167.
51. Parker et al. Aspiration and evaluation of gastric residuals in the NICU: state of the science. J Perinat Neonatal Nurs. 2015 ; 29(1): 51–59.
52. Poets et al. Myth: Gastroesophageal Reflux is a Pathologic Entity in the Preterm Infant. Semin Fetal Neonatal Med, 16 (5), 259-63. Oct 2011.
53. Richards et al. Continuous Versus Bolus Intragastric Tube Feeding for Preterm and Low Birth Weight Infants with Gastro-oesophageal Reflux Disease. Cochrane Database Syst Rev. July 2014.
54. Rogers, Abrams, et al. Continuous Feedings of Fortified Human Milk Lead to Nutrient Losses of Fat, Calcium and Phosphorous. Nutrients. 2 (3), 230-240. March 2010.
55. Rosen et el. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, JPGN, Vol 66 (3), 516-554. March 2018.
56. Ross JR, Finch C, Ebeling M, Taylor SN. Refeeding syndrome in very-low-birth-weight intrauterine growth-restricted neonates. *J Perinatol*. 2013 Sep; 33(9):717-20. doi: 10.1038/jp.2013.28. Epub 2013 Mar 28.
57. Ross, E. S. and Philbin, K. (2011). Supporting oral feeding in fragile infants: An evidenced-based method for quality bottle feedings of pre-term, ill and fragile infants. The Journal of Perinatal and Neonatal Nursing. 25(4). 349-357.
58. Sables-Baus, S. and Zuk, J. (2012). An exemplar for evidence-based nursing practice using the magnet model as the framework for change: oral feeding practice in the neonatal intensive care unit. Journal of Pediatric Nursing. 27, 577-582.
59. Sables-Baus, S. et al. (2013) Infant Directed Oral Feeding for Premature and Critically Ill Hospitalized Infants. Chicago: National Association of Neonatal Nurses.
60. Salama GS et al. Intravenous lipids for preterm infants: a review. *Clin Med Insights Pediatr*. 2015 Feb 9;9:25-36. doi: 10.4137/CMPed.S21161. eCollection 2015. Review.
61. Salguero Olid A. A systematic review about prophylactic L-carnitine administration in parenteral nutrition of extremely preterm infants. *Farm Hosp*. 2018 Jul 1; 42(4):168-173. doi: 10.7399/fh.10976.
62. Seigel JK, Smith PB, Ashley PL, Cotton CM, Herbert CC, King BA, Maynor AR, Neill S, Wynn J, Bidegain M. Early administration of oropharyngeal colostrum to extremely low birth weight infants. *Breastfeed Med*. 2013 Dec; 8(6):491-5. doi: 10.1089/bfm.2013.0025. Epub 2013 Jun 27.
63. Senterre T et al. Electrolyte and Mineral Homeostasis after optimizing early macronutrient intakes in VLBW infants on parenteral nutrition. *J Pediatr Gastroenterol Nutr*. 2015 Oct; 61(4):491-8. doi: 10.1097/MPG.0000000000000854.
64. Shaker, C. S. (2012). Feed me only when I am cueing: moving away from a volume-driven culture in the NICU. Neonatal Intensive Care. 25(3) 27-32.
65. Shaker, C. S. (2013). Cue-based feeding in the NICU: Using the infant's communication as a guide. Neonatal Network. 32(6). 404-408.
66. *Singapore Med J*. 2016 Nov; 57(11):616-618. doi: 10.11622/smedj.2016002. Epub 2016 Jan 6.

67. Sivalingam, Jadcherla, et al. Effects of Esophageal Acidification on Troublesome Symptoms: An Approach to Characterize True Acid GERD in Dysphagic Neonates. Dysphagia, 332 (4), 509-9=519. August 2017.
68. Smits et al. Associateion between gastroesophageal reflux and pathologic apneas in infants: a systematic review, 26 (11), 1527-38. Nov 2014.
69. Vanek VW et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutr Clin Pract*. 2012 Aug; 27(4):440-91. doi: 10.1177/0884533612446706. Epub 2012 Jun 22.
70. Vlaardingerbroek H et al. Parenteral lipid administration to very low birth weight infants – early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis. *Am J Clin Nutr*. 2012 Aug; 96(2):255-68. doi: 10.3945/ajcn.112.040717. Epub 2012 Jun 27.

Respiratory:

1. Bailes SA, Firestone KS, Dunn DK, McNinch NL, Brown MF, Volsko TA. Bailes, S., Firestone, K., Dunn, D., McNinch, N., Brown, M., & Volsko, T. (2016). *Respiratory Care, 61(*3), 333-339.
2. Bashing T. Murk is, Kieran S. Reddy VK, Oleti TP (2019) 'Nasal Mask' in comparison with 'Nasal Prongs' or "rotation of Nasal mask with NASAP prongs' reduce the incidence of nasal injury in preterm neonates supported on nasal continuous possible pressure (nCPAP): A randomized controlled trial. PLoS ONE 14(1): e0211476. Doi:10.1371/journal.pone.0211476
3. Brett J. Manley, PhD1,2, Lex W. Doyle, MD1,2,3,4, Louise S. Owen, MD1,2,4, and Peter G. Davis, MD Extubating Extremely Preterm Infants: Predictors of Success and Outcomes following Failure *J Pediatr* 2016;173:45-9).
4. Carlos A. Puyo, MD; Thomas E. Dahms, PhD Target Ranges of Oxygen Saturation in Extremely Preterm Infants SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network* Innate Immunity Mediating Inflammation Secondary to Endotracheal Intubation *Arch Otolaryngol Head Neck Surg*. 2012;138(9):854-858. doi:10.1001/archoto.2012.1746
5. Chawla, S., (2017) Markers of Successful Extubation in Extremely Preterm Infants, and Morbidity After Failed Extubation *(J Pediatr 2017;189:113-9)*.
6. Chien-Yi, C. et al. (2016). Quality Improvement of Nasal Continuous Positive Airway Pressure Therapy in Neonatal Intensive Care Unit. *Pediatrics and Neonatology* (2017) 58 229-235 Http://do.doi.org/10.1016/j.pedneo.2016.04005
7. Claassen, C., Hillman, N., Brown, K., Williams, H., & Strand, M. (2019). Comparison of bubble CPAP devices using RAM cannula for extubation failure in very low birth weight infants: Randomized and Cohort Studies. *Neonatology, 115*, 28-35
8. COFN Clinical Report – Premedication for Nonemergency Endotracheal Intubation in the Neonate. AAP. 2010. *Pediatrics*. Vol 125 (3). 808-815.
9. Colin J. Morley Nasal CPAP or Intubation at Birth for Very Preterm Infants, *N Engl J Med* 2008;358:700-8. May 27, 2010 vol. 362 no. 21
10. Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD000104. DOI: 10.1002/14651858.CD000104.pub4
11. Cools, Filip & Offringa, Martin. (1999). Meta-analysis of elective high frequency ventilation in preterm infants with respiratory distress syndrome. *Archives of disease in childhood. Fetal and neonatal edition*. 80. F15-20. 10.1136/fn.80.1.F15.
12. Doyle, J, et al. (2016) Apnea of Prematurity and caffeine pharmacokinetics: potential impact on hospital discharge. *J Perinatol*. 2016 Feb; 36 (2):141-4. doi: 10.1038/jp.2015.167. Epub 2015 Nov 12.
13. Drescher GS, Hughes CW. Comparison of Interfaces for the Delivery of Noninvasive Respiratory Support to Low Birthweight Infants. [ncbi.nlm.nih.gov] *Respir Care*. 2018 Oct;63(10):1197-1206. doi: 10.4187/respcare.05978. PMID: 30237275
14. Drescher, G. & Hughes, C. (2018). Comparison of Interfaces for the Delivery of Noninvasive Respiratory Support to Low Birthweight Infants. *Respiratory Care*, 63 (10) 1197-1206 DOI: http://doi.org/10.4187/respcare.05978

15. Eichenwald E, Martin R, Kim M. Mechanical ventilation in neonates *UpToDate* .Literature review current through: Jan 2019. | This topic last updated**:** Jun 29, 2018. Topic 5032 Version 30.0
16. Ethawi YH, Abou Mehrem A, Minski J, Ruth CA, Davis PG. High frequency jet ventilation versus high frequency oscillatory ventilation for pulmonary dysfunction in preterm infants. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No.: CD010548. DOI: 10.1002/14651858.CD010548.pub2
17. Evaluating the Effect of Flow and Interface Type on Pressures Delivered with Bubble CPAP in a Simulated Model. [ncbi.nlm.nih.gov] *Respir Care*. 2016 Mar;61(3):333-9. doi: 10.4187/respcare.04251. Epub 2015 Nov 3. PMID: 26534997 [PubMed - indexed for MEDLINE] Free Article
18. Evaluation of a nasal cannula in noninvasive ventilation using a lung simulator. [ncbi.nlm.nih.gov] *Respir Care*. 2015 Apr;60(4):508-12. doi: 10.4187/respcare.03560. Epub 2014 Dec 9. PMID: 25492958 [PubMed - indexed for MEDLINE] Free Article
19. Factors influencing delivered mean airway pressure during nasal CPAP with the RAM cannula. [ncbi.nlm.nih.gov] *Pediatr Pulmonol*. 2016 Jan;51(1):60-9. doi: 10.1002/ppul.23197. Epub 2015 Apr 7. PMID: 25851534 [PubMed - indexed for MEDLINE]
20. Feltman et al. Rocuronium for Nonemergent Intubation of Term and Preterm Infants. *J Perinatol*. 2011. Vol 31, 38-43.
21. Foglia et al. Factors Associated with Adverse Events During Tracheal Intubation in the NICU. Neonatology. 2015: 108 (1): 23-29.
22. Gerdes JS, Sivieri EM, Abbasi S. Green EA, Dawson JA, Davis PG, De Paoli AG, Roberts CT. Assessment of resistance of nasal continuous positive airway pressure interfaces. [ncbi.nlm.nih.gov] *Arch Dis Child Fetal* Neonatal Ed. 2018 Dec 19. pii: fetalneonatal-2018-315838. doi: 10.1136/archdischild-2018-315838. [Epub ahead of print] PMID: 30567774 [PubMed - as supplied by publisher]
24. Green, E., Dawson, J., Davis, P., DePaoli, A., & Roberts, C. (2018). Assessment of resistance of nasal continuous positive airway pressure interfaces." *Arch Dis Child Fetal Neonatal Ed,* 0, F1-F5.
25. Hatch et al. Endotracheal Intubation in Neonates: A Prospective Study of Adverse Safety Events in 162 Infants. *J Peds*. 2016. Vol 168: 62-66.
26. Hatch et al. Interventions to Improve Patient Safety During Intubation in the Neonatal Intensive Care Unit. *Pediatrics*. 2016. Vol 138 (4): e1-e9.
27. International survey on periextubation practices in extremely preterm infants Article *in* Archives of Disease in Childhood - Fetal and Neonatal Edition · June 2015 DOI: 10.1136/archdischild-2015-308549 · Source: PubMed
28. Iyer NP, Chatburn R. Lam, R., Schilling, D., Scottoline, B., Platteau., A., Niederhausen, M., MacDonald, K., McEvoy, E. (2017). The effect of extended continuous positive airway pressure on lung volumes in stable premature infants: A Randomized controlled trial. *American Journal of Respiratory Critical Care, 195:*A4936 https://doi.org/10.1164/rccm.201606-1162PP PubMed: 27626508
30. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD003212. DOI: 10.1002/14651858.CD003212.pub3
31. Matlock DN[1,2], Bai S[3], Weisner MD[4], Comtois N[5], Beck J[5,6,7,8], Sinderby C[5,6,8], Courtney SE[9]. Tidal volume transmission during non-synchronized nasal intermittent positive pressure ventilation via RAM® cannula. *J Perinatol.* 2019 May; 39(5):723-729. doi: 10.1038/s41372-019-0333-x. Epub 2019 Feb 12.
32. McPherson. Premedication for Endotracheal Intubation in the Neonate. *Neonatal Network*, 2018. Vol 37 (4). 238-247. doi: 10.1891/0730-0832.37.4.238. Epub 2018 Jul 1.
33. Michael Z, Spyropoulous F, et al Boston Children's Hospital, 2018 "current evidence does not support routine use of furosemide for the prevention of BPD. However, symptomatic management of pulmonary edema justifies its use for selected patients." *Clinical Medicine Insights: Pediatrics*. Vol 12: 1-12, 2018

34. Mukerji, A. & Belik, J. (2015). Neonatal Nasal intermittent positive pressure ventilation efficacy and lung pressure transmission. *Journal of Perinatology*, 35, 716-719; doi:10.1038/jp.2015.61
35. Norman et al. Rapid Sequence Induction is Superior to Morphine for Intubation of Preterm Infants: A Randomized Controlled Trial. J Peds. 2011. Vol 159 (6): 893-899
36. Nzegwu NI, Mack T, DellaVentura R, Dunphy L, Koval N, Levit O, Bhandari V. Papile LA, Tyson JE, Stoll BJ, Wright LL, Donovan EF, Bauer CR, Krause-Steinrauf H, Verter J, Korones SB, Lemons JA, Fanaroff AA, Stevenson DK. A multicenter trial of two dexamethasone regimens in ventilator-dependent premature infants. *N Engl J Med*. 1998 Apr 16;338(16):1112-8.
38. Plyer, N., & Chatburn, R. (2015).Evaluation of Nasal Cannula in Noninvasive Ventilation Using a Lung Simulator. *Respiratory Care*, 60 (4) 508-512; DOI: https://doi.org/10.4187/respcare.03560
39. Roberts et al. Premedication for Nonemergent Neonatal Intubations: A Randomized Controlled Trial Comparing Atropine and Fentanyl to Atropine, Fentanyl, and Mivacurium. *Pediatrics*. 2006. Vol 118 (4): 1583-1591.
40. Sahni M, Mowes AK. Bronchopulmonary Dysplasia. [Updated 2019 May 4]. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing*; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539879/
41. Schmidt, B, et al. (2006) Caffeine Therapy for Apnea of Prematurity. *N Engl J Med 354* 2112-2121
42. Singh N, McNally MJ, Darnall RA. Does the RAM Cannula Provide Continuous Positive Airway Pressure as Effectively as the Hudson Prongs in Preterm Neonates? [ncbi.nlm.nih.gov] *Am J Perinatol*. 2018 Nov 5. doi: 10.1055/s-0038-1675330. [Epub ahead of print] PMID: 30396227 [PubMed - as supplied by publisher]
43. Spindel, E., McEvoy, C. (In process). CPAP Drives Lung Growth and Pulmonary Function in Moderately Preterm Primates. *OHSU*.
44. Stark AR, Carlo WA, Tyson JE, Papile LA, Wright LL, Shankaran S, Donovan EF, Oh W, Bauer CR, Saha S, Poole WK, Stoll BJ; Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med*. 2001 Jan 11;344 (2):95-101.
45. Stewart, A., et al. (2011) Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. Cochrane Database Syst Rev. Sep 7; (9):CD001817
46. Systematic use of the RAM nasal cannula in the Yale-New Haven Children's Hospital Neonatal Intensive Care Unit: a quality improvement project. [ncbi.nlm.nih.gov] *J Matern Fetal Neonatal Med*. 2015 Apr;28(6):718-21. doi: 10.3109/14767058.2014.929659. Epub 2014 Jun 30. PMID: 24874561 [PubMed - indexed for MEDLINE]
47. Van Alfen-van der Velden et al, Effects of Midazolam and Morphine on Cerebral Oxygenation and Hemodynamics in Ventilated Premature Infants. *Biol Neonate*. 2006; 90: 197-202. Epub 2006 May 22 PMID: 16717443 DOI: 10.1159/000093489
48. Subramaniam, Ho, Davis. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. Cochrane Systematic Review, 14 June 2016.
49. Robbins, et al. Early extubation attempts reduce length of stay in extremely preterm infants even if re-intubation is necessary. J Neonatal Perinatal Med. 2015;8(2):91-7.
50. Walsh, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. J Pediatr. 2005; 146:798-804.
51. Wai et al. Early Cumulative Supplemental oxygen predicts bronchopulmonary dysplasia in high risk extremely low gestational age newborns. J Pediatr. 2016 Oct;177:97-102.e2.
52. Murki, et al. High-Flow nasal cannula versus nasal continuous positive airway pressure for primary respiratory support in preterm infants with respiratory distress: A randomized controlled trial. Neonatology. 2018; 113(3);235-241.
53. Abdel-Hady et al. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: A randomized controlled trial. Early Hum Dev. 2011 Mar;87(3):205-8.

54. Lam et al. The effect of extended continuous positive airway pressure on changes in lung volumes in stable premature infants: A randomized controlled trial. J Pediatr. 2020 Feb;217:66-72.e1.
55. Abman, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. J Pediatr. 2017 February: 18:12028.e1
56. DeMauro SB, D'Agostino JA, Bann C, et al. Developmental outcomes of very preterm infants with tracheostomies. J Pediatr. 2014;164(6):1303-1310.e1302.
57. Jun Luo, et al. Improved Growth and developmental activity post tracheostomy in preterm infants with severe BPD. Pediatr Pulmonol. 2018 September;53(9);1237-1244.doi:10.1002/ppul.24087.
58. Cammack B, et al. Impact of tracheostomy on language and cogniftie development in infants with severe bronchopulmonary dysplasia. J Perinatol. 2020; 40:299-305.

Cardiovascular:

1. Batton, B et al. Evolving blood pressure dynamics for extremely preterm infants. *J Perinatol*. 2014
2. Baud et al. Two-year neurodevelopmental outcomes of extremely preterm infants treated with early hydrocortisone: treatment effect according to gestational age at birth. *Arch Dis Child Fetal Neonatal Ed* 2018
3. Bell et al. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *N Engl J Med* 1980
4. Benitz. Treatment of the patent ductus arteriosus in preterm infants: time to accept the null hypothesis. *J Perinatol* 2010
5. Brooks et al. Is surgical ligation of patent ductus arteriosus necessary? The Western Australia experience of conservative management. *Arch Dis Child Fetal Neonatal Ed* 2005
6. Clyman. PDA TOLERATE STUDY. Presentation. PAS 2018
7. Corticosteroids for treating hypotension in preterm infants. Cochrane Systematic Review - Intervention Version published: 07 December 2011
8. Costarino et al. Sodium restriction versus daily maintenance replacement in very low birth weight premature neonates: a randomized, double blind therapeutic trial. *J Pediatr* 1992
9. Dionne J, Hypertension in infancy: diagnosis, management, and outcome. Pediatr Nephrol 2012.
10. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Systematic Review - Intervention Version published: 21 July 2003
11. Durrmeyer X et al. Abstention or intervention for isolated hypotension in the first 3 days of life in extremely preterm infants: association with short-term outcomes in the EPIPAGE 2 cohort study. *Arch Dis Child Fetal Neonatal Ed* 2017
12. Early blood pressure, antihypotensive therapy and outcomes at 18-22 months' corrected age in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2016
13. Early volume expansion for prevention of morbidity and mortality in very preterm infants. Cochrane Systematic Review - Intervention Version published: 19 April 2004
14. Fajardo et al. Effect of positive end expiratory pressure on ductal shunting and systemic blood flow in preterm infants with patent ductus arteriosus. *Neonatology* 2013
15. Flynn J. Etiology, clinical features and diagnosis of neonatal hypertension. 2014 [cited 2015, March 29th.]. Available from: http://www.uptodate.com/contents/etiology-clinical-features-and-diagnosis-of-neonatal-hypertension.
16. Hartnoll et al. Randomized controlled trial of postnatal sodium supplementation on oxygen dependency and body weight in 25-30 week gestational age infants. *Arch Dis Child Fetal Neonatal Ed*. 2000
17. Jenkins RD, Characteristic of hypertension in premature infants with and without chronic lung disease: a long-term multi-center study. Pediatr Nephrol 2017; 32:2115
18. Kaempf et al. What happens when the patent ductus arterisous is treated less aggressively in very low birth weight infants? *J Perinatol* 2012
19. Kaempf et al. What happens when the patent ductus arterisous is treated less aggressively in very low birth weight infants? *J Perinatol* 2012

20. Miyanoshita et al. Furosemide directly stimulates prostaglandin E2 production in the thick ascending limb of Henle's loop. *J Pharmacol Exp Ther* 1989
21. Mohamed et al. Patent ductuss arteriosus in premature infants: to treat or not to treat? *J Perinatol* 2017
22. Munro et al. Hypotensive Extremely Low Birth Weight Infants Have Reduced Cerebral Blood Flow. *Pediatrics* 2004
23. Ofman et al. Early low-dose hydrocortisone: is the neurodevelopment affected? *J Perinatol* 2018
24. Sehgal A, Ramsden A. Treating hypotension in the preterm infant: when and with what: a critical and systematic review. *J Perinatol*. 2008
25. Semberova et al. Spontaneous closure of the patent ductus arteriosus in infants <1500 g. *Pediatrics* 2017
26. Sung et al. Mandatory closure versus nonintervention for patent ductus arteriosus in very preterm infants. *J Pediatr* 2016
27. Vanhaesebrouck et al. Conservative treatment for the patent ductus arteriosus in the preterm. *Arch Dis Child Fetal Neonatal Ed* 2007
28. Wickremasinghe et al. Neurodevelopmental outcomes following two different treatment approaches for patent ductus arteriosus. *J Pediatr* 2012
29. Willem-Pieter de Boode. Clinical monitoring of systemic hemodynamics in critically ill newborns. *Early Human Development* 2010

Neurology:

1. Woodward et al. Neonatal MRI to predict Neurodevelopmental Outcomes in Preterm Infants. *N Engl J Med* 2006; 355:685-694.
2. Setänen S1, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. *Acta Paediatr*. 2013 May;102(5):492-7.
3. Van't Hooft, J. et al. Predicting developmental outcomes in premature infants by term equivalent MRI: systematic review and meta-analysis. *Syst Rev*. 2015 May 17;4:71.
4. Kidokoro et al. New MRI Imaging assessment tool to define brain abnormalities in very preterm infants at term. *AJNR Am J Neuroradiol*. 2013; 34(11): 2208–2214.
5. Hintz et al. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. *Pediatrics*. 2015 Jan;135(1):e32-42.
6. Hintz et al. Preterm Neuroimaging and School-Age Cognitive Outcomes. *Pediatrics*. 2018 Jul;142(1).
7. Novak, Iet al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy. Advances in Diagnosis and Treatment. *JAMA Pediatrics*. 2017. 171(19) 897-907.
8. Spittle, AJ. et al. Early diagnosis and Treatment off Cerebral Palsy in Children with Preterm Birth. *Clin Perinatology*. 2018. 409-420 (45).
9. Edwards, AD et al. Effect of MRI on Preterm Infants and their Families: a randomized controlled trial with nested diagnostic and economic evaluation, *Arch Dis Child, Fetal and neonatal edition*. 2017; 103:F15-F21.
10. Burkitt K, Kang O, Jyoti R, Mohamed AL Chaudhari T. Comparison of cranial ultrasound and MRI for detecting BRAIN injury in extremely preterm infants and correlation with neurological outcomes at 1 and 3 years. *Eur J Pediatr*. 2019 Jul;178(7):1053-1061.
11. Timmy Ho, Dmitry Dukhovny, John A.F. Zupancic, Don A. Goldmann, Jeffrey D. Horbar, DeWayne M. Pursley. Choosing Wisely in Newborn Medicine: Five Opportunities to Increase Value. *Pediatrics*. 2015. Aug 136(2).
12. Brew, Nadine & Walker, David & Wong, Flora. (2014). Cerebral Vascular Regulation and Brain Injury in Preterm Infants. American journal of physiology. Regulatory, integrative and comparative physiology. 306. 10.1152/ajpregu.00487.2013.
13. Stoll BJ, Hansen NI, Bell EF, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *JAMA*. 2015;314(10):1039–1051. doi:10.1001/jama.2015.10244.

14. Stoll, Barbara & Hansen, Nellie & Bell, E.F. & Walsh, Michele & Carlo, W.A. & Shankaran, S. & Laptook, A.R. & Sánchez, P.J. & Vanmeurs, Krisa & Wyckoff, Myra & Das, A. & Hale, E.C. & Ball, M.B. & Newman, N.S. & Schibler, Kurt & Poindexter, B.B. & Kennedy, K.A. & Cotten, Charles & Watterberg, Kristi & Higgins, R.D.. (2016). Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993 to 2012. Obstetric Anesthesia Digest. 36. 76-77. 10.1097/01.aoa.0000482610.95044.1b.
15. Al-Abdi et al "A systematic rev and meta-analysis of the timing of early IVH in preterm neonates". J Clin Neonataol 2014:3(2): 76-88.
16. Chollat C, Sentilhes L, Marret S. Fetal Neuroprotection by Magnesium Sulfate: From Translational Research to Clinical Application. *Front Neurol*. 2018;9:247. Published 2018 Apr 16. doi:10.3389/fneur.2018.00247.
17. Lim et al Reducing Germinal Matrix0-IVH: Perinatal and Delivery Room Factors *Neoreviews* Aug19, 2019 PMID: 31371554 DOI:10.1542/neo.20-8-e452.
18. Practice, Committee. (2017). Committee Opinion No. 684: Delayed Umbilical Cord Clamping After Birth. Obstetrics and gynecology. 129. e5-e10. 10.1097/AOG.0000000000001860.
19. Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: neonatal resuscitation: 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations (Reprint). *Pediatrics* (2015) 136 (Suppl. 2):S120–66. 10.1542/peds.2015-3373D) .
20. American Academy of Pediatrics Statement of Endorsement. Delayed umbilical cord clamping after birth. *Pediatrics*. 2017;139(6):e20170957.
21. Sauer CW et al, Intubation Attempts Increase the Risk for Severe Intraventricular Hemorrhage in Preterm Infants-A Retrospective Cohort Study *J Pediatr*. 2016 Oct;177:108-113. doi: 10.1016/j.jpeds.2016.06.051. Epub 2016 Jul 26.
22. S S Miller, H C Lee & J B Gould, Hypothermia in very low birth weight infants: distribution, risk factors and outcomes. *Journal of Perinatology* volume 31, pages S49–S56 (2011).
23. Adr_eJ. du Plessis Cerebrovascular Injury in Premature Infants : Current Understanding and Challenges for Future Prevention *Clin Perinatol* 35 (2008) 609–641.
24. Osborn D, Evans N, Kluckow M. Randomized trial of dobutamine versus dopamine in preterm infants with low systemic blood flow. *J Pediatr* 2002;140(2):183–91.
25. Weindling AM, Kissack CM. Blood pressure and tissue oxygenation in the newborn baby at risk of brain damage. *Biol Neonate* 2001;79(3–4):241–5.
26. Soul JS, Hammer PE, Tsuji M, et al. fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res* 2007;61(4):467–73.
27. Reviewed in Am J Physiol Regul Integr Comp Physiol. 2014 Jun 1;306(11):R773-86. doi: 10.1152/ajpregu.00487.2013. Epub 2014 Mar 19.
28. Kochan M., et al Elevated midline head positioning of extremely low birth weight infants: effects on cardiopulmonary function and the incidence of periventricular-intraventricular hemorrhage" *Journal of Perinatology* doi.org/10.1038/s41372-018-0261-1.
29. Kaiser JR1, Gauss CH, Pont MM, Williams DK., Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. *J Perinatol*. 2006;26(5):279–285.
30. Cerebral vascular regulation and brain injury in preterm infants. (Am J Physiol Regul Integr Comp Physiol. 2014;306(11):R773–R786
31. C. Monnikendam, et al Dysnatremia in extremely low birth weight infants is associated with multiple adverse outcomes. *Journal of Perinatology* volume 39, pages 842–847 (2019) DOI: 10.1038/s41372-019-0359-0.
32. Dalton J, Dechert RE, Sarkar S. Assessment of association between rapid fluctuations in serum sodium and intraventricular hemorrhage in hypernatremic preterm infants. *Am J Perinatol*. 2015;32:795–802.

33. Baraton L, Ancel PY, Flamant C, Orsonneau JL, Darmaun D, Roze JC. Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. *Pediatrics*. 2009;124:e655–61.
34. van der Lugt NM, Smits-Wintjens VE, van Zwieten PH, Walther FJ. Short and long term outcome of neonatal hyperglycemia in very preterm infants: a retrospective follow-up study. *BMC Pediatr*. 2010;10:52. Published 2010 Jul 20. doi:10.1186/1471-2431-10-52.
35. Seminars in Fetal & Neonatal Medicine 20 (2015) 164e172.
36. Altimier, Leslie & Phillips, Raylene. (2018). Neuroprotective Care of Extremely Preterm Infants in the First 72 Hours After Birth. Critical Care Nursing Clinics of North America. 30. 563-583. 10.1016/j.cnc.2018.07.010.
37. Rhee CJ, da Costa CS, Austin T, Brady KM, Czosnyka M, Lee JK. Neonatal cerebrovascular autoregulation. Pediatr Res. 2018;84(5):602–610. doi:10.1038/s41390-018-0141-6
38. Chollat, Clément & Marret, Stéphane. (2018). Magnesium sulfate and fetal neuroprotection: Overview of clinical evidence. Neural Regeneration Research. 13. 2044. 10.4103/1673-5374.241441.
39. du Plessis, Adre. (2009). Cerebrovascular Injury in Premature Infants: Current Understanding and Challenges for Future Prevention. Clinics in perinatology. 35. 609-41, v. 10.1016/j.clp.2008.07.010.
40. Bermick, Jennifer & Dechert, Ronald & Sarkar, Subrata. (2014). Assessment of Association between Rapid Fluctuations in Serum Sodium and Intraventricular Hemorrhage in Hypernatremic Preterm Infants. American journal of perinatology. 32. 10.1055/s-0034-1396691.
41. Vesoulis, Zachary & Mathur, Amit. (2017). Cerebral Autoregulation, Brain Injury, and the Transitioning Premature Infant. Frontiers in Pediatrics. 5. 64. 10.3389/fped.2017.00064.
42. Sood, Beena & McLaughlin, Kathleen & Cortez, Josef. (2015). Near-infrared spectroscopy: Applications in neonates. Seminars in fetal & neonatal medicine. 20. 10.1016/j.siny.2015.03.008.
43. Hand IL, Shellhaas RA, Milla SS. (2020). AAP COFN Clinical Report – Routine Neuroimaging of the Preterm Brain. *Pediatrics*, Volume 146, number 5, November 2020

Infectious Disease:

1. Alcock, G., Liley, H.G., Cooke, L. & Gray, P.H. (2017). Prevention of neonatal late-onset sepsis: a randomized controlled trial. *BMC Pediatrics*, 17:98.
2. Dong, Y., Speer, C.P. (2015). Late-onset neonatal sepsis: recent developments. *Arch Dis Child Fetal Neonatal Ed.* 100, F257-F263.
3. Dudek, C.J., Shah, C., Zayas, J. & Rathore, M.H. (2016). The many faces of late onset group B Streptococcus. *Pediatric Infectious Diseases: Open Access.* Vol. 1 No. 3:14.
4. Jeffrey HE, G.A. (2005). Antibiotic regimens for suspected late onset sepsis in newborn infants (review). *Cochrane database of systematic reviews.* Issue 3. Art. No.: CD004501.
5. Lin, F-Y. C., Weisman, L.E., Troendle, J. & Adams, K. (2003). Prematurity is the major risk factor for late-onset group B streptococcus disease. *The Journal of Infectious diseases*. 188, 267-271.
6. Puopolo, K.M. & Baker, C.J. Group B. streptococcal infection in neonates and young infants. (2018). *Up To Date.* #H17.
7. Resende, D.S., Peppe, A.L.G., Reis, H.D., Abdallah, V.O.S., Ribas, R.M. & Filho, R.P.G. (2014). Late onset sepsis in newborn babies: epidemiology and effect of a bundle to prevent central line associated bloodstream infections in the neonatal intensive care unit. *The Braziian Journal of Infectious Diseases*. 19 (1), 52-57.
8. Rubin, L.G., Sanchez, P.J., Siegel, J., Levine, G., Saiman, L. & Jarvis, W.R. (2002). Evaluation and treatment of neonates with suspected late-onset sepsis: A survey of Neonatologists' practices. *Pediatrics.* 110, e42.
9. Shah, B.A. & Padbury, J.F. (2014). Neonatal sepsis: An old problem with new insights. *Virulence.* 5 (1)170-178.
10. Sivanandan, S., Soraisham, A.S. & Swarnam, K. (2011). Choice and duration of antimicrobial therapy for neonatal sepsis and meningitis. Review article. *International Journal of Pediatrics.* Volume 2011 Article ID: 712150, 9 pages.

11. Stoll, B.J., Hansen, N., Fanaroff, A.A., Wright, L.L., Carlo, W.A., Ehrenkranz, R.A., Poole, K. (2002). Late onset sepsis in very low birth weight neonates: The experience of the NICHD neonatal research network. 110; 285.

Hematology:

1. Andrew M., et al A randomized, controlled trial of platelet transfusions in thrombocytopenic premature infants *J Pediatr* 1993; 123:285-291. doi.org/10.1016/S0022-3476(05)81705-6
2. Campbell, Y. N., Machan, M. D., & Fisher, M. D. (2016). The Jehovah's Witness population: Considerations for preoperative optimization of hemoglobin. *American Association of Nurse Anesthetists Journal*, 84,173–178
3. *Cervantes L.L., Zuniga J.A. (2018)* Strategies to Avoid Neonatal Blood Transfusions for Families of the Jehovah's Witness Faith *Nursing for Women's Health*, 22 (4) , pp. 332-337.
4. Curley A., et al Randomized Trial of Platelet-Transfusion Thresholds in Neonates *N Engl J Med*. 2019 Jan 17;380(3):242-251. DOI: 10.1056/NEJMoa1807320
5. Fogarty, M., Osborn, D. A., Askie, L., Seidler, A. L., Hunter, K., Lui, K., Tarnow-Mordi, W. (2018). Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology*, 218(1), 1–18. https://doi.org/10.1016/j.ajog.2017.10.231
6. Katheria, A.C. et al. (2019). LB 1: Premature Infants Receiving Cord Milking or Delayed Cord Clamping: A Randomized Controlled Non-inferiority Trial. *American Journal of Obstetrics & Gynecology*, Volume 220 , Issue 1 , S682
7. Kim D. H. (2018). Transfusion practice in neonates. *Korean journal of pediatrics*, *61*(9), 265–270. doi:10.3345/kjp.2018.06849
8. Ohls, R. K., Roohi, M., Peceny, H. M., Schrader, R., & Bierer, R. (2012).A randomized, masked study of weekly erythropoietin dosing in preterm infants. *The Journal of Pediatrics*, 160, 790-795.https://doi.org/10.1016/j.jpeds.2011.10.026
9. Sauer, C. W., & Marc-Aurele, K. L. (2016). Attempting to Honor Beliefs of Jehovah's Witnesses at the Edge of Viability in an Infant Born at 23 Weeks' Gestational Age. *The American journal of case reports*, *17*, 375–378. doi:10.12659/AJCR.898002
10. Sparger KA., et al Platelet Transfusion Practices Among Very-Low-Birth-Weight Infants *JAMA Pediatr*. 2016 Jul 1;170(7):687-94. doi: 10.1001/jamapediatrics.2016.0507.

Developmental:

1. Akshoomoff, N., Joseph, R., Taylor, H.G., Allred, E., Heeren, T., O'Shea, T., Kuban, K., (2017). Academic Achievement Deficits and their Neuropsychological Correlates in Children Born Extremely Preterm. *Journal of Developmental & Behavioral Pediatrics*. 38(8):627–637.
2. Altimier L. & Phillips R. (2016). The neonatal integrative developmental care model: Advanced clinical applications of the seven core measures for neuroprotective family-centered developmental care. Newborn and Infant Nursing Reviews, 16(4), 230-244.
3. Altimier, L. & Philips, R. (2013). Neonatal Integrative Developmental Care Model: Seven Neuroprotective Core Measures for Family-Centered Developmental Care. *Newborn & Infant Nursing Reviews*, (13) 9-22.
4. Baley, J. (2015). Skin-to-skin care for term and preterm infants in the neonatal ICU. *Pediatrics*. 136(3).
5. Brandon, D.H., Silva, S.G., Park, J., Malcolm, W., Kamhawy, H., & Holditch-Davis, D. (2017). Timing for the introduction of cycled light for extremely premature infants: A randomized controlled trial. *Research in Nursing & Health*. 40(4):294-310.
6. Buss, C., Entringer, S., Swanson, J.M., & Wadhwa, P.D. (2012). The role of stress in brain development: The gestational environment's long-term effects on the brain. *Cerebrum*, Mar-Apr(4).
7. Byrne R, Noritz G, Maitre N, PhD on behalf of the NCH Early Developmental Group. Implementation of Early Diagnosis and Intervention Guidelines for Cerebral Palsy in a High-Risk Infant Follow-Up Clinic. *J Ped Neurol*. 2017.

8. Coughlin M., Gibbins S., Hoath S. (2009). Core measures for developmentally supportive care in neonatal intensive care units: Theory, precedence and practice. Journal of Advanced Nursing, 65(10), 2239-2248. doi:10.1111/j.1365-2648.2009.05052.x
9. Coughlin, M.E. (2017). *Trauma-informed care in the NICU: Evidence-based practice guidelines for neonatal clinicians*. New York, NY: Springer Publishing.
10. DeMaster, D., Bick, J., Johnson, U., Montroy, J.J., Landry, S., Duncan, A.F. (2018). Nurturing the preterm infant brain: leveraging neuroplasticity to improve neurobehavioral outcomes. *Pediatric Research*. Oct. 16.
11. Gardener, S. Carter, B., Enzem-Hines, M., Hernandez, J. (2011). The neonate and the environment: Impact on Development. In Gardener, S. & Merenstein, Eds., *Handbook of Neonatal Intensive Care*. St. Louis, Missouri: Elsvier.
12. Graven, S.N., & Browne, J.V. (2008). Sensory development in the fetus, neonate, and infant: Introduction and overview. *Newborns and Infant Nursing Reviews*, 8(4).
13. Hutchinson; E.A., De Luca, C.R., Doyle, L.W., Roberts, G., & Anderson, P.J. (2013). School-age Outcomes of Extremely Preterm or Extremely Low Birth Weight Children. *Pediatrics*. 131(4).
14. in cerebral palsy: advances in diagnosis and treatment. *JAMA Pediatr* 2017.
15. Kapellou, O., Counsell, S.J., Kennea, N., Dyet, L., Saeed, N., Stark, J. . . . Edwards, A.D. (2006). Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med*. Aug; 3(8): e265.
16. Kilpatrick S, Papile L, Macones G. Guidelines for Perinatal Care, 8th Edition. AAP Committee on Fetus and Newborn and ACOG Committee on Obstetric Practice. 2017.
17. Kuo D, Lyle R, Casey P, Stille C. Care System Redesign for Preterm Children After Discharge From the NICU. *Pediatrics*. 2017.
18. Kuppala V, Tabangin M, Haberman B, Steichen J, Yolton K. Current state of high-risk infant follow-up care in the United States: results of a national survey of academic follow-up programs. J Perinatol 2012.
19. Lea C, Smith-Collins A, & Luyt K. (2017). Protecting the premature brain: Current evidence-based strategies for preventing perinatal brain injury in preterm infants. *Archives of Disease in Childhood: Fetal & Neonatal*. 102:F176–82.
20. Liu W.F., Laudert S., Perkins B., Macmillan-York E., Martin S., & Graven S. (2007). The development of potentially better practices to support the neurodevelopment of infants in the NICU. Journal of Perinatology, 27(Suppl. 2), S48-S74.
21. Lockridge, R. (2018). Neonatal neuroprotection: Bringing the best practices to the bedside in the NICU. *The American Journal of Maternal/Child Nursing*, 43(2):66-76.
22. McGrath J.M., Cone S., & Samra H.A. (2011). Neuroprotection in the preterm infant: Further understanding of the short- and long-term implications for brain development. Newborn Infant Nursing Reviews, 11, 109-112.
23. Montirosso, R., Del Prete, A., Bellu, R., Tronick, E., & Borgatti, R. (2012). Level of NICU Quality of Developmental Care and Neurobehavioral Performance in Very Preterm Infants. Pediatrics, 129(5).
24. Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention
25. Poggi Davis, E., Buss, C., Muftuler, L.T., Head, K., Hasso, A., Wing, D.A., . . . Sandman, C.A. (2011). Children's Brain Development Benefits from Longer Gestation. Frontiers in Psychology, 2(1).
26. Pugliese M., Rossi C., Guidotti I., Gallo, C., Della Casa E., Bertoncelli N., . . .Ferrari, F. (2013). Preterm birth and developmental problems in infancy and preschool age. Part II: Cognitive, neuropsychological and behavioural outcomes. The Journal of Maternal-Fetal & Neonatal Medicine, 26(16), 2154-2159.
27. Shah P., Kaciroti N., Richards B., Oh, W., & Lumeng J.C. (2016). Developmental outcomes of late preterm infants from infancy to kindergarten. Pediatrics, 138(2).
28. Spittle A, Morgan C, Olsen J, Novak I, Cheong J. Early Diagnosis and Treatment of Cerebral Palsy in Children with a History of Preterm Birth. *Clin Perinatol* (45) 2018.
29. Stiles, J., Jernigan, T.L. (2010). The Basics of Brain Development. *Neuropsychology Review*. 20:327–348.

30. Zwaigenbaum L et al. Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research. *Pediatrics* 2015;136:S41–S59.

Skin and Thermoregulation:

1. ACoRN Editorial Board. (2012). Acute care of at-risk newborns: A resource and learning tool for health care professionals. (2012 Update). Vancouver: Author.
2. Agren, J. (2015). The Thermal Environment of the Intensive Care Nursery. In R.J. Martin, A.A. Fanaroff, & M.C.Walsh Eds., *Fanaroff and Martin's Neonatal Perinatal Medicine* (pp. 503-511). Philadelphia: Elsevier Saunders.
3. Amaya R. (2015). Safety and efficacy of active Leptospermum honey in neonatal and paediatric wound debridement. J Wound Care. 2015;24(3):95–103
4. Baghel P., et al. (2009). A comparative study to evaluate the effect of honey dressing and silver sulfadiazene dressing on wound in healing in burn patients. Indian J Plast Surg. 2009;42(2):176–181. doi:10.4103/0970-0358.59276.
5. Baumgart, S. (2008). Iatrogenic hyperthermia and hypothermia in the neonate. Clinics in Perinatology, 35, 183-197. Blackburn, S. T. (2007). Maternal, fetal, & neonatal physiology: A clinical perspective. (3rd ed.). St. Louis: Saunders Elsevier.
6. Brand MC, Boyd HA. (2015). Thermoregulation. In Core Curriculum for Neonatal Intensive Care Nursing . 5th ed, Verklan MT, Walden M. eds. Elsevier, St. Louis. 95-109.
7. Carter D., et al. (April 20, 2016). Therapeutic Manuka Honey: No Longer So Alternative. Frontiers in Microbiology 7(569): 1-11. Doi:10.3389/fmicb/2016.00569
8. Challenges in the Neonatal/Pediatric Wound Care Arena
9. Cloherty J.P, Eichenwald E.C, Stark AR (2008) Manual of neonatal care 6th edition. Lippincott, Williams & Wilkins. Philadelphia.
10. Cooper RA, Jenkins L. (2009). A comparison between medical grade honey and table honeys in relation to antimicrobial efficacy. Wounds. 21(2):29–36
11. Dr. Rene Amaya Pediatric Wound Care Center of Houston
12. Esser, M. (2017). Leptospermum Honey for Wound Care in an Extremely Premature Infant. Advances in Neonatal Care. 2017 Feb; 17(1): 27-32.
13. Food and Drug Administration. (2008). 510 (k) Summary for Derma Sciences Medihoney Dressings with Active Manuka Honey. http://www.accessdata.fda.gov/cdrh_docs/pdf8/K080315.pdf.
14. Food and Drug Administration. 510 (k) Summary for Derma Sciences Medihoney Dressings with Active Manuka Honey. http://www.accessdata.fda.gov/cdrh_docs/pdf8/K080315.pdf Published 2008.
15. Gardner SL., Hernandez, JA. (2016). Heat Balance. In Merenstein and Gardner's Handbook of Neonatal Intensive Care. 8th ed. Elsevier, St. Louis. 105-125.
16. Hackman, P. (2001). Recognizing and understanding the cold-stressed term infant. Neonatal Network, 20(8), 35-41.
17. http://outside-us.dermasciences.com/sites/default/files/videos/pdfs/Medihoney-Pediatrics.pdf
18. https://issuu.com/reemsaibi/docs/dermasciences_medihoney_full_presen Published May 3, 2016.
19. https://www.springmedical.nl/wp-content/uploads/BARRIER-CREAM-with-Studies-Dec-2014.pdf
20. Https://www.utmb.edu/kaleidoscope/Neonatal%20Wound%20Care.pdf
21. Ikuta, LM., & Beauman, SS. (Eds.). (2011). Thermoneutral Environment. In NANN Policies, Procedures, and Competencies for Neonatal Nursing Care. Glenview, IL. 181-183.
22. Joseph R., Derstine S., Killian M. (2017). Ideal Site for Skin Temperature Probe Placement on Infants in the NICU. In Advances for Neonatal Care. Vol. 17, 114-122.
23. Jurica, S. A., Čolić, A., Gverić-Ahmetašević, S., Lončarević, D., Filipović-Grčić, B., Stipanović-Kastelić, J., & Rešić, A. (2016). Skin of the very premature newborn - physiology and care. *Paediatria Croatica*, *60*(1), 21–26. https://doi-org.dml.regis.edu/10.13112/PC.2016.4 [doi-org.dml.regis.edu]

24. Knobel-Dali, R.B. (2014). Role of Effective Thermoregulation in Premature Neonates. *Dove Medical Press, Volume 2014:4 Pages 147—156*. https://doi.org/10.2147/RRN.S52377 [doi.org]
25. Little Patients, Big Outcomes – The use of Medihoney in treating Pediatric Wounds (May 2014)
26. Mohr, L., et al. Neonatal Case Studies Using Active Leptospermum Honey. Journal WOCN 2014;4(3): 213-218.
27. Oryan, A. (2016). Biological Properties and Therapeutic Activities of Honey in Wound Healing: A Narrative Review and Meta-analysis. Journal of Tissue Viability. http://do.doi.org/10.1016/j.jtv.2015.12.002.
28. Poindexter, B.B., & Ehrenkranz, R.A. (2015). Nutrient Requirements and Provision of Nutritional Support in the Premature Neonate. In R.J. Martin, A.A. Fanaroff, & M.C.Walsh Eds., *Fanaroff and Martin's Neonatal Perinatal Medicine* (pp. 592-612). Philadelphia: Elsevier Saunders.
29. Polin R.A & Spitzer A. R. (2007) Fetal and Neonatal secrets. 2nd edition. Elsevier. Philadelphia.
30. Retrieved from http://www.dermasciences.com/medihoney
31. Saikaly, S., Khachemoune, A. Honey and Wound Healing: An Update. American Journal of Clinical Dermatology. 2017; 18(2): 237-251. DOI 10.1007/s40257-016-0247-8

Social:

1. Altimer, L. & Philips, R. (2016). The neonatal integrative developmental model: Advanced clinical applications of the seven core measures for neuroprotective family-centered developmental care. *Newborn and Infant Nursing Reviews*, 16(4), 230-244.
2. Coughlin, M.E. (2017). Trauma-informed care in the NICU: Evidence-based practice guidelines for neonatal clinicians. *New York, NY: Springer Publishing*.
3. Focus on the Brain (2006). *Videa Health Communications, Inc.*
4. Kelly, H. (2017). Putting families at the heart of their baby's care. *Journal of Neonatal Nursing*, 24(1), 13-16.
5. Read, K. & Rattenbury, L. (2018). Parents as Partners: Lessons from the Baby Friendly Initiative in Exeter. *Journal of Neonatal Nursing*, 24(1), 17-20.