Guidelines for Acute Care of the Neonate

Edition 29, 2021–2022

Updated: July 2021

Arnold J. Rudolph, MMBCh (1918 - 1995)

Section of Neonatology
Department of Pediatrics
Baylor College of Medicine
Houston, Texas

Baylor College of Medicine

Texas Children's Hospital®

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Foreword

It is with a great deal of optimism and humility that we reflect on the past year since the prior edition to the guidelines was published. We are beginning to see the sun peek out on what has been a challenging time. A year ago, we would not have thought that COVID-19 would still be a part of daily life. However, persistence, dedication and science are hopefully prevailing.

During the past year, we continued to stay focused on our true north – working every day to ensure that the most fragile of patients and their families receive the very best care possible. This Section of Neonatology has continued to focus on evidence-based, compassionate and collaborative care. Drs. Fernandes, Pammi and Katakam have worked tirelessly to ensure that this 29th edition of the Baylor Neonatology Guidelines, first created by Dr. James Adams, would be exceptional. All of the contributors to the Guidelines seek to provide bedside clinicians with up to date, evidence-based, practical guidelines to be used in providing care to our patients. These guidelines are an invaluable resource to our Section, as well as to neonatologists and others caring for babies all over the world.

The editors, section editors, and chapter authors (including community neonatology colleagues, nurse practitioners, dietitians, and fellows) have taken great care in preserving relevant material from prior editions and adding new information. They have continued to incorporate the GRADE system of categorizing evidence supporting these guidelines.

The Baylor Neonatology Guidelines is one of the most valuable resources of the Neonatology Section. These guidelines help ensure that we provide high-quality care to NICU patients and their families, here at Texas Children's Hospital and in NICUs regionally, nationally and internationally. I am immensely grateful I have had the opportunity to work with this team of dedicated editors and authors. They have given their time, knowledge and clinical experience to create this important work to improve the outcomes of babies worldwide, and, for all they do, I am grateful.

Tammy I. Kang, MD MSCE FAAHPM
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Preface

We are pleased to release the 29th revision of "Guidelines for the Acute Care of the Neonate", a compendium of multidisciplinary collaboration between members of the Newborn Center at Texas Children's Hospital and Baylor College of Medicine. This edition is dedicated to faculty and staff at Baylor College of Medicine Section of Neonatology, who have worked tirelessly during the pandemic to take care of our patients in the newborn center. In spite of changing workflow and ever changing COVID guidelines, sacrificing their own safety at times, enduring loss, our staff have continued to provide the best possible care to each patient and fulfill our patient care mission.

The 'Baylor Neo Guidelines', as this handbook is fondly referred to, is meant to serve as a resource for neonatology fellows, pediatric housestaff, nurse practitioners, nurses and other clinicians who care for neonatal patients in Baylor-affiliated hospitals. This body of work is reflective of general principles, concepts, and treatment recommendations that are agreed upon by the authors, editors, and section members. When appropriate, national guidelines are referenced and regional traits unique to the southeast Texas or Houston are highlighted. The guidelines are reviewed and revised annually as new evidence becomes available. Users should refer to the most recent edition of these guidelines, which may be downloaded from the 'Physician publications' tab of the Baylor Neonatology website (www.neonate.net).

Our chapter authors and section editors have worked diligently to create the content you see within. We wish to acknowledge the exceptional work by Myrthala Miranda-Guzman, our Guidelines Administrative Coordinator, without which this task would have been impossible. We look forward to serving you in the coming years.

Sincerely,

Caraciolo J. Fernandes, MD, MBA
Mohan Pammi, MD, PhD, MRCPCH
Lakshmi Katakam, MD, MPH

Disclaimer

These are guidelines only and may not be applicable to populations outside the BCM Affiliated Hospitals. These guidelines do not represent official policy of Texas Children's Hospital, Ben Taub General Hospital, BCM, or the BCM Department of Pediatrics, nor are they intended as universal practice guidelines or standards of care. Specific circumstances often dictate deviations from these guidelines. Each new admission and all significant new developments must be discussed with the fellow on call and with the attending neonatologist on rounds. All users of this material should be aware of the possibility of changes to this handbook and should use the most recently published guidelines.

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All authors are members of the faculty at Baylor College of Medicine in the Department of Pediatrics, Section of Neonatology and attending physicians at Texas Children's Hospital, unless otherwise noted. Allied health contributors are all members of the Texas Children's Hospital staff. Authors are listed in alphabetical order throughout.

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Section 1: Care of Preterm Infant

Editors: George Mandy and Nathan Sundgren

1.1 General Care (Babies < 1500 g)

Definitions

- **Premature** - less than 37 completed weeks' (259 days) gestation at birth
- **Low Birth Weight (LBW)** - less than 2500 grams birth weight (7% of total births in the U.S.)
- **Very Low Birth Weight (VLBW)** - less than 1500 grams birth weight (3% of total births in the U.S.)
- **Extremely Low Birth Weight (ELBW)** - less than 1000 grams birth weight (1% of total births in the U.S.)
- **Small for Gestational Age (SGA)** - less than 10th percentile by weight, or 2 standard deviations below the mean by weight for gestational age
- **Intrauterine Growth Restriction (IUGR)** - deviations from the growth pattern established by fetal measurements on second trimester ultrasound

Example of Admission Orders

No two infants are the same and appropriate orders vary by gestation and birth weight. Each order, including all medication doses and IV rates, must be individualized. In current practice, each infant has a basic admission order set in the EMR. Additional orders are added per individual indication. The following categories of orders are common in VLBW infants.

Indicate

- Unit of admission (e.g., NICU) and diagnosis.

Order

- A humidified convertible incubator is preferred for infants with BW < 1250 grams or < 32 weeks. If servo-control mode of incubator is used, indicate servo skin temperature set point (usually set at 36.5°C).
- If only radiant warmer is available, use plastic wrap blanket to reduce evaporative water loss for babies who weigh 1250 grams or less. Always use radiant warmer in servo-control mode.

Monitoring Orders

- Cardio-respiratory monitor.
- Oximeter - oxygen saturation target 90-95% for premature infants and term babies with acute respiratory distress (alarm limits 88-96%).
- Vital signs and blood pressure by unit routines unless increased frequency is indicated.
- Umbilical artery catheter (UAC) or peripheral arterial line to BP monitor if invasive monitoring is done.

Metabolic Management Orders

- I & O measurements.
- Type and volume of feeds or NPO.
- IV fluids or parenteral nutrition.
- If arterial line is in place, order heparinized NS at keep open rate per unit guidelines.

  If a double lumen UVC or PICC, order heparinized NS at 0.3 cc/hr for UVC, 0.5 cc/hr for PICC

Respiratory Orders

- If infant is intubated, order ET tube and size.
- Standard starting ventilator settings for infants with acute lung disease:

  Ventilator orders should include mode and settings:

  CPAP –Bubble CPAP, level of continuous airway pressure

  SIMV – rate, PIP, Ti, PEEP

  A/C – PIP, Ti, PEEP, Back Up Rate

  VG –Vt, Pmax, PEEP, Rate, Ti

  FiO_2 – as needed to maintain target saturations

Diagnostic Imaging

- Order appropriate radiographic studies.
- Order cranial US to be performed between 7 and 14 days of life.

Labs

- Admission labs: CBC with differential and platelets, blood type, Rh, Coombs, glucose
- Obtain results of maternal RPR, HIV, GBS and hepatitis screens.
- Order other routine labs.
- Order labs to manage specific conditions as needed (e.g., electrolytes at 12 to 24 hours of life).
- Order newborn screen at 24 to 48 hours of age and DOL 14.

Medication Orders

Medication orders commonly include:

- **vitamin K** – 0.5 mg IM.
- **eye prophylaxis** – erythromycin ophthalmic ointment.
- **surfactant replacement (as indicated)** – (indicate BW, product and dose needed) **(Sec 15- Respiratory Care).**
- **antibiotics** – if infant is considered to be at risk for sepsis **(Ch 8.2-Bacterial Sepsis).**
- **caffeine citrate (for infants BW 1250 g or less)** – 20 mg/kg loading dose followed by 5-10 mg/kg/day given once daily. Initiate therapy within first 10 days of life.
- **Vitamin A (for infants BW 1000 g or less)** – if available, give 5000 IU intramuscularly every Monday Wednesday and Friday for a total of 12 doses.
- **Prophylactic indomethacin – see below (**for babies $\leq$ 26 weeks gestation or $\leq$ 800 g. birth weight)

Screens and Follow-up

- Order hearing screen before hospital discharge. Hearing screens should be performed when the baby is medically stable, > 34 weeks postmenstrual age and in an open crib.

Table 1–1. Admission labs	
CBC, platelets	at admission
Blood culture, ABG	at admission, if appropriate
Glucose screening	at 30 min of age
Electrolytes, glucose BUN	12 or 24 hours of age (depends on infant's size and metabolic stability)
Calcium (ionized)	at 24 and 48 hours of age
Total Serum Bilirubin	at 24 hours of age or if visibly jaundiced (depends on size, presence of bruising, ABO-Rh status)
Newborn screens:	
First screen	at 24 to 48 hours of age
Second screen	repeat newborn screen at 14 days

Table 1–2. Labs during early hospitalization, days 1 to 3	
Electrolytes, glucose, BUN	every 12 to 24 hours (depends on infant's size and metabolic stability)
Calcium (ionized)	24 and 48 hours of age
TSB	every 24 hours (depends on size, presence of bruising, ABO-Rh status, pattern of jaundice)
Hematocrit	every 24 to 48 hours (depends on size, previous hematocrit, and ABO-Rh status)

- Order ophthalmology screening for ROP if:
  - » less than or equal to 1500 grams birth weight or 30 weeks' gestation or less

    or
  - » 1500 to 2000 grams birth weight or greater than 30 weeks' gestation with unstable clinical course where physician believes infant is at risk for ROP.
- Before discharge,
  - » observe infant in car safety seat for evidence of apnea, bradycardia, or oxygen desaturation,
  - » offer CPR training to parents,
  - » schedule high-risk follow-up clinic as recommended below,
  - » write orders for palivizumab as appropriate.
- Schedule other laboratory screening tests as recommended below.

Suggested Lab Studies

These labs are appropriate for many VLBW admissions to NICU and are provided as a general guideline. Many babies will not require this volume of tests, others will require more. Review this list with the Attending Neonatologist. Review scheduled labs during daily rounds and eliminate those no longer necessary **(Table 1–1 and Table 1–2).**

Follow-up

In addition to high risk developmental follow up, many VLBW infants will require specific follow-up for CNS, cardiac, renal, ophthalmologic, or otologic function as well.

Cranial ultrasounds (US)-Order US for infants ≤ 1500 grams birth weight between 7 and 14 days of age. When the baby reaches term or at discharge, another US is recommended to detect cystic periventricular leukomalacia (PVL). Infants with US that demonstrates significant IVH require follow-up ultrasounds (weekly, every other week, or monthly) to identify progression to hydrocephalus.

Screening for retinopathy of prematurity (ROP) –Initial and follow- up eye exams by a pediatric ophthalmologist should be performed at intervals recommended by the American Academy of Pediatrics. If hospital discharge or transfer to another neonatal unit or hospital is contemplated before retinal maturation into zone III has taken place or if the infant has been treated by ablation for ROP and is not yet fully healed, the availability of appropriate follow-up ophthalmologic examination must be ensured and specific arrangements for that examination must be made before such discharge or transfer occurs.

Development Clinic – TCH Infants who weigh less than 1500 grams at birth should be scheduled for the Desmond Developmental Clinic at four months adjusted age. Infants with HIE, Twin-Twin Transfusion syndrome or those requiring ECMO should also be referred. Patients in these categories should have an initial developmental consultation and evaluation before discharge. Other infants whose clinical course places them at high risk will be scheduled on an individual basis.

Hearing screen – Perform a pre-discharge hearing screen on all infants admitted to a Level 2 or 3 nursery. Infants with congenital cytomegalovirus (CMV), bronchopulmonary dysplasia (BPD), or meningitis and infants treated with ECMO might have a normal screen at discharge but later develop sensorineural hearing loss.

Monitoring for anemia – Laboratory testing (a hemoglobin/hematocrit with a reticulocyte count, if indicated) to investigate the degree of physiologic anemia of prematurity should be considered as needed based upon clinical status, need for positive pressure or oxygen support, size, recent phlebotomies, and most recent hematocrit. Frequency of such testing may vary from every 1 to 2 weeks in the sick, tiny premature infant on positive pressure support to once a month or less in a healthy, normally growing premature infant. Efforts should be made to cluster such routine sampling with other laboratory tests.

1.2 Specialized Care for ELGAN Babies

The following care procedures are recommended initial management for Extremely Low Gestational Age Neonates born at ≤ 28 weeks.

Prompt Resuscitation and Stabilization

Initiate prompt resuscitation and stabilization in the delivery room with initiation of CPAP, or intubation and surfactant replacement if needed.

Volume Expansion

Avoid use of volume expanders. But if given, infuse volume expanders over 30 to 60 minutes. Give blood transfusions over 1 to 2 hours. A pressor agent such as dopamine is preferable to treat nonspecific hypotension in babies without anemia, evidence of hypovolemia, or acute blood loss.

Respiratory Care

Determination of the need for respiratory support in these infants after delivery should include assessment of respiratory effort and degree of distress. ELBW infants who are vigorous and have good respiratory effort at birth should be placed on NCPAP immediately. If respiratory distress develops or pulmonary function subsequently deteriorates, the infant should be intubated and given early rescue surfactant (within first 2 hours). **(Ch 15.3-Management of Respiratory Distress)** The goal of care is maintenance of adequate inflation of the immature lung and early, selective surfactant replacement in those exhibiting respiratory distress to prevent progressive atelectasis. Achieving adequate lung inflation and assuring correct ET tube position before dosing are essential for uniform distribution of surfactant within the lung (correct ET position may be assessed clinically or by radiograph).

After initial surfactant treatment, some babies will exhibit a typical course of respiratory distress and require continued ventilation and/or repeat surfactant doses. However, many will have rapid improvement in lung compliance. Rapid improvement in lung compliance necessitates close monitoring and prompt reduction in ventilator PIP (or VT) and FiO_2. Initial reduction in ventilator settings after surfactant should be determined by clinical assessment (e.g., adequacy of chest rise). Volume Guarantee is the preferred initial mode of ventilation for all ELGAN infants since it provides a "self-weaning" function. As lung compliance improves, ventilator PIP is progressively reduced to maintain the chosen target tidal volume. Monitor clinically and obtain blood gases within 30 minutes of dosing and frequently thereafter. When ventilator support has been weaned to minimal levels, attempt extubation and place infant on nasal CPAP. Minimal support includes:

- FiO_2 30% or less
- PIP 20 cm or less

  Vt 4-4.5 ml/kg (VG)
- Rate less than 25/min if on SIMV
- PEEP 5-6 cm

In extremely immature infants, the decision to extubate must be individualized. Rapid extubation after surfactant administration may not be possible or desirable in some of these infants.

Caffeine Citrate

Evidence indicates that caffeine citrate started during the first 10 days of life in infants with BW 1250 grams or less decreases the rate of bronchopulmonary dysplasia without short term adverse effects and improves neurodevelopmental outcomes at 18 months. All infants with a BW 1250 grams or less (whether or not on positive pressure ventilation) should be started on caffeine citrate (20 mg/kg loading dose followed by 5 to 10 mg/kg maintenance dose) within the first 10 days of life. It should be continued until drug therapy for apnea of prematurity is no longer needed.

Prophylactic Indomethacin

Prophylactic indomethacin significantly reduces occurrence of symptomatic PDA, PDA ligation and, to a lesser extent, grade IV IVH in ELGAN babies. Administer indomethacin (if available) during the first 12 hours of life to babies less than or equal to 26 weeks gestation or less than or equal to 800 grams birth weight as follows:

- First dose: (within first 12 hours) – 0.1 mg/kg of birth weight
- Second dose: (24 hours after first) – 0.1 mg/kg of birth weight
- Third dose: (48 hrs. after initial dose) – 0.1 mg/kg of birth weight

Monitor platelet count daily. Subsequent doses should be held if infant is oliguric (< 0.5 ml/kg/hr), platelets fall below 50,000, overt bleeding occurs or infant requires corticosteroids for circulatory support.

Measures to Minimize Blood Pressure Fluctuations or Venous Congestion

- Do admission weight and measurements. Infants in Incubator/ warmers should have daily weights performed using the in-bed scale. Infants with NCPAP should be weighed with NCPAP in place to preserve infant's FRC.
- Take vital signs from monitors.
- Routine suctioning during the first 24 to 48 hours of life usually is not necessary. If routine suctioning becomes necessary, sedation may be needed to blunt effects.
- Minimize peripheral IVs, heel punctures, etc. Use the umbilical venous catheter (UVC) for glucose infusions. Infuse normal or half normal saline via the umbilical arterial catheter (UAC), and use the UAC to draw needed blood gases, lab work, and glucose screening.
- Repeatedly observe infants for signs of loss of airway or of airway dysfunction related to ET-tube displacement or obstruction.
- A humidified convertible incubator is preferred. If a radiant warmer is used for a VLBW infant, cover infant with plastic wrap to reduce evaporative water and heat loss.

Suggested Reading

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2. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GH, Halliday HL. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. Neonatology. 2017;111(2):107-125. PMID: 27649091.

Section 2: Cardiac Care

Editors: Sharada H. Gowda and Scott W. Osborne

2.1 Cardiovascular Physiology

At birth, infants must make rapid cardiopulmonary adaptations to the extrauterine environment. One of the most complex adaptations is the transition from the fetal to the postnatal circulatory pattern.

Fetal Circulation

The fetal circulation is a 'circulation in parallel', wherein blood is pumped from the heart to the placenta as well as the rest of the body. Gas exchange in the fetus occurs in the placenta, an organ of high flow and low resistance, which receives 50-55% of the fetal cardiac output.

- **Maternal placental circulation -** Maternal blood enters the intervillous space via uterine spiral arteries, bathing the fetal villi with blood, and leaving via uterine veins, located at the basilar layer of the intervillous space.
- **Fetal placental circulation** -The fetal vessels are closed within these villi, which project into the intervillous space, and have no direct connection with the maternal blood.
- **Crossing the placenta -** Maternal nutrients and other components cross the placental barrier, via simple or facilitated diffusion, active transport, bulk flow, pinocytosis, or breaks in the three tissue layers within the villus in order to reach fetal blood.

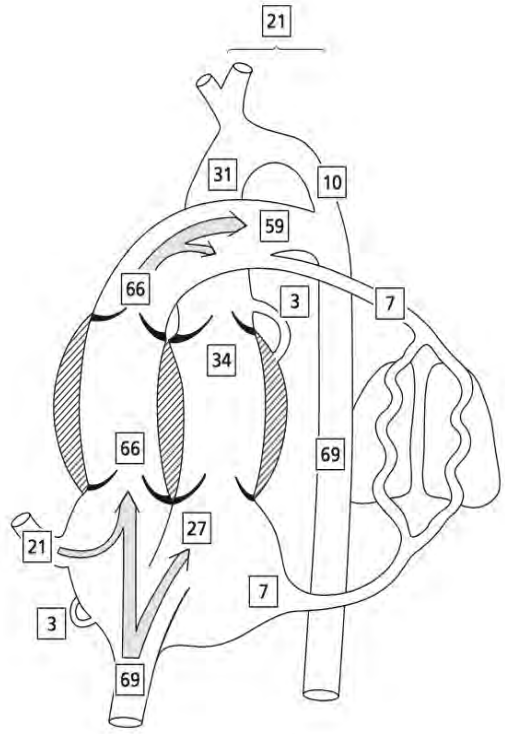
Oxygenated blood (PaO_2 30 mmHg, SaO_2 70%) leaves the placenta through the single umbilical vein. It then bypasses the hepatic vasculature and right heart via fetal shunts (ductus venous, foramen ovale), ensuring the blood stays oxygen-rich as it enters the left heart. This arrangement allows the left heart, which provides one-third of the fetal cardiac output, to preferentially pump this oxygenated blood to the brain, myocardium, and peripheral circulation. **Fig 2-1** depicts the distribution of fetal blood flow as percentages of the combined fetal cardiac output.

The right heart provides two-thirds of the fetal cardiac output, as it receives deoxygenated blood from the venae cavae, diverts it away from the lungs and across the ductus arteriosus to the descending aorta and to umbilical arteries (PaO_2 15 mmHg, SaO_2 30%) for reoxygenation in the placenta. The low oxygen tension of the fluid-filled fetal alveoli induces hypoxic pulmonary vasoconstriction, which elevates the pulmonary vascular resistance (PVR) and facilitates the right-to-left shunting of blood through the ductus arteriosus. Additionally, fetal hypoxia is also a contributing stimulus to the production of prostaglandin E, which maintains ductal patency.

Transitional Circulation

After birth, as a crying baby takes its first breaths of air, the mechanical stretch of the newly inflated lungs and relief of alveolar hypoxia, decrease the PVR and dramatically increase pulmonary blood flow. Concurrently, clamping the umbilical cord removes the low-resistance placental flow, resulting in a rise in the systemic vascular resistance (SVR). Both cold stress and catecholamine surges further increase SVR. As left-sided heart pressures increase and right-sided pressures fall, the foramen ovale closes. Decrease in intraluminal ductal blood flow and relief of fetal hypoxia begin the process of functional

Figure 2-1. Distribution of blood flow as percentages of combined fetal cardiac output.



PDA closure. The right ventricular output falls, while the left ventricular output increases (newborn LVO is 200-250 ml/kg/min), such that the two outputs are equal. The end-result is an oxygenator (pulmonary circulation) that is in series with the systemic circulation.

Under normal conditions, this process of transition is largely completed within 24 hours. However, in some pathologic states, it may persist for 3 to 10 days. During this time, the function of a circulation in series is disturbed by persistent patency of the ductus arteriosus and foramen ovale, and the potential for abnormal mixing of blood between the systemic and pulmonary circulations. Blood may flow either along the pulmonary-to-systemic circuit (right-to-left shunt) and cause hypoxemia or it may flow along the systemic-to-pulmonary circuit (left-to-right shunt) and cause pulmonary congestion. The direction of shunting is primarily driven by the relationship between systemic and pulmonary vascular resistance. The main determinants of resistance to blood flow in the pulmonary circuit are the degree of alveolar hypoxia and the size of the vascular bed (e.g. an infant with hypoplastic lungs).

Disturbances of the transitional circulation can be associated with parenchymal pulmonary disease, persistent pulmonary hypertension of the newborn (PPHN), congenital heart disease, and patent ductus arteriosus (PDA). Each is discussed in its respective section.

Table 2-1. Considerations for improving oxygen transport balance

Minimizing oxygen consumption

- Ensure normothermia
- Treat agitation and pain
- Decrease work of breathing via respiratory support
- Treat arrhythmia
- Treating underlying comorbidities (e.g., sepsis)
- Controlling seizures

Maximizing oxygen delivery

- Increasing blood oxygen content through RBC transfusion
- Optimize alveolar oxygen tension and lung volumes, avoiding atelectasis or overinflation
- Improving cardiac output
  - » Correction of acidosis
  - » Assisted ventilation
  - » Administration of volume
  - » Inotropic support
  - » Improve SVR:PVR balance to favor systemic blood flow if there is high Qp:Qs
  - » Administer PGE if there is outflow obstruction

Oxygen Physiology

Oxygen Delivery

Oxygen delivery (DO_2) is the amount of oxygen available to the body in one minute. It is the product of cardiac output (CO) and arterial oxygen content (CaO_2).

$$DO_2 = CO \times CaO_2$$

CaO_2 includes the oxygen bound to hemoglobin within the red blood cells plus the oxygen dissolved in the blood:

$$CaO_2 = 1.37 \text{ (ml } O_2\text{/g Hb)} \times \text{Hb (g/dl)} \times SaO_2 + [0.003 \times PaO_2]$$

Increasing the arterial oxygen content, via blood transfusion and raise in hemoglobin levels or augmenting the cardiac output will improve oxygen delivery **(Table 2-1)**.

Oxygen Consumption

The Fick principle can be used to determine cardiac output (CO) if the following are known:

- Amount of oxygen consumed per time (VO_2)
- Oxygen content of arterial blood (CaO_2)
- Oxygen content of venous blood (CvO_2)

CO can be calculated using these variables as it is a product of oxygen consumption and the difference in arterial-venous oxygen content:

$$CO = VO_2 \times (CaO_2 - CvO_2)$$

VO_2 is affected by both oxygen delivery and oxygen extraction:

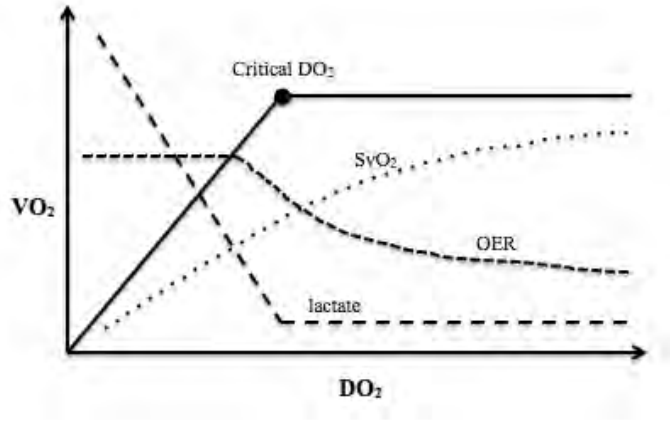
$$VO_2 = CO/(CaO_2 - CvO_2)$$

Balancing Oxygen Delivery and Consumption

By driving the process of aerobic respiration at the cellular level, oxygen molecules are the final electron acceptor in a series of reactions that result in the synthesis of ATP. Under normal resting conditions, oxygen delivery equals oxygen consumption with significant reserve to carry out this process and easily meet the body's energy needs.

Figure 2-2. Relationship between oxygen delivery and consumption.

As oxygen delivery (DO_2) falls relative to oxygen consumption (VO_2), the mixed venous saturation (SvO_2) decreases and oxygen extraction ratio (OER) increases as the organism compensates by attempting to extract more oxygen



Adapted from Assuncao, Murillo Santucci Cesar de, Corrêa, Thiago Domingos, Bravim, Bruno de Arruda, & Silva, Eliézer. (2015). How to choose the therapeutic goals to improve tissue perfusion in septic shock. *Einstein (São Paulo)*, *13*(3), 441-447. Epub August 21, 2015. https://dx.doi.org/10.1590/S1679-45082015RW3148.

When either oxygen delivery falls or oxygen consumption rises, an organism attempts to maintain an adequate ATP supply to meet the increased demand, first by redistribution of blood flow, capillary recruitment, and increased oxygen extraction.

At a critical DO_2, these compensatory mechanisms fail, and the organism turns to anaerobic metabolism with resultant lactic acidosis in an attempt to meet the increased energy requirements **(Fig 2-2)**. If the underlying imbalance is unable to be restored, the integrity of cell membranes is lost as ATP-pumps fail, and the hypoxia results in cell death.

Assessment of Oxygen Delivery and Consumption

Lactate - The presence of an elevated lactate (>2.0 mmol/L) tends to be a late finding that represents ongoing anaerobic cellular respiration and an impaired balance between oxygen delivery and consumption. Optimal measurement of lactate is through a specimen obtained via arterial puncture or indwelling catheter. Capillary specimens may be used as a method of trending lactate levels but should not be considered diagnostic

Mixed venous saturation and oxygen extraction ratio - Oxygen extraction is normally 25% to match the delivery and consumption. If arterial saturation is at 100%, then the mixed venous saturation is 75%. When oxygen extraction increases in the setting of rising energy needs, the oxygen extraction ratio (OER) becomes a useful measurement.

$$OER = VO_2/DO_2 = (SaO_2 - SvO_2)/SaO_2$$

Beyond the critical DO_2 inflection point **Fig 2-2,** when the OER exceeds 50-70% (or SvO_2 is 30-50%), the gradient of the VO_2/DO_2 curve demonstrates a near 1:1 relationship, indicating that all delivered oxygen is extracted. **Table 2-2** describes a general interpretation of OER numbers.

Table 2-2. Interpretation of oxygen extraction ratio (OER)	
25-30%	Normal
30-40%	Elevated
40-50%	Impending shock
>50%	Onset of shock, tissue hypoxia, lactate begins to accumulate

Near-infrared spectroscopy (NIRS) - Local tissue oxygen saturation can be measured using (NIRS) to assess the microcirculation for aberrations in oxygen delivery and consumption. NIRS-derived tissue SO_2 readings may serve as surrogates for SvO_2 in calculating OER at the bedside (weak recommendation, low quality evidence). Trend in NIRS measurements should be interpreted within the context of the patient's clinical status and other markers of DO_2-VO_2 balance. A deviation decreasing from a patient's baseline may yield more information than a saturation value at any given point in time. Some fluctuation from the baseline may be expected during periods of agitation, handling, or procedures.

Cardiac Output

Systemic cardiac output (CO) is the volume of blood ejected from the left ventricle in a minute. It is the product of the heart rate (HR) and stroke volume (SV); Stroke volume is the volume of blood ejected from the left ventricle per beat. The systemic blood pressure (BP) is a product of the cardiac output and systemic vascular resistance (SVR). The neonate depends mainly on heart rate and preload to increase cardiac output.

$$CO = SV \times HR$$

$$BP = CO \times SVR$$

Stroke volume is dependent on three factors:

1. **Preload -** is the end-diastolic volume (EDV), or volume in the ventricle after filling. Preload increases with increased circulating blood volume, venous tone, ventricular compliance, atrial contractility, or with decreased intrathoracic pressure. As per the Frank-Starling mechanism, increasing preload leads to increased stretching of cardiac muscle fibers, leading to increased force of contraction and stroke volume **(Fig 2-3)**.

Figure 2-3. Relationship of CO and EDV
Figure 2-4. Relationship of LV Pressure and ESV

Figure 2-3

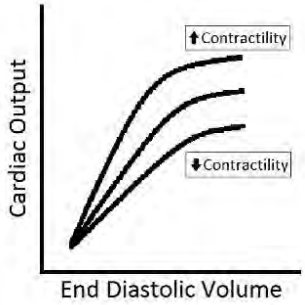
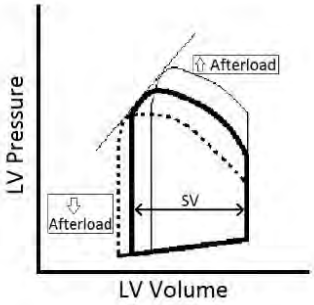


Figure 2-4



2. **Contractility -** the force and velocity of a contraction. Increased contractility leads to an increase in stroke volume **Fig 2-3**.
3. **Afterload -** the force that resists myocardial fiber contraction during systole. It is directly related to ventricular wall stress, and the end-systolic volume (ESV) or volume in the ventricle after ejection. An increase in afterload will decrease stroke volume for a given preload **Fig 2-4**.

Balance of Pulmonary and Systemic Blood Flow

Normally at birth, blood flow through the lungs (Qp) is equal to the blood flow through the left heart and the systemic circulation (Qs), resulting in a Qp: Qs ratio that is close to 1. This balance is disturbed in many forms of congenital heart disease. Large right-to-left shunts (e.g. pulmonary atresia) can result in Qp < Qs and ratio <1, indicating that there is insufficient pulmonary blood flow, which can present as cyanosis. In contrast, large left-to-right shunts (e.g. large VSD) can result in Qp>Qs and ratio >1, which is reflective of excessive pulmonary blood flow state and can present as congestive heart failure (CHF).

Calculation of Qp:Qs and Resistance

$$\frac{Q\ pulmonary}{Q\ systemic} = \frac{Aorta\ O2\ sat - SVC\ O2\ sat}{Pulm\ venous\ O2\ sat - Pulm\ artery\ O2\ sat}$$

$$PVR = \frac{Mean\ PA\ pressure - Mean\ LAP}{Pulmonary\ blood\ flow}$$

$$SVR = \frac{Mean\ aortic\ P - Mean\ RAP}{Systemic\ blood\ flow}$$

Where LAP – Left atrial pressure

RAP – Right atrial pressure

The Qp:Qs ratio can be altered by changes in systemic and peripheral vascular resistance (SVR, PVR), as shown in **Table 2-3.**

Table 2-3. Interventions to alter SVR and PVR	
Factors that Increase SVR: • Hypothermia • Oxygen • Agitation/crying • Knee-chest position • Meds: Dopamine, Epinephrine, Norepinephrine	**Factors that Decrease SVR:** • Hyperthermia • Metabolic acidosis • Meds: PGE (↓), Nitroprusside
Factors that Increase PVR: • Hypercarbia, respiratory acidosis • Metabolic acidosis • Low FiO_2 – subambient FiO_2, alveolar hypoxemia • Pulmonary vascular under- or maldevelopment • Meds: Catecholamines	**Factors that Decrease PVR:** • Hypocarbia, respiratory alkalosis • Supplemental oxygen • Meds: iNO, PGE (↓↓)

Evaluation of Suspected Cardiac Disease

Vital Signs

Pulse Oximetry-Pulse oximeter probes should be attached to the right hand and either foot to give pre-ductal and post-ductal saturations to provide information regarding blood flow patterns through the PDA. In severe aortic coarctation or interruption, oxygen saturation in the feet is lower than in the right hand. This differential cyanosis is due to shunting of deoxygenated blood in the pulmonary artery through the PDA into the aorta. In D-TGA with severe coarctation or D-TGA with pulmonary hypertension, oxygen saturation in the feet is higher than in the right hand, a phenomenon known as reverse differential cyanosis. This occurs due to shunting of oxygenated blood from the pulmonary artery through the PDA into the aorta.

Blood Pressure - Blood pressure measurements have little utility in the diagnosis of cardiac diseases. However, an upper extremity to lower extremity systolic BP gradient may indicate aortic coarctation. Cuff BP can be influenced by an infant's state of distress and agitation and may give erroneous readings. A normal newborn may have up to a 15 mmHg gradient between upper and lower extremities. Non-invasive BP measurements are better for monitoring hemodynamic changes than for making a diagnosis.

Physical Examination Findings

Pulses - Systemic hypoperfusion is characterized by weak central and peripheral pulses, delayed capillary refill time, and hypotension is common in cardiac lesions with ductal-dependent systemic blood flow. In coarctation of aorta, there may be a delay between radial/brachial and femoral pulses. Other cardiac conditions associated with systemic hypoperfusion include cardiomyopathies and arrhythmias.

Color - Central cyanosis is a manifestation of arterial oxygen desaturation. The degree of cyanosis depends on the concentration of desaturated hemoglobin ($\geq$ 5 g/dl). Infants with polycythemia have more profound cyanosis despite relatively modest arterial desaturation. Conversely, anemic infants may appear pink despite significant arterial desaturation. Infants that are cold may have significant peripheral cyanosis that is not due to arterial oxygen desaturation.

Respiratory Status - Cardiac lesions with systemic hypoperfusion leading to acidosis and those causing pulmonary over circulation can lead to respiratory distress, including tachypnea with or without increased work of breathing.

Cardiac Impulse - Palpation of cardiac impulse can provide clues to cardiac disease. Cardiac impulse will be felt on the right chest wall in dextrocardia. An increased right or left ventricular impulse indicates increase in ventricular blood volume.

Heart Sounds - Auscultation of heart sounds and murmurs is rarely diagnostic in newborns. Auscultation of the second heart sound (S2) is important in diagnosing cardiac disease. A single S2 is associated with significant pulmonary hypertension, TGA, and pulmonary atresia. The characteristic "to-and-fro" systolic-diastolic murmur is heard in conditions such as absent pulmonary valve syndrome, truncus arteriosus with truncal stenosis and regurgitation. Heart murmurs may be absent in severe heart disease; and therefore cannot be used to exclude congenital heart disease.

Abdomen - Hepatomegaly may be present in conditions with elevated systemic venous pressure, such as congestive heart failure and total anomalous pulmonary venous connection.

Workup

Hyperoxia Test - The hyperoxia test may be a useful tool for differentiating between pulmonary and cardiac causes of hypoxemia. The infant is placed on 100% oxygen for $\geq$ 10 minutes and a pre-ductal (right radial) arterial blood gas sample is obtained and compared to a pre-test specimen. If this results in a rise in PaO_2 greater than 20-30 mmHg (with typical PaO_2 >150 mmHg) or increase of 10% in SpO_2 is observed, a pulmonary etiology is likely. In infants with fixed right to left cardiac shunts or in conditions where mixing of systemic and pulmonary circulations occur, there will be a minimal rise in PaO_2 (with typical PaO_2 <100 mmHg). The hyperoxia test does not rule out cardiac disease. Cardiac lesions in which the hyperoxia test may not be diagnostic include large left to right shunts, systemic hypoxemia, and mixing of pulmonary and systemic venous return with unobstructed pulmonary blood flow (TAPVR without obstruction).

Laboratory Tests - Basic lab tests such as CBC, ABG with lactate, and Chem10 should be considered. In ill-appearing infants, such as those with increasing tachypnea or poor perfusion, an ABG with lactate should be obtained urgently.

Radiography - Heart size can be inferred by comparing the width of the cardiothymic silhouette to the width of the chest wall. Cardiomegaly is present if this ratio is > 0.65. The degree of pulmonary vascularity (normal, increased, or decreased) may indicate the type of cardiac lesion.

EKG/ECHO - Except for arrhythmias, an EKG is rarely diagnostic for cardiac diseases in the newborn period. Endocardial cushion defects are characterized by superior QRS axis. Echocardiography is the gold standard for delineating cardiac anatomy.

CT/MRI - These modalities may be useful in select cases.

- **CT Angiogram -** useful to delineate coronary artery anatomy, pulmonary artery size, ductal anatomy, and relationship of vasculature to other structures in the chest. Likely requires CV Anesthesia consultation for the procedure.
- **Cardiac MRI** - can be helpful in delineating anatomy, quantifying ventricular function and blood flow, and diagnosis of etiologies of cardiomyopathies. Requires CV Anesthesia consultation for the procedure.

2.2 Circulatory Insufficiency or Cardiogenic Shock

Shock is defined as inadequate oxygen delivery to meet metabolic needs and oxygen consumption resulting in hypoxia. Circulatory insufficiency occurs when inadequate tissue perfusion to multiple organs secondary to cardiac pump failure due to low cardiac output.

Parameters that suggest inadequate tissue perfusion include:

- Low arterial systolic , diastolic or mean blood pressure
- Reduced urine output

- Poor capillary refill, peripheral pallor, or cyanosis
- Lactic acidosis
- Increased oxygen extraction ratio reflected in increased arterial-venous O_2 content difference or decreased mixed venous oxygen saturation

Blood Pressure

Despite being an easily measured circulatory parameter, BP is an insensitive indicator of organ blood flow and tissue oxygen delivery. The other indicators of circulatory status described previously must be evaluated and clinically correlated. **Tables 2-4 and 2-5** represent BP thresholds in the preterm and term neonatal population.

Pathophysiology of Hypotension

Assessment of physical exam and correlating the individual systolic or diastolic blood pressure values will delineate etiology of the hypotension. Treatment of hypotension should be guided and interventions directed accordingly. Systolic hypotension is indicative of decreased stroke volume, which can result from decreased preload, impaired ventricular contractility, or increased afterload **(Table 2-6)**. Diastolic hypotension can be secondary to impaired filling, diminished systemic vascular resistance or depleted/inadequate intravascular volume **(Table 2-7)**.

Management of Circulatory Insufficiency

Figure 2-5 describes an overview of the management of circulatory insufficiency by etiology.

Role of echocardiography

In patients with hypoxemia of unclear etiology or refractory to interventions, an echocardiogram should be done early to rule out structural heart disease (strong recommendation, moderate quality evidence). In patients with structurally normal hearts, echocardiography should be considered to evaluate cardiac function and measure cardiac output. Echo can be used to evaluate preload, afterload, and contractility so that medical therapy can be tailored appropriately. In LV dysfunction, agents that cause an increase in afterload may lead to further deterioration and, therefore, should be avoided. Assessments of RV and LV filling can help guide fluid management, Knowledge of whether the patient is in a high versus low cardiac output state can guide therapy in patients with RV dysfunction. Echo provides us information on hemodynamic status to tailor appropriate therapeutic agents, and evaluate the effect of the targeted interventions.

Table 2-4. Blood pressure thresholds (3rd percentile) according to post conceptual age in preterm infants

Postconceptual Age (weeks)	Systolic (3rd percentile)	Mean (3rd percentile)	Diastolic (3rd percentile)
24	32	26	15
25	34	26	16
26	36	27	17
27	38	27	17
28	40	28	18
29	42	28	19
30	43	29	20
31	45	30	20
32	46	30	21
33	47	30	22
34	48	31	23
35	49	32	24
36	50	32	25

Adapted by permission from BMG Publishing Group Limited from Archives of Disease in Childhood: Fetal & Neonatal Education by Northern Neonatal Nursing Initiative in Systolic blood pressure in babies less than 32 weeks gestation in the first year of life. 80:F38-F42 ©1999.

Table 2-5. Blood pressure thresholds according to postnatal age in healthy term neonates

Threshold		Day 1	Day 2	Day 3	Day 4
95th percentile	Systolic	78	83	86	88
	Mean	57	62	64	65
50th percentile	Systolic	65	69	70	71
	Mean	48	51	53	55
5th percentile	Systolic	54	57	59	63
	Mean	39	41	41	43

Data adapted from: Kent AL, Kecskes Z, Shadbolt B, Falk MC. Normative blood pressure data in the early neonatal period. Pediatr Nephrol. ©2007 Sep;22(9): 1335-41. doi: 10.1007/s00467-007-0480-8. Epub 2007 Apr 17. PMID:17437131.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

PPHN is characterized by a delay in transitioning from higher fetal pulmonary vascular resistance to low postnatal circulation. There may also be persistence of right-to-left shunting resulting in severe hypoxemia. Elevated PVR further diminishes pulmonary blood flow and thus pulmonary venous return, leading to decreased left ventricular preload and cardiac output.

The causes of PPHN can be classified into 3 overlapping categories based on underlying pathophysiology:

- **Underdevelopment-** Hypoplastic pulmonary vasculature with decreased cross-sectional area and blood flow results in a decreased surface area for gas exchange and a fixed increase in PVR (e.g., CDH, pulmonary hypoplasia).
- **Maldevelopment-** Remodeled pulmonary vascular bed with increased smooth muscle wall thickness and distal extension of muscle to vessels that are usually non-muscular (e.g., idiopathic/genetic, meconium-aspiration syndrome, CDH, intrauterine closure of the ductus with NSAID exposure, intrauterine hypoxia/stress) resulting in increased PVR.
- **Maladaptation -** Pulmonary vascular bed that is structurally normal but is abnormally reactive (constricted) due to parenchymal lung disease and inflammatory processes (e.g., asphyxia, sepsis, hypoxia, meconium-aspiration syndrome, RDS, pneumonia)

PPHN usually presents in the first 24 hours of life, and is associated with cyanosis and respiratory distress. It should be suspected in conjunction with lung or cardiac disorders as well as in clinical scenarios when intrauterine stress is apparent (e.g., asphyxia, meconium-staining of amniotic fluid). Exam findings might include a prominent precordial impulse and a narrowly-split, accentuated P2 component of the second heart sound.

Hypoxemia that is poorly responsive to supplemental oxygen is the hallmark of PPHN. Oxygenation is typically labile, but preserved ventilation. The extracardiac right-to-left shunting via PDA can produce differential cyanosis, which can be detected by the gradient between pre- and post-ductal PaO_2 and oxygen saturations.

Echocardiography in patients with PPHN can be used to discern the degree and direction of intra and extra cardiac shunting, evaluate RV and LV function, and rule out structural heart disease. Presence of tricuspid regurgitation, septal flattening and RV dilation are suggestive of elevated right ventricular pressure. Calculating the TR jet to estimate RV pressure and assess whether they are systemic or suprasystemic will aid in therapeutic interventions.

Medical intervention in PPHN is directed towards pulmonary vasodilation and reducing PVR thereby increasing pulmonary blood flow and oxygenation. In the newborn, treatment includes supplemental oxygen, ventilatory support, and surfactant therapy with the goal of maintaining preductal saturations between 91% and 95%. Vasodilation is achieved primarily through oxygen and inhaled nitric oxide (iNO), but additional pulmonary vasodilators (e.g., milrinone, sildenafil) may be needed. iNO is indicated for treatment of PPHN in mechanically ventilated term and late preterm newborns to improve oxygenation and reduce the need for ECMO (strong recommendation, moderate quality evidence,). Oral sildenafil may be considered for treatment of PPHN, especially if iNO is not available (weak recommendation, low quality evidence). Intravenous sildenafil may be considered for PPHN in critically ill patients, especially those with an unsatisfactory response to iNO. If necessary, oxygen delivery can be further optimized by improving arterial oxygen content through transfusion of red blood cells.

Other means of mitigating PVR include lung recruitment via mechanical ventilation, prevention of acidosis, and minimizing agitation through sedation and if needed, neuromuscular blockade. During the first few hours of life, the target values for infants with acute PPHN include pCO_2 of 40-50, pH >7.25, and lactate <5 mmol/L.

If LV function is normal, an agent like norepinephrine or vasopressin can raise SVR while simultaneously lowering PVR. If function is poor, cardiac output can be augmented with

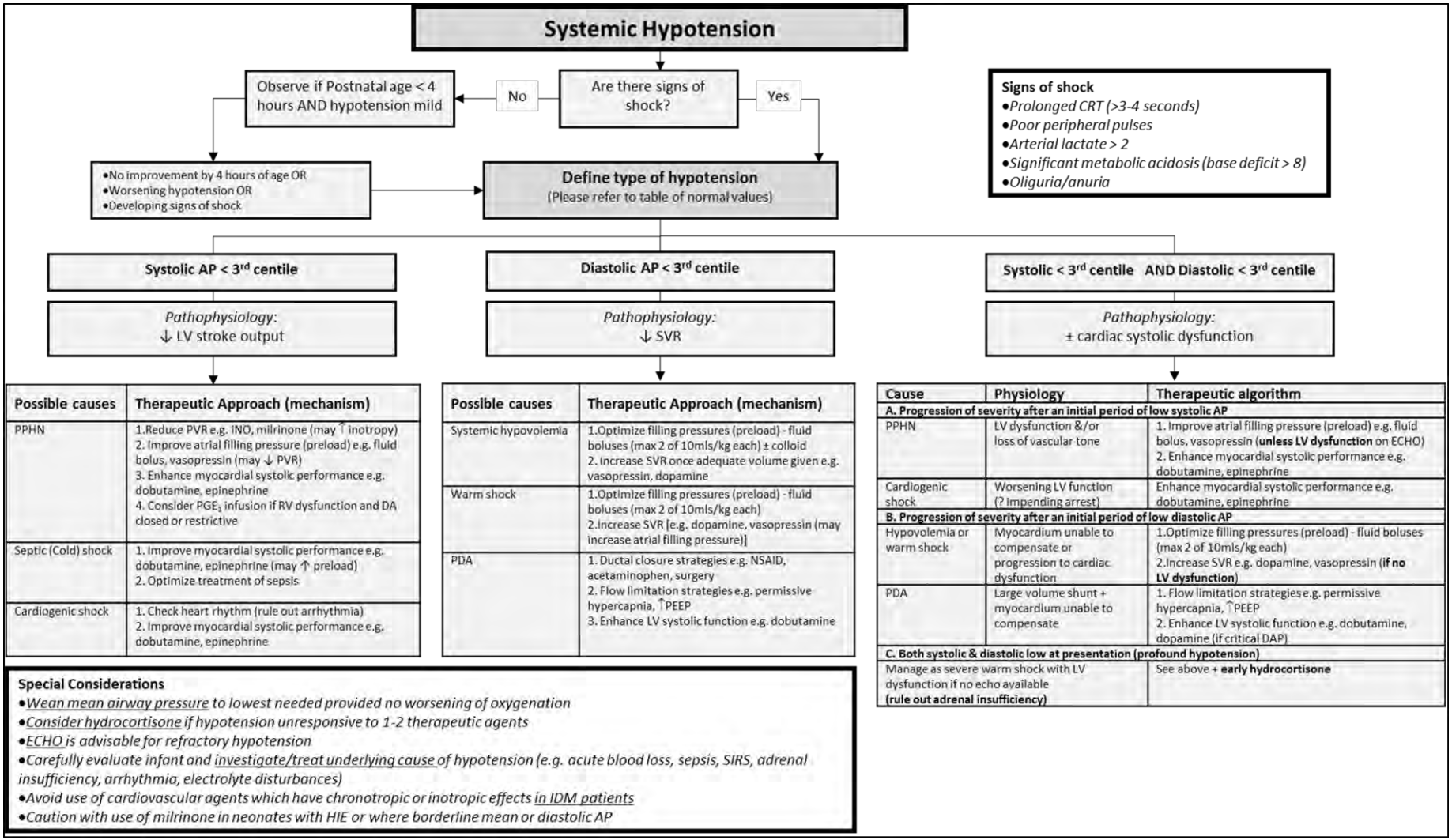
Table 2-6. Factors contributing to circulatory failure

	Pathophysiology	Clinical Examples
Decreased Preload	• Decreased pulmonary blood flow resulting in decreased left atrial volume or obstruction to pulmonary venous return secondary to PAPVR/TAPVR	• PPHN • Mean airway pressure impairing systemic venous return • Obstructed /Anomalous pulmonary venous return
	• Impaired diastolic filling	• Hypertrophic obstructive cardiomyopathy • Cardiac tamponade • LVNC
Increased Afterload	• Failure of adaptation after change in loading conditions leading to impaired contractility. • CHD with increased resistance	• Loss of "low-resistance" placenta after birth • Post PDA ligation syndrome • CoA, IAA, critical AS
	• Cold shock	• Vasoconstriction due to redistribution of blood to vital organs
	• Elevated SVR	• Exogenous vasopressors
Pump failure	• Structural anomalies	• Many CHD such as HLHS, Shone's complex
	• Arrhythmias	• SVT • VT • Junctional rhythm • AF • AVNRT etc
	• Impaired contractility due to myocardial injury/Ischemia	• HIE • Cardiomyopathy • Congenital anomalies of coronary arteries

Table 2-7. Common factors contributing to diastolic hypotension

Pathophysiology	Clinical Examples
Enlarged vascular bed	• Patent ductus arteriosus • Bronchopulmonary sequestration, giant hemangioma, arteriovenous malformation
Vasodilation	• Systemic inflammatory response syndrome (NEC or septic shock) • Medication (phenobarbital, midazolam, morphine, etc.) • Autonomic dysregulation
Hypovolemia	• Capillary leak (NEC or septic shock) • Hemorrhage (intracranial, feto-maternal, etc.) • Transepidermal water loss • Excessive urine losses (physiologic diuresis, post-obstructive diuresis, diabetes insipidus)

Figure 2-5. Algorithm for assessment and treatment of hypotension according to systolic, diastolic, and combined systolic and diastolic categories.



Possible causes	Therapeutic Approach (mechanism)
PPHN	1.Reduce PVR e.g. INO, milrinone (may ↑ inotropy) 2. Improve atrial filling pressure (preload) e.g. fluid bolus, vasopressin (may ↓ PVR) 3. Enhance myocardial systolic performance e.g. dobutamine, epinephrine 4. Consider PGE_1 infusion if RV dysfunction and DA closed or restrictive
Septic (Cold) shock	1. Improve myocardial systolic performance e.g. dobutamine, epinephrine (may ↑ preload) 2. Optimize treatment of sepsis
Cardiogenic shock	1. Check heart rhythm (rule out arrhythmia) 2. Improve myocardial systolic performance e.g. dobutamine, epinephrine

Possible causes	Therapeutic Approach (mechanism)
Systemic hypovolemia	1.Optimize filling pressures (preload) - fluid boluses (max 2 of 10mls/kg each) ± colloid 2. Increase SVR once adequate volume given e.g. vasopressin, dopamine
Warm shock	1.Optimize filling pressures (preload) - fluid boluses (max 2 of 10mls/kg each) 2.Increase SVR [e.g. dopamine, vasopressin (may increase atrial filling pressure)]
PDA	1. Ductal closure strategies e.g. NSAID, acetaminophen, surgery 2. Flow limitation strategies e.g. permissive hypercapnia, ↑PEEP 3. Enhance LV systolic function e.g. dobutamine

Cause	Physiology	Therapeutic algorithm
A. Progression of severity after an initial period of low systolic AP		
PPHN	LV dysfunction &/or loss of vascular tone	1. Improve atrial filling pressure (preload) e.g. fluid bolus, vasopressin (**unless LV dysfunction** on ECHO) 2. Enhance myocardial systolic performance e.g. dobutamine, epinephrine
Cardiogenic shock	Worsening LV function (? impending arrest)	Enhance myocardial systolic performance e.g. dobutamine, epinephrine
B. Progression of severity after an initial period of low diastolic AP		
Hypovolemia or warm shock	Myocardium unable to compensate or progression to cardiac dysfunction	1.Optimize filling pressures (preload) - fluid boluses (max 2 of 10mls/kg each) 2.Increase SVR e.g. dopamine, vasopressin (**if no LV dysfunction**)
PDA	Large volume shunt + myocardium unable to compensate	1. Flow limitation strategies e.g. permissive hypercapnia, ↑PEEP 2. Enhance LV systolic function e.g. dobutamine, dopamine (if critical DAP)
C. Both systolic & diastolic low at presentation (profound hypotension)		
Manage as severe warm shock with LV dysfunction if no echo available **(rule out adrenal insufficiency)**		See above + **early hydrocortisone**

Special Considerations

- *Wean mean airway pressure to lowest needed provided no worsening of oxygenation*
- *Consider hydrocortisone if hypotension unresponsive to 1-2 therapeutic agents*
- *ECHO is advisable for refractory hypotension*
- *Carefully evaluate infant and investigate/treat underlying cause of hypotension (e.g. acute blood loss, sepsis, SIRS, adrenal insufficiency, arrhythmia, electrolyte disturbances)*
- *Avoid use of cardiovascular agents which have chronotropic or inotropic effects in IDM patients*
- *Caution with use of milrinone in neonates with HIE or where borderline mean or diastolic AP*

inotropes (e.g., Dobutamine, Dopamine or Epinephrine). Right or left ventricular dysfunction in the setting of elevated PVR may be an indication for a lusitrope like milrinone (weak recommendation, low quality evidence). PgE_1 infusion may be considered as a means to unload a high-pressure right ventricle by reopening a closed PDA or maintaining ductal patency in preterm and term neonates with no VSD (weak recommendation, very low quality evidence). Normothermia and euglycemia should be maintained. Comorbidities should be treated (e.g., surfactant for lung disease, antibiotics for sepsis).

Extracorporeal membrane oxygen (ECMO) may be necessary when hypoxic respiratory failure is refractory to the therapies described above. Consider ECMO if PaO_2 <100 mmHg or OI >25. ECMO is not recommended in infants <34 weeks and/or <2kg.The indications for ECMO are discussed in the specific ECMO section

There is limited evidence available regarding treatment of PPHN in preterm neonates. Strategies aimed at optimizing lung recruitment and oxygen saturations are similar to those used in term infants. Use of iNO for the prevention of CLD or treatment of pulmonary hypertension that is associated with CLD is not routinely recommended and should be limited to patients enrolled in an IRB approved study protocol. A trial of iNO may be considered once ventilation and oxygen delivery have been optimized and treatment with surfactant is considered in patients with echocardiographic evidence of pulmonary hypertension.

Cardiogenic Shock

Cardiogenic shock is characterized by inadequate tissue perfusion that results from poor myocardial contractility related to one of the following:

- hypoxia, acidosis, or both, most commonly a result of perinatal asphyxia, heart disease, or lung disease
- hypoglycemia
- high cardiac output resulting in myocardial ischemia or cardiac failure secondary to a large PDA or an A-V fistula
- myocardial ischemia or infarction related to an anomalous coronary artery
- myocardial insufficiency related to myocarditis or primary cardiomyopathies
- myocardial ischemia or cardiac failure related to severe left ventricular obstructive disorders
- circulatory collapse related to arrhythmias, cardiac surgery or ECMO.

Cardiogenic shock presents with respiratory distress due to pulmonary edema and hepatomegaly secondary to decreased venous return with resultant hepatic congestion. Diminished peripheral pulses and prolonged capillary refill, cardiomegaly, hepatomegaly, and gallop rhythm may be present.

Treatment approaches to cardiogenic shock fall into four major areas:

- **Fluid restriction and diuretics-**Reduction of systemic venous return leading to decreased preload thus relieving hepatic congestion and pulmonary edema. One must be cautious and not reduce preload to a degree that further impairs cardiac output.
- **Augmentation of myocardial contractility-**Multiple agents can be used. Dobutamine, epinephrine, and dopamine improve cardiac output by improving inotropy and chronotropy. Milrinone may be preferred when RV dysfunction predominates.
- **Afterload reduction and systemic vasodilators**-Decrease SVR and thereby reducing myocardial afterload. Milrinone is a PDE III inhibitor. Phosphodiesterase III is located primarily in the cardiac sarcoplasmic reticulum and in the smooth muscle in arteries and veins. PDE III inhibition prevents cGMP metabolism in the smooth musculature and results in vasodilation in both arteries and veins. Nicardipine and Nitroglycerin, isosorbide dinitrate/ mononitrate, and sodium nitroprusside belong to a subclass of vasodilators known as nitrodilators that work by increasing nitric oxide (NO) within the vascular smooth muscle
- **Management of arrhythmia-(Ch 2.5-Arrhythmias)**

Septic Shock

Abnormal peripheral vasoregulation with or without myocardial dysfunction are the primary mechanisms for the hypotension accompanying septic shock in the neonate. Neonates with septicemia may present with tachycardia, poor perfusion and "normal" blood pressure (high SVR) or with hypotension and either adequate perfusion (warm shock, vasodilation) or inadequate perfusion (cold shock, vasoconstriction). These distinctions are important for directing appropriate therapy.

Hemodynamic consequences of septic shock relate to effects of endotoxin on pre- and post-capillary sphincters, especially alpha-adrenergic receptors, and the release of various vasoactive substances (histamine, serotonin, epinephrine/norepinephrine, kinins). Initially, constriction of pre- and post-capillary sphincters produces ischemic anoxia at the cellular level. As anaerobic metabolism and lactic acidosis dominate, the pre-capillary sphincter relaxes and the stage of stagnant anoxia is established. During this stage, profound capillary pooling occurs, capillary permeability increases, and intravascular fluid is lost to the interstitial compartment. This loss of effective blood volume decreases venous return to the heart, leading to a reduction in cardiac output, further exacerbating tissue hypoperfusion. SVR may be low, high, or normal during this process.

Effects of vasoactive substances on the lung include an increase in pulmonary capillary wedge pressure leading to an increase in fluid filtration from microvasculature in the lung resulting in pulmonary interstitial edema.

Early stages of septic shock manifest by an intense peripheral vasoconstriction with maintenance of normal or elevated arterial pressure. Mechanism of organ failure in sepsis may relate to decreased oxygen utilization associated with mitochondrial dysfunction in addition to poor oxygen delivery to tissues. A progressive fall in urine output, hypotension and metabolic (lactic) acidosis occur.

The treatment of septic shock is dictated by the stage of the systemic inflammatory response syndrome (i.e., whether it is warm or cold shock):

- **Volume resuscitation:** Normal Saline, FFP, Cryoprecipitate and PRBC can be used as clinically indicated. This increases circulating blood volume and venous return to the heart improving preload and cardiac output. Close monitoring for pulmonary edema is warranted and requires use of assisted ventilation. After restoring effective preload, augment SVR with a peripheral vasoconstrictor (e.g., vasopressin, norepinephrine or epinephrine).
- **Vasoactive agents:** If the presentation is characterized by a vasodilatory response (e.g., warm shock), the goal of therapy is to augment SVR with agents like vasopressin or nor epinephrine. If there is LV dysfunction, then an inotropic agent such as dopamine or epinephrine should be considered.
- **Corticosteroids** Neonates have a limited reserve of enzymes necessary for the synthesis of cortisol, increasing their risk for relative adrenal insufficiency (RAI) under stresses, such as sepsis. Steroids block the effects of endotoxin and inflammatory mediators on vascular tone and improve integrity of the capillary membrane. They also increase response of receptors to endogenous and exogenous catecholamines.

Hypovolemic Shock

Hypovolemia is an uncommon cause of hypotension in preterm infants, especially in the absence of evident blood loss.

Common etiologies of hypovolemia in the first 24 hours of life are due to blood loss from:

- Umbilical cord or placental laceration, such as placenta previa or velamentous cord insertion
- Redistribution of fetal blood volume to placenta associated with maternal hypotension, cesarean section, atonic uterus, etc.
- Placental abruption
- Acute twin-to-twin transfusion syndrome
- Intrapartum (terminal) asphyxia or umbilical cord compression (e.g. tight nuchal cord) may prevent placental transfusion to fetus or occasionally results in mild blood loss into the placenta (in general, however, intrapartum asphyxia is not associated with serious hypovolemia)
- IVH
- Intraabdominal hematoma secondary to malpositioned UAC/UVC

Recognition of ongoing bleeding and resuscitation with PRBC and FFP is necessary in addition to supporting ventilation and minimizing oxygen consumption.

Autonomic Dysregulation of the Premature Infant

Hypotension in the VLBW infant can be common and is likely to be multifactorial in etiology. Immaturity of the autonomic nervous system often results in decreased systemic vascular tone. This is further complicated by the premature myocardium's inability to adapt to the increased afterload that accompanies removal of the low resistance placental circuit. In this population, insensible water loss, relative adrenal insufficiency, and patent ductus arteriosus further contribute to the diastolic hypotension, which tends to respond best to agents which augment SVR. Additionally, the myocytes and the calcium-dependent contraction mechanisms of the premature heart are underdeveloped, limiting their ability to augment contractility in response to inotropes.

Patent Ductus Arteriosus

Persistent patent ductus arteriosus in small premature infants may cause increasing left-to-right shunting, progressive pulmonary edema, and deterioration of respiratory function. It is a primary cause of diastolic hypotension in VLBW infants. Its clinical presentation and management are discussed in **Ch 2.3-Congenital Heart Disease.**

Adrenal Insufficiency

Adrenal insufficiency most likely contributes to or plays a complicating role in the development of hypotension in certain at-risk neonates like premature infants or those with an underlying endocrine abnormality. In these at-risk patient groups, consider hydrocortisone to support the blood pressure, particularly when the hypotension is refractory to inotropic agents.

Diagnosis of Chronic Heart Failure

In general, heart failure results from disorders that impair the ability of the ventricles to adequately fill, adequately eject, or both. This can occur in structurally normal and abnormal hearts though usually for different reasons. In structurally normal hearts, etiologies for ventricular dysfunction include cardiomyopathy (e.g., dilated, hypertrophic), myocarditis, myocardial ischemia, arrhythmia, sepsis, renal failure, BPD, and interstitial lung disease. Heart failure may also be caused by volume overload (e.g., VSD, PDA, AP window, AVSD, arteriovenous malformation) or increased afterload (e.g., aortic stenosis, coarctation of aorta, pulmonary stenosis, systemic hypertension) in the setting of preserved ventricular contractility. In some cases, these etiologies may overlap (volume or pressure overload associated with ventricular dysfunction). The most common symptoms for heart failure in the NICU population are tachycardia, tachypnea, tiring or diaphoresis with feeds, poor weight gain, irritability, and decreased PO feeding. On physical exam, an S3 gallop may be present in infants with diminished cardiac output or volume overload in addition to signs of poor perfusion, and/or hepatomegaly.

Work up includes ECG, ECHO, and CXR. Additionally, MRI , Cardiac CT and/or catheterization may be considered. Laboratory tests include BNP to assess severity of right atrial enlargement and monitor response to therapy, troponin to evaluate for myocarditis or ischemia, CBC to evaluate for anemia, electrolytes to evaluate for safety of initiating diuretics or angiotensin-converting enzyme inhibitors, BUN and creatinine to assess renal function, and liver function tests which may be elevated in hepatic congestion.

Goals of therapy for heart failure are to relieve symptoms, slow progression, and improve survival and quality of life. In patients with volume or pressure overload due to specific defects, appropriate intervention (often surgical) depends on the specific lesion. Pharmacologic therapy may include renin-angiotensin-aldosterone system inhibition, diuretics, beta-blockers, or inotropes depending on the clinical situation. Some medications, such as beta blockers, spironolactone, and

angiotensin-converting enzyme [ACE] inhibitors, have been shown to reverse LV remodeling and improve survival in some heart failure populations.

Early involvement of the TCH Heart Failure team should be considered, especially when diagnosis is consistent with one that may progress to need for transplant or ventricular assist device.

Medical Therapy

Volume expansion -Bolus infusions of volume expanders are not recommended unless specific evidence of hypovolemia is present. There is no relationship between hematocrit, blood volume, and blood pressure in non-specific hypotension in premature infants. Effects of bolus infusion of volume expanders, if used, are transient and may be detrimental. Repeated boluses may lead to fluid overload or increased risk of IVH. In premature infants, excess fluid intake is associated with higher mortality.

Crystalloid and colloid fluids have been shown to have equivalent efficacy except in instances of active hemorrhage or profound anemia. Initial hematocrit may be useful in estimating the magnitude of volume replacement but subsequent hematocrit values cannot be used as a sole guide to determine adequacy of volume replacement. We recommend normal saline boluses in 10 mL/kg increments until colloids such as PRBCs are available. Use of 5% albumin infusions is not recommended as it is associated with fluid retention and increased risk of impaired gas exchange. Transfusion of whole blood or packed red blood cells may be necessary up to a maximum central hematocrit of 55%. Monitoring arterial pressure, body weight, serum sodium, and urine output is essential. Central venous pressure measurements and cardiac size on x-ray may also be helpful in assessment of the fluid status of the neonate.

Corticosteroids-block the effects of endotoxin and inflammatory mediators on vascular tone and the integrity of the capillary membrane. Corticosteroids also induce the enzyme involved in transformation of norepinephrine to epinephrine and increase the responsiveness of the receptors for endogenous and exogenous catecholamines.

They have been shown to increase BP within 2-6 hours in refractory hypotension. Some observational studies have reported a statistical association between hypotension and serum cortisol levels < 15 mcg/dl ("relative adrenal insufficiency") in preterm infants. However, these levels are poor predictors for actual occurrence of hypotension or response to treatment with hydrocortisone. We do not recommend routine measurement of cortisol levels.

(1) Give a single dose of 1 mg/kg IV Hydrocortisone

(2) If hypotension and circulatory dysfunction persists or recurs over next 4-6 hours, continue treatment with hydrocortisone 1 mg/kg/dose every 8 hours for 24-48 hours, and taper off steroids by day 5 if tolerated (strong recommendation, low quality evidence)

(3) As BP improves, attempt to wean off pressor agents

The safety and long-term benefits of short-course hydrocortisone therapy for hypotension are not clear. Use of corticosteroids in premature infants has been associated with adverse neurologic outcome and increased risk of intestinal perforation, especially if used in conjunction with indomethacin. Therefore, we do not recommend concurrent administration of hydrocortisone and indomethacin. Hyperglycemia and impaired bone mineralization have also been associated with corticosteroid use.

Dobutamine - stimulates myocardial α-1 and β-1 receptors resulting in increased contractility and heart rate. Although it also stimulates both β-2 and α-1 receptors in the vasculature, the cumulative result is some vasodilation in addition to the inotropic and chronotropic effects. Dobutamine increases cardiac output by augmenting stroke volume. Though it has been consistently shown to be inferior to dopamine in raising BP, both SVC flow and pulmonary blood flow have been shown to be higher in patients treated with dobutamine. The use of dobutamine may be considered for inotropic support when left ventricular function is impaired based on clinical or echocardiographic evidence (weak recommendation, low quality evidence). Therapy should be initiated at 5 mcg/kg/min and titrated to effect. Usual dosing range for neonates is 2-15 mcg/kg/min.

Dopamine is the most frequently prescribed medication for nonspecific hypotension, though its overall use has declined in the last decade. It is no longer the preferred agent in pediatric and adult patients due to its effect on heart rate and its arrhythmogenic potential. Dopamine stimulates both adrenergic and dopaminergic receptors. In adults, it has been shown to have variable dose-related activation of receptors, but it is unclear if similar receptor activation occurs in neonates. Moreover, it appears that neonates have activation of receptors at lower doses with variable results. For example, at 6-8 mcg/kg/min some neonates demonstrate an increase in left ventricular output with a moderate increase in MBP while others demonstrate a decrease in left ventricular output with a larger increase in MBP. Dopamine has also been shown to increase oxygen consumption, cause hyponatremia, decrease thyrotropin secretion, and increase PVR > SVR. When used, it should be started at 5 mcg/kg/min and titrated to effect (strong recommendation, low quality evidence). If no effect is seen with doses of 10-15 mcg/kg/min, addition of another agent should be considered.

Epinephrine-potent stimulator of α and β receptors. It increases heart rate, stroke volume, SVR, and PVR (the increase in SVR is roughly equal to the increase in PVR). Epinephrine has been shown to be equal to dopamine in increasing BP, but was also associated with higher heart rate, hyperglycemia, and increased lactates in studies using moderate to high dosing ranges. Epinephrine may be considered in patients when improvement of systolic performance is desired and may be a better option than dopamine when concern for hypoxic respiratory failure is present. Dosing should be initiated at 0.01-0.03 mcg/kg/min and titrated to effect. Usual dosing range should be 0.01-0.3 mcg/kg/min.

Milrinone-is an inotropic drug that increases cAMP levels by direct inhibition of phosphodiesterase and prevention of cAMP degradation. It has an inotropic effect on the heart and a dilating effect on veins and arterioles, and does not depend on neurotransmitter stores or receptors. Milrinone can simultaneously increase cardiac output and decrease PVR, without a significant increase in myocardial oxygen demand. It

has been shown to improve oxygenation in severe PPHN. Milrinone is, also, of benefit in patients weaning from cardiopulmonary bypass and those with right ventricular failure. In the neonatal population, it is used in patients with low cardiac output associated with congenital heart disease or myocardial dysfunction. (weak recommendation, low quality evidence).

Milrinone can cause hypotension and should be considered only when blood pressure is adequate. Toxicities include arrhythmias, tremor, thrombocytopenia, and vomiting. It should be avoided in patients with oliguria or anuria due to increased risk of toxicity. Recommended starting dose is 0.375 mcg/kg/min (no loading dose necessary) and range is 0.375-0.75 mcg/kg/min.

Vasopressin-induces vasoconstriction via multiple mechanisms and has minimal to no inotropic or chronotropic effect. Its effects on the cardiovascular system are not fully understood, but vasoconstrictive effects are preserved during hypoxia and severe acidosis. A retrospective review of use at TCH showed that it increased BP and urine output without causing hyponatremia. Vasopressin should be considered when goal of treatment is systemic vasoconstriction, especially when oxygenation is a concern in the setting of normal LV function (weak recommendation, low quality evidence). It should also be considered a viable option in hypotension when tachycardia or increased inotropy would be contraindicated. Vasopressin is usually started at 0.01 units/kg/hr and titrated to effect. Usual dosage range is 0.005-0.04 units/kg/hr.

Inhaled Nitric Oxide is a selective pulmonary vasodilator which causes smooth muscle relaxation by activating guanylyl cyclase leading to increased cGMP levels. Treatment with iNO has been shown to reduce need for ECMO in patients with hypoxic respiratory failure among term and near-term population. Use in prevention of BPD has not been well studied and is not recommended at this time. It can be used for the purpose of "rescue" in select premature infants with severe pulmonary hypertension. iNO should be considered in infants with hypoxic respiratory failure where decreased preload is a concern due to inadequate pulmonary blood flow. In addition, select premature and term neonates may benefit from iNO in the setting of persistent or severe pulmonary hypertension.

Initiation of therapy is recommended in patients with a gestational age greater than 34 weeks, if a patient requires mechanical ventilation has an Oxygenation Index (OI) of at least 25 on two separate measurements.

$$\mathbf{OI = (Mean\ Airway\ Pressure \times FiO_2) / PaO_2) \times 100}$$

Before initiating iNO it is important to exclude congenital heart disease.

Inhaled nitric oxide is administered via the ventilator circuit at an initial dose of 20 ppm. Optimal lung recruitment is necessary prior to iNO administration. Response to therapy is defined as an improvement in PaO_2 of at least 10 mmHg or increase in oxygen saturations of at least 5% 30 minutes after initiation. Higher doses confer no additional benefit and should not be used.

If there is no response to optimized ventilation plus 20 ppm of iNO, the patient is classified as a non-responder and we recommend to wean iNO from 20 ppm to 10 ppm to 5 ppm every 15 minutes. At 5 ppm, we recommend to wean by increments of 1 ppm every hour until discontinued.

If a patient is a responder to iNO and stable for 4 hours, begin to wean FiO_2 by decrements of 2-5%. When FiO_2 has decreased to 60% and patient is stable, wean iNO from 20 ppm to 10 ppm to 5 ppm every hour. At 5 ppm attempt to wean by decrements of 1 ppm every 1-2 hours. Before discontinuation, increase FiO_2 by 10%. If patient is on sildenafil, consider timing discontinuation of iNO one hour after the sildenafil dose is given. After discontinuing iNO, wean FiO_2 back to baseline within 2 hours. If patient is not able to wean successfully, consider weaning slowly by going from 1 ppm to 0.5 ppm before discontinuing during next wean attempt.

Wean iNO with caution at concentrations below 5 ppm because precipitous deterioration in oxygenation has been reported at these low levels. When iNO is discontinued it may be necessary to increase FiO_2 as much as 15%.

When using iNO, NO and nitrogen dioxide (NO_2) levels are continuously monitored. If the NO_2 level reaches >3 check the delivery system, ventilator circuit, and detection device, and decrease the NO concentration by 50% every 15 minutes until the NO_2 concentration is below 3 PPM. If the NO_2 level ever exceeds 5 PPM, attempt to discontinue iNO.

Measure methemoglobin (metHb) concentration 24 hours after initiation of therapy. If metHb concentrations are greater than 7%, wean iNO if possible. If high met Hb levels persist despite weaning or discontinuing therapy, consider treatment with PRBC transfusion, IV methylene blue, or IV vitamin C, based upon clinical situation. At iNO doses of 20 ppm, levels of metHb greater than 5% to 10% are uncommon and rarely produce acute symptoms.

Circulatory Insufficiency: Special Considerations

Infants of diabetic mothers (IDM) - Close attention to underlying pathophysiologic mechanism prior to initiating vasoactive medications is needed. Patients usually have intact systolic function and impaired compliance with diastolic dysfunction. **(Table 2-8)**

Systemic hypotension in pulmonary hypertension - Inadequate pulmonary blood flow and decreased pulmonary venous return leads to decreased left ventricular preload and cardiac output. Pulmonary vasodilator therapy, support of the right ventricle, and monitoring of biventricular function are important elements of treatment. **(Table 2-9)**

Treatment of Heart Failure (Selected Therapies)

Diuretics-Diuretics act to decrease cardiac preload by reducing extracellular fluid volume. Despite the lack of long term efficacy and mortality data from pediatric clinical trials, diuretics are routinely used for symptom relief in the acute management of symptomatic heart failure. Loop diuretics (e.g., furosemide) are the first line agents for treatment of heart failure (weak recommendation, low quality evidence). If diuresis with loop diuretic is inadequate, addition of a thiazide diuretic may be considered. Oral bioavailability of furosemide is poor and consider using a 1:2 conversion factor when transitioning from IV to PO furosemide dosing.

Table 2-8. Infant of diabetic mother

Pathophysiology	Septal/myocardial hypertrophy	
Clinical feature	LVOTO due to hyper contractile myocardium	Decreased ventricular compliance, ventricular filling and diastolic function
Suggested therapy	Increase SVR	Volume repletion, heart rate control
Caution	Inotropes (hypertrophied myocardium with diminished LV volume, suicide left ventricle	Chronotropes (tachycardia with decreased diastolic filling time

ACE Inhibitors-By inhibiting the production of angiotensin II and aldosterone, ACE inhibitors cause vasodilation, reduction in systemic vascular resistance, decrease in afterload, and an increase in cardiac output. In addition, ACE inhibitors attenuate cardiac remodeling that contributes to heart failure progression. Because of its short half-life, captopril requires frequent dosing, from 2-4 times daily. Enalapril has a longer duration of action due to the long half-life of its active metabolite enalaprilat and can be administered once to twice daily. Due to lack of data comparing ACE inhibitors, the selection is generally based on ease of dosing, patient response, and tolerability (weak recommendation, low quality evidence). Adverse effects of ACE inhibitors include hypotension, hyperkalemia, increased blood urea nitrogen (BUN), increased serum creatinine, anuria, acute kidney injury, and rare angioedema. The use of ACE inhibitors in preterm infants has been associated with a high incidence of acute kidney injury.

β-blockers-In adults, β-blockers have been shown to decrease mortality and morbidity through reversal of adrenergic myocardial dysfunction, attenuation of neuro hormonal systems, antiarrhythmic effect, and negative chronotropic effect. It is unclear if beta blockers exert the same effects and benefits for pediatric patients with heart failure. Propranolol is the most commonly used agent for treating hypertension and arrhythmias among infants. Carvedilol, a non-selective β-antagonist with α-1 adrenergic blocking activity, is commonly used in pediatric heart failure patients. It has vasodilatory, anti-oxidant, anti-proliferative, and anti-apoptotic properties. Although carvedilol has not been directly compared with other β-blockers, the broad suppression of adrenoceptors is believed to contribute to improved outcomes in patients with chronic heart failure. Propranolol and carvedilol are available as a liquid formulation, allowing for ease of administration in infants and young children.

Adverse effects of β-blockers include hypotension and mild worsening of heart failure symptoms, especially at onset of treatment. Therefore, it should be avoided in acute decompensated heart failure. Contraindications include symptomatic bradycardia/heart block and significant hypotension. Caution is recommended in patients with reactive airway disease.

2.3 Congenital Heart Disease

Congenital heart disease typically presents in the newborn period but can present up to the first year of life. Most serious and life-threatening lesions that require urgent intervention usually present within the first several days of life. Timing and mode of presentation depend upon the type of lesion, ductus arteriosus closure, and fall in pulmonary vascular resistance. A differential for congenital heart diseases based on symptoms is presented in **Table 2-10.** Other differential diagnoses to consider when working up a patient for congenital heart disease include sepsis, primary pulmonary disease, anemia, and metabolic disorders.

Table 2-9. Systemic hypotension in pulmonary hypertension

Pathophysiology	Elevated Pulmonary Vascular Resistance		
Ventricular Function	(a) intact ventricular function	(b) impaired ventricular function	(c) severely impaired ventricular function
Remarkable echocardiographic findings:			
RV afterload	**+**	**++**	**++++**
RV contractility	**++**	**+/-**	**-----**
LV preload	N/-	N/-	-
LV afterload (systolic function)	N/-	--	**----**
Ventricular septum	N	Flat	Bowing to left venricle
Tricuspid Regurgitation (TR) Jet velocity	N	N/+	**++**
Tricuspid Annular Plane Systolic Excursion (TAPSE)	N	**+**	**++**
Suggested vasoactive therapy approach:	Pulmonary vasodilators, Epinephrine Milirinone if DBP within normal	In addition to previous: Consider norepinephrine or vasopressin	

Asymptomatic Neonates-Early detection of neonatal CHD remains challenging because clinical findings may be subtle or absent immediately after birth. Studies have shown that pulse oximetry is an effective, though not infallible, screening measure. Thus, the American Academy of Pediatrics (AAP), the American Heart Association (AHA), and the American College of Cardiology Foundation (ACCF) have recommended universal screening of all newborns with pulse oximetry to improve identification of infants with CHD (**Ch 12.10-Newborn Screening**). In addition to pulse oximetry screening, careful review of the history and physical examination of the infant remain imperative.

Basic Physiology & Management of Neonatal Cardiac Disease

Presentation in newborn period

Cyanosis-bluish discoloration of the tissues results when the absolute level of reduced hemoglobin in the capillary bed exceeds 5 g/dL. The appearance of cyanosis depends upon the total amount of reduced hemoglobin rather than the ratio of reduced to oxyhemoglobin.

Shock- hypoxemia and hypoperfusion resulting in increased oxygen extraction ratio, and DO_2/VO_2 mismatch.

Lactic Acidosis- increased lactate production due to anaerobic metabolism occurring after critical oxygen extraction ratio is exceeded.

Differential Cyanosis- difference of >5% in the oxygen saturation measured in the right hand (preductal) and either foot (postductal) identifies infants with differential cyanosis. Differential cyanosis also occurs in infants with structurally normal hearts who have persistent pulmonary hypertension of the newborn.

Reversed Differential Cyanosis- may occur in patients with transposition of the great arteries (TGA) associated with either coarctation or pulmonary hypertension. In these infants, oxygen saturation is higher in the lower extremity as the most oxygenated blood is pumped by the left ventricle to the pulmonary artery, across the PDA and to the aorta.

Ductal Dependent Pulmonary Circulation

Right-sided obstructive lesions

Critical Pulmonary Stenosis - characterized by complete or near complete obstruction of right ventricular outflow with resultant decrease in pulmonary blood flow. Ductal patency needs to be maintained pharmaceutically (PgE) postnatally. Depending upon the degree of obstruction, balloon valvuloplasty of the pulmonary valve or surgical valvuloplasty may be considered.

Pulmonary Atresia with intact ventricular septum- the atretic pulmonary valve may result in varying degrees of hypoplasia of the right ventricle. Pulmonary blood flow is provided by a PDA and requires PgE. The right ventricle may be significantly hypertensive and in certain cases may provide coronary blood flow in a retrograde fashion to the myocardium (RV dependent coronary circulation). Cardiac catheterization is needed to delineate coronary anatomy and feasibility of pulmonary valve perforation or PDA stenting. Surgical interventions may include the single ventricle pathway, eventual biventricular repair, or orthotopic cardiac transplantation.

Tricuspid Atresia- no communication exists between the right atrium and right ventricle, resulting in right ventricular hypoplasia and obligatory right-to-left atrial shunting. PgE may be needed to provide pulmonary blood flow. Physiology depends upon associated lesions (VSD, pulmonary stenosis, coarctation, TGA). Surgical interventions depend on the

Table 2-10. Differential diagnosis of cardiac lesions based on symptoms*

Severe cyanosis caused by separate circulations and poor mixing
- D-Transposition of great arteries (D-TGA)
- D-Transposition of great arteries and VSD
- Double-outlet right ventricle with sub-pulmonary VSD (Taussig-Bing)

Ductal dependent pulmonary blood flow
- Tetralogy of Fallot (TOF)
- Double-outlet right ventricle with subaortic VSD and pulmonary stenosis
- Tricuspid atresia
- Pulmonary atresia with intact ventricular septum
- Critical pulmonary stenosis
- Ebstein anomaly
- Single ventricle with pulmonary stenosis
- Persistent pulmonary hypertension

Mild cyanosis caused by complete mixing with normal or increased pulmonary blood flow
- Total anomalous pulmonary venous connection (TAPVC)
- Truncus arteriosus
- Single ventricle without pulmonary stenosis
- Double-outlet right ventricle with sub-aortic VSD

Systemic hypoperfusion and congestive heart failure with mild or no cyanosis
- ***Ductal dependent systemic blood flow***
  - » Aortic stenosis (AS)
  - » Coarctation of the aorta
  - » Aortic arch interruption
  - » Hypoplastic left heart syndrome (HLHS)
  - » Multiple left heart defects
- ***Not ductal dependent***
  - » Myocardial diseases (cardiomyopathy, myocarditis)
  - » Cardiac tumor
  - » Arteriovenous malformation
  - » Hypertension

No cyanosis with no or mild respiratory disease
- Normal murmurs
- Pulmonary stenosis (PS)
- Ventricular septal defect (VSD)**
- Atrial septal defect (ASD)
- Patent ductus arteriosus (PDA)**
- Endocardial cushion defect**
- Aortopulmonary window**
- L-Transposition of great arteries (L-TGA)
- Arteriovenous malformation
- Hypertension

* Adapted with permission from Zahka, KG. Approach to the neonate with cardiovascular disease. In: Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff & Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 9th ed. St. Louis, Mo: Elsevier; ©2011; 1243.

** May present with left-to-right shunt and congestive heart failure

physiology and may include aortopulmonary shunts, pulmonary banding, and eventual Fontan palliation.

Ebstein Anomaly- inferior displacement of the posterior and septal tricuspid leaflets resulting in an "atrialized" right ventricle. The right ventricular cavity size is reduced, the tricuspid valve is regurgitant (often severely), and right ventricular outflow is obstructed. This increases right atrial size producing the characteristic chest radiograph where the cardiac silhouette fills the thoracic cavity. There may be functional pulmonary atresia if right ventricular function is insufficient to generate enough force to open the pulmonary valve. Cyanosis results from right-to-left shunting at the atrial level, but typically improves as pulmonary vascular resistance (PVR) decreases in the neonatal transition period. Surgical interventions depend upon right ventricular size and function and the ability to repair the tricuspid valve.

Tetralogy of Fallot (TOF) - classically, is a constellation of four anatomic defects: an overriding aorta, right ventricular hypertrophy, pulmonary stenosis (PS), and an anterior malaligned ventricular septal defect. The clinical presentation depends upon the degree of pulmonary stenosis. "Pink tets" have limited PS and saturations may be stable in the 90's. Infants with significant PS have decreased pulmonary blood flow (Qp:Qs <1), resulting in cyanosis and hypoxia (expected saturations 75-85%). In these lesions, pulmonary blood flow may be ductal-dependent and PgE may be required to maintain ductal patency. Interventions that increase pulmonary blood flow by altering PVR may be helpful. Palliation with a PDA stent or BT shunt may be needed in the neonatal period prior to complete surgical repair. "Tet spells" (hypercyanotic spells) are thought to relate to infundibular spasm causing an acute decrease in pulmonary blood flow. Measures that may temporize these events include knee to chest positioning, sedation, volume expansion, and vasoactive medications to raise SVR. Beta blockade may reduce spasm and increase diastolic filling time.

Also within the spectrum of tetralogy are:

TOF with pulmonary atresia – the pulmonary valve is atretic requiring alternative pathways to provide pulmonary blood flow. The range includes pulmonary arteries that may be reasonably well-developed and supplied by a PDA to absent pulmonary arteries with blood flow supplied by major aortopulmonary collateral arteries (MAPCAs). Imaging and cardiac catheterization is necessary to delineate anatomy to determine interventional strategy. This may include ductal stenting and later definitive repair or pulmonary artery rehabilitation and eventual unifocalization for MAPCAs.

TOF with Absent Pulmonary Valve – the pulmonary valve is hypoplastic or absent and there is resultant stenosis and pulmonary insufficiency. In utero, this may cause dilation of the normally-connected pulmonary arteries, often severe, which postnatally results in bronchial compression and respiratory failure. Neonatal repair is typical with respiratory failure continuing post-operatively due to severe airway malacia.

Acyanotic Lesions with Left to Right Shunt

Patients with defects involving a large left to right shunt typically become symptomatic over time due to increased pulmonary blood flow (Qp:Qs >1) and present with respiratory distress, pulmonary congestion, and eventually congestive heart failure. Oxygen saturations are usually normal. Examples of diseases in this category include VSD, ASD, atrioventricular septal defects, PDA, and AP window. ASDs are typically not symptomatic in the first year of life; an infant with a symptomatic ASD should be evaluated for left-sided obstructive lesion as a cause of augmented left to right shunting. Medical therapy for infants who show signs of pulmonary over circulation includes diuretics (furosemide, diuril, aldactone) and ACE inhibitors (captopril/enalapril). Palliation with pulmonary artery banding may be appropriate in symptomatic infants who have not reached an adequate size or age for definitive repair.

Complete Mixing with Normal or Increased Pulmonary Blood Flow

Total Anomalous Pulmonary Venous Connection (TAPVC) - In TAPVC, mixing occurs as pulmonary venous return joins systemic venous return at the level of the SVC, right atrium, coronary sinus, or IVC. Cardiac output is dependent upon right to left shunting through an atrial septal defect. If pulmonary venous return is unobstructed, there is increased pulmonary blood flow leading to tachypnea and respiratory distress with mild cyanosis. Repair is usually performed in the first month of life. In obstructed TAPVC, however, pulmonary venous hypertension and edema develop along with profound systemic hypoxia. Obstructed TAPVC is most likely to occur with infracardiac type TAPVC but can occur with all types. Surgical repair is emergent and may be complicated by postoperative pulmonary artery hypertension.

Truncus Arteriosus- a failure of septation of the great vessels resulting in complete mixing of the circulations in a single truncal vessel. In the absence of obstruction to pulmonary blood flow, as pulmonary vascular resistance decreases after birth, partitioning of the cardiac output favors the pulmonary circulation. The infant may present with mild tachypnea and saturations of approximately 85% (or lower if there is branch pulmonary stenosis or pulmonary edema). As PVR decreases and Qp:Qs becomes elevated, oxygen saturations may be normal. The infant may also have a wide pulse pressure due to diastolic runoff from the aorta to the low-resistance pulmonary circuit or incompetence of the truncal valve, resulting in poor coronary and systemic perfusion. Close attention should be given to ST segments as an indicator of myocardial ischemia. Workup should include serum ionized calcium due to the association with DiGeorge Syndrome. Truncus arteriosus is typically repaired in the first month of life.

In these lesions, supplemental oxygen and other interventions that decrease PVR may be deleterious due to increase in pulmonary blood flow at the expense of systemic blood flow. In a similar fashion, PgE is usually not helpful and may lead to worsened systemic perfusion (unless coarctation or interrupted aortic arch is present).

Parallel Circulations with Poor Mixing

Dextro-Transposition of the Great Arteries (D-TGA)- characterized by ventriculoarterial discordance where the aorta leaves the right ventricle supplying deoxygenated blood to the systemic circulation, while the pulmonary artery leaves the left ventricle, sending oxygenated blood back to the pulmonary circulation. With the two circulations in parallel, communication is required at the atrial, ventricular, and/or ductal levels. Atrial-level shunting is most critical for mixing and is needed regardless of presence of a VSD. Ductal-level

shunting (L→R) increases LA pressure and further improves atrial-level mixing. Management in the neonatal period includes PgE and balloon atrial septostomy, if needed. Surgical repair, the arterial switch procedure, is usually performed in the first 2 weeks of life.

Double-Outlet Right Ventricle (DORV) - Neonates with DORV have more than 50% of both great arteries arising from the right ventricle. These arteries may be normally-related, malposed (side-by-side), or transposed (aorta rightward of the pulmonary artery).

The most common forms in descending order are:

DORV with subaortic VSD and PS - results in TOF-like physiology as blood from the left ventricle passes through the VSD to the aorta. Cyanosis is generally progressive and these infants may have cyanotic spells.

DORV with sub-pulmonary VSD and side-by-side great arteries (the Taussig-Bing anomaly) - blood flows from the left ventricle and preferentially enters the pulmonary artery resulting in transposition physiology (saturations in pulmonary artery > saturations in aorta). Balloon atrial septostomy may be required and surgical repair is generally during the neonatal period.

DORV with subaortic VSD and no PS - with little obstruction to pulmonary blood flow, congestive heart failure develops as PVR drops, similar to VSD physiology. Diuretics are the mainstay of medical therapy with surgical intervention usually in early infancy.

Single ventricle

Single ventricle physiology involves complete mixing of systemic and venous blood, which may occur at various levels (e.g. atrial-level shunting in tricuspid or mitral atresia). The oxygen saturation in the ventricle and great arteries depend on the relative systemic and pulmonary blood flow which is dictated by pulmonary and systemic vascular resistance. If pulmonary blood flow is unrestricted, a decrease in PVR may lead to increased pulmonary blood flow and decreased systemic oxygen delivery. One of the great arteries typically originates from the hypoplastic outlet chamber. Goals in the neonatal period include preservation of pulmonary arterial anatomy with maintenance of low PVR, relief of subaortic obstruction, if present, and repair of any pulmonary venous obstruction. Surgical repair is staged **(Hypoplastic Left Heart Syndrome (HLHS) Section below).**

Ductal-Dependent Lesions for Systemic Blood Flow

In these lesions, the PDA is essential to maintain systemic blood flow (R→L). At the time of ductal closure, these infants present with signs of poor systemic perfusion characterized by weak or absent peripheral pulses, metabolic acidosis, and shock.

Coarctation (usually juxtaductal) and Interrupted Aortic Arch (IAA) - results in increased afterload and diminished perfusion to distal tissues due to narrowing or obstruction of the aorta. Management in the neonatal period includes PgE and therapies for CHF and/or poor systemic perfusion if present. Prenatal concern for arch obstruction is a frequent reason for admission to the WT NICU.

The arch watch protocol is as follows:

- If suspicion of coarctation is low prenatally and pulses are easily palpable, vital signs are normal (HR, RR) and BP gradient < 20 mmHg, the patient can be observed with q6h 4 extremity BPs and potentially no serial labs. Cardiology should be consulted and an echocardiogram obtained.
- If prenatal suspicion for coarctation is high or BP gradient is > 20 mmHg or other VS are abnormal, urgently consult Cardiology, order PgE to the bedside (if not already infusing) and consider central venous and arterial access for frequent monitoring of labs. Echocardiogram should be urgently obtained.

Repair is done in early infancy when the patient is stable. In females with coarctation, Turner syndrome should be considered. Patients with IAA should be screened for DiGeorge Syndrome (22q11) deletion due to its high likelihood (~50%).

Hypoplastic Left Heart Syndrome (HLHS)-involves varying degrees of left-sided valvular stenosis with LV and/or aortic hypoplasia. Management in the preoperative period includes PgE administration and careful prevention of excessive pulmonary blood flow. Surgical repair typically involves three stages: (1) Norwood procedure in the neonatal period, characterized by an atrial septectomy, creation of a "neoaorta" to provide systemic blood flow and a mechanism to provide pulmonary blood flow via either an aortopulmonary shunt Blalock-Taussig shunt (BTS) or RV to PA shunt (Sano shunt); (2) the bidirectional Glenn procedure at 3-6 months of age, which involves takedown of the BTS or Sano shunt and connection of SVC to the right pulmonary artery; and (3) the Fontan procedure is done at 2-4 years of age, involves connecting the IVC to the right pulmonary artery, fully separating the pulmonary and systemic circulations.

Critical Aortic Stenosis- presents in a similar fashion to HLHS and requires PgE infusion. Balloon dilation is the procedure of choice if left-sided structures are amenable to biventricular repair. A Norwood approach may be needed if there is marked annular hypoplasia, unicuspid aortic valve, ventricular hypoplasia/dysfunction, or associated subaortic obstruction.

Shone's complex (or variant) - a constellation of left-sided anomalies of varying degrees. Classically, this includes parachute mitral valve, supravalvar ring, coarctation of the aorta, and subaortic obstruction with multiple levels of resistance leading to decreased cardiac output and left-atrial hypertension. PgE infusion is often required.

General Care of Neonates with Congenital Heart Disease Care Environment

Maintaining an environment with appropriate neurodevelopmental stimuli remains essential for the care of these neonates. Attention to pain, discomfort, and agitation are vital in the cardiac patient as these behaviors increase oxygen demand in a patient already at risk for suboptimal oxygen delivery. Use of non-pharmacologic comfort measures such as developmental positioning aids, bundling, and oral sucrose should be considered. Sedatives and/or narcotics should be judiciously provided in cases of pain or agitation not alleviated by non-pharmacologic measures. Elevated temperature or cold stress may increase oxygen consumption. Therefore,

normothermia should be ensured by maintaining servo-controlled temperature regulation or frequent measurement of body temperature if the infant is dressed and bundled. While low-ambient lighting is common practice in the NICU, it does impair ability to assess physical appearance of the neonate. Overall appearance, skin color, and perfusion should be assessed regularly under appropriate lighting.

Monitoring

Monitoring should include vital signs, continuous pulse oximetry, and physical assessment. Continuous blood pressure monitoring should be considered during periods of clinical instability and during periods of changing physiology. Upper extremity cuff blood pressure monitoring may be employed during periods of stability and should be performed every 3 hrs. Four-extremity blood pressure monitoring should be performed upon admission for all patients and regularly in those with suspicion for aortic arch hypoplasia. Multi-site (cerebral, somatic) NIRS should be considered at admission. Laboratory investigations may include regular monitoring of blood gas and lactate levels, particularly when there is concern for inadequacy of systemic blood flow or cardiac output. Optimal measurement of lactate is obtained by arterial puncture or indwelling line. Capillary lactate specimens may be used as a method for trending lactate levels but should not be considered diagnostic or be interpreted without consideration of the overall clinical picture. Additionally, electrolytes, BUN, and creatinine should be followed, particularly for those receiving diuretic therapy. Renal indices may also serve as a surrogate maker for systemic blood flow.

Vascular Access

For those with unclear physiology or expected to have surgery in the first week of life, it is recommended to establish umbilical artery and umbilical venous access at the time of delivery or admission. Peripherally inserted central venous catheters should be considered if umbilical venous access cannot be established. These catheters should be removed when no longer necessary. Despite clinical stability, the potential for decompensation requiring urgent therapy (PgE, adenosine, vasoactive medications, and volume resuscitation) exists for many neonates with cardiac disease. Therefore, maintaining peripheral access can be important in these infants once central lines are removed. In general, preoperative infants with a diagnosis of HLHS prior to stage I repair, IAA awaiting arch advancement, and coarctation of the aorta to be repaired with a thoracotomy should not have peripheral arterial line placed in right arm since the site is likely needed for surgery.

Nutrition

Nutritional support remains of critical importance for this group of neonates. Infants with CHD generally have an increased basal metabolic rate and without appropriate nutritional support may experience negative nitrogen balance in the perioperative period. The majority will not be fed enterally in the first day of life. A reasonable approach is to provide adequate dextrose-containing clear intravenous fluid until the cardiac diagnosis is elucidated and anticipated course discussed. All neonates with PgE-dependent lesions should receive TPN to avoid negative nitrogen balance. If enteral feeding is provided, consideration of adequacy of mesenteric blood flow must be considered. Safe enteral feeding has been documented during PgE infusion. For infants with PgE-dependent systemic blood flow who are expected to have cardiac surgery within the first month of life, there is a risk for mesenteric hypoperfusion. Therefore, those infants should receive an exclusive human milk diet (EBM or DEBM) without fortification in the pre-operative period with slow progression of feeding volume up to 40-60 ml/kg/day (weak recommendation, low quality evidence). In addition, infants with PgE-dependent pulmonary blood flow may also have risk for mesenteric hypoperfusion. For these infants, they should also receive an unfortified human milk diet until need for PgE is determined with slow advancement of feeds by 20 mL/kg/day as tolerated (weak recommendation, low quality evidence); advancement to full feeds depends upon the specific lesion and predicted clinical course. If PgE is being trialed off, infants should have feeds held for the first 24-48 hours off PgE. If the infant remains hemodynamically stable, feeds can be restarted at the previous volume and advanced per protocol. For those neonates, controversy remains regarding safety of providing orogastric/nasogastric tube feeds. Although many practitioners believe that the neonate's behavior of refusal of oral feeding may be an early indication of bowel hypoperfusion/ischemia, there is no evidence to support this belief.

Evidence in premature neonates suggests that oral care with colostrum prior to initiation of enteral feeds may help develop a healthier microbiome. Although not yet studied in neonates with CHD, oral care with colostrum should be started for infants with ductal-dependent cardiac disease while NPO.

Growth failure is a common problem in this population, especially in the setting of pulmonary over-circulation physiology characterized by tachypnea and increased work of breathing. The dietary regimen should be individualized according to clinical needs and may include fortification of EBM or provision of higher calorie formula (24-30 kcal/oz.). Neonates with cardiac disease are at higher risk of necrotizing enterocolitis (NEC) primarily in association with mesenteric hypoperfusion. Premature infants are at even greater risk due to intestinal immaturity. As caloric density is increased, careful attention should be given to osmolality of the feeding, as hyperosmolar solutions may predispose to NEC.

Respiratory Management

Consideration of cardiopulmonary interaction and effect of respiratory support on cardiac function is critical in this population. Increased work of breathing increases oxygen consumption, which in the face of impaired cardiac output or without a compensatory increase in oxygen delivery, may lead to tissue hypoxia. Provision of positive pressure ventilation may ease the work of breathing and improve oxygen transport balance. However, some patients may have a mild-moderate degree of increased work of breathing but demonstrate adequate balance of oxygen delivery and consumption and appear comfortable on exam. Such patients may be treated medically and followed closely for signs of decompensation. Care should be taken to optimize pH, alveolar oxygen tension, and lung volumes, avoiding atelectasis or hyperinflation. Positive pressure ventilation leads to a decrease in LV afterload but may impair systemic venous return and decrease right ventricular output.

Prematurity

Preterm infants with cardiac disease have higher morbidity and mortality than term infants with similar conditions, even at late

preterm gestation. These infants have impaired temperature regulation, limited hemodynamic reserve, and immature cardiac muscle, brain, kidney, lungs, and intestines. Morbidities associated with immaturity include IVH, seizures, impaired neurodevelopment, metabolic acidosis, renal failure, infection, respiratory insufficiency, BPD, NEC, and feeding difficulties. Preterm infants have a less muscularized pulmonary vasculature, which places them at risk for earlier onset of pulmonary over circulation with increased risk for heart failure owing to the immature myocardium. Low birth weight is associated with increased surgical mortality and therefore surgery is often delayed until an appropriate weight has been attained. However, delayed surgery may lead to worsening of clinical status and is also associated with increased mortality and morbidities such as poor growth, and prolonged exposures to central venous access, elevated pulmonary blood flow, ventricular volume overload, PgE, and hypoxemia. This requires great attention to trend in the clinical status and regular communication with cardiovascular teams.

Antiplatelet Therapy

Based on numerous factors post-operatively, CHD patients may require antiplatelet therapy to maintain stent patency. Antiplatelet therapy is utilized with aspirin, an irreversible inhibitor of platelet aggregation acting for the duration of the platelet lifespan (roughly 10 days). Aspirin dosing ranges from 3-10 mg/kg/day. We recommend utilization of the aspirin 81 mg chewable tablet in dosing formulations of 20.25 mg (1/4 tab), 40.5 mg (1/2 tab), or 81 mg depending on the patient's size. We do not recommend the use of aspirin suspension (restricted to cath lab) due to the potential of dosing variability with poor solubility in suspension and this product cannot be found outpatient. Aspirin absorption may be inhibited or erratic if administered jejunally or rectally.

Interdisciplinary Considerations

Optimal care of these neonates requires collaboration between the neonatology and cardiology services, and at times cardiovascular intensive care and cardiovascular surgery. Daily rounds should be interdisciplinary and include shared decision-making with continuing discussions as changes arise. These infants may also have associated conditions necessitating input from other clinical services. Genetic evaluation and consultation should be considered for neonates with congenital heart defects. For those undergoing surgical intervention, nephrology should be consulted in anticipation of post-operative peritoneal dialysis. Routine renal and head ultrasonography in the absence of additional anomalies is not indicated.

Cardiac Developmental Outcomes Program

Infants with critical heart disease have been found to be at greater risk for and have higher rates of developmental, learning, and/or behavior problems later in life. These issues are often subtle and not easily recognized at early ages. The Cardiac Developmental Outcomes Program at Texas Children's Heart Center provides regular neurodevelopmental assessments and referrals for children from infancy through adolescence who have undergone cardiac procedures during the early stages of life. All hospitalized infants that have undergone cardiac surgery or cath procedures at less than 3 months of age should be referred (at least one week prior to discharge). Exceptions to this include infants who have undergone PDA ligation alone or those with Down Syndrome (should be referred to Meyer Center Developmental Down Syndrome Clinic instead)

- **In EPIC:** Enter *CONSULT* in the orders section, and click on **Developmental Pediatrics**
- **For reason for consult, enter:** *Cardiac surgery/ Cath procedures at less than 3 months of age*
- **For preferred provider, enter:** *Dr. Sarah Risen*
- **In the comments section, indicate that you are referring to:** *The Cardiac Developmental Outcomes Program (CDOP)*

Stabilization During Clinical Decompensation

Deterioration of clinical status may occur within minutes or over several days. The aim of monitoring is to prevent decompensation by allowing the team to intervene accordingly. Indicators of impending shock or arrest include increased oxygen extraction with low NIRS values, rising lactate levels (late sign), poor pulses and perfusion, agitation, diaphoresis, hypoxemia, tachycardia or bradycardia. In the event of clinical instability, rapid response is critical. IV access should be ensured as soon as possible. Laboratory investigations (ABG with lactate, chemistry, hemoglobin/hematocrit) and ancillary studies should be ordered as indicated.

Treatment of Ductal-Dependent Lesions

Prostaglandin E_1 (PgE)

Prostaglandin E_1 is indicated for the treatment of ductal-dependent lesions to ensure ductal patency until surgery can be performed (strong recommendation, low quality evidence,). In general, the more severe the cyanosis or the systemic hypoperfusion, the more urgent the administration of PgE. If there is doubt regarding diagnosis and the infant is symptomatic, it is reasonable to begin treatment with PgE while further evaluation is undertaken. PgE decreases both SVR and PVR, but PVR to a greater degree and may lead to pulmonary over circulation in at-risk infants.

The response of the ductus arteriosus to PgE is related to the time since spontaneous closure. Cyanosis in newborn infants is usually recognized shortly after ductal closure. Therefore, these infants respond well to PgE. Those with cyanosis at several weeks of age should not be assumed to be unresponsive to PgE, especially in a preterm infant. If the ductus arteriosus had recently closed, it may still respond to treatment.

Infants with coarctation of the aorta may be able to survive for several days with marginal blood flow through the obstruction prior to decompensation. Although they might respond to PgE, they have the highest likelihood of not responding and of needing urgent surgery.

Long-term infusion of PgE does permit a period for maturation of the lungs and nutrition, especially in preterm or SGA infants. The risk that pulmonary vascular disease will develop within several months is small. Therapeutic response is indicated by increased pH in those with acidosis or by an increase in oxygenation (P_aO_2) usually evident within 30 minutes.

Adverse events include hypotension, fever, flushing, and apnea which is most frequent in premature infants and at higher doses but can also occur in full-term infants. Apnea can occur several hours after starting PgE. Using the lowest effective dose can decrease the risk of apnea. Reported long-term adverse effects include electrolyte abnormalities, hyperostosis, and gastric outlet obstruction. Use of caffeine for apnea induced by PgE administration is not studied.

Patent Ductus Arteriosus (PDA)

A persistent PDA in the preterm infant presents a unique management challenge. The degree of shunting through the PDA is directly related to size and volume of shunt through the ductus arteriosus and indirectly related to PVR. In the setting of low PVR, a large left-to-right shunt will lead to volume overload of left atrium and ventricle. A substantial increase in LV output is required to maintain systemic blood flow. Diastolic blood pressure may be diminished by shunting through the ductus, leading to impaired myocardial and coronary perfusion and a "steal" of blood from peripheral organs. Signs of a significant PDA include hyperactive precordium, wide pulse pressure, bounding pulses, respiratory failure, pulmonary edema, and both systolic and diastolic hypotension. Retrograde flow in the abdominal aorta is associated with risk for NEC and feeding difficulties.

Appropriate management of PDA in the preterm infant remains controversial because of lack of effect of treatment on long-term outcome. No benefits have been established for treatment of an asymptomatic PDA, a PDA during the first 3 days of life, or a small PDA not requiring positive pressure support. It is not necessary to withhold feedings in such patients. Treatment of a large PDA may reduce short-term need for mechanical ventilation but no benefits on long-term outcome have been established. Currently available strategies include: (1) prevention (2) conservative management, or (3) treatment of symptomatic PDA (medical or surgical).

Prophylactic Indomethacin

In randomized trials, the use of prophylactic indomethacin in VLBW and ELBW infants was found to reduce the incidence of symptomatic PDA, PDA surgical ligation, and severe IVH. However, there is no evidence of effect on mortality or reduction in severe neurodevelopmental delay. In observational studies the use of prophylactic indomethacin was reported to be associated with an increase in the rates of spontaneous intestinal perforation. In patients with an increased risk of intestinal ischemia, such as those with IUGR, the risks of prophylactic indomethacin may outweigh the benefits. We do not recommend routine use of prophylactic indomethacin in infants with the following risk factors: a history of absent or reversed end diastolic flow in the umbilical artery, IUGR, or perinatal asphyxia.

In infants without risk factors, administer indomethacin (if available) during the first 12 hours of life to babies ≤ 26 weeks gestation or ≤ 800 grams birth weight as follows:

- **First dose:** (within first 12 hours) – 0.1 mg/kg of birth weight
- **Second dose:** (24 hours after first dose) – 0.1 mg/kg of birth weight
- **Third dose:** (48 hours after initial dose) – 0.1 mg/kg of birth weight

Monitor platelet count daily. Subsequent doses should be held if infant is oliguric (< 0.6 ml/kg/hr), thrombocytopenic (platelets < 50,000), has overt signs of bleeding, or infant requires treatment with corticosteroids.

Table 2-11. Indomethacin dosage

Age at first dose	Dose 1 (mg/kg)	Dose 2 (mg/kg)	Dose 3 (mg/kg)
<48 Hours	0.2	0.1	0.1
2-7 Days	0.2	0.2	0.2
7 Days	0.2	0.25	0.25

Treatment of PDA

Medical or surgical treatment usually is reserved for symptomatic infants with a hemodynamically-significant PDA (hsPDA) with large left to right shunts (left-sided cardiac enlargement) or signs of myocardial dysfunction on echocardiogram. Treatment reduces short term need for mechanical ventilation in some of these patients but no benefits on long-term outcome have been established. **Fig 2-6** shows the recommended approach to the management of the hsPDA in preterm infants. Conservative management includes modest restriction of fluid intake ± diuretics, avoidance of further decrease in PVR, permissive hypercapnia, or increased PEEP as shunt limiting strategies, and use of vasoactive medications. Extreme volume restriction or diuresis is of no benefit in clinically significant PDA and may further impair systemic perfusion. Total fluid intake in ELBW infants of more than 150-170 ml/kg/day in the first days of life is a risk factor for symptomatic PDA.

Ibuprofen Treatment

Pharmacologic closure of symptomatic PDA with cyclo-oxygenase inhibitors is the treatment of choice if conservative management is inadequate (strong recommendation, moderate quality evidence).

Contraindications to ibuprofen treatment include active bleeding or infection, platelet count < 60,000 or coagulopathy, NEC, significant renal dysfunction (serum creatinine > 1.6 mg/dL or urine output < 0.6 ml/kg/ hr) or clinical condition requiring ductal dependent blood flow.

Administration and Monitoring

- **First dose:** 10 mg/kg of birth weight
- **Second dose:** (24 hours after initial dose) 5 mg/kg of birth weight
- **Third dose:** (48 hours after initial dose) 5 mg/kg of birth weight. Include birth weight on all orders for ibuprofen lysine.

The drug should be infused over 15 minutes through the IV port closest to insertion site. Safety of administration via umbilical catheter has not been evaluated and is not recommended. Ibuprofen is incompatible with TPN. If necessary interrupt TPN for 15 minutes and flush with normal saline or dextrose prior to and after ibuprofen administration.

If PDA closes or is significantly improved after an interval of 48 hours or more from completion of the first course of treatment, no further doses are necessary. It is recommended that second and third dose be withheld if urine output < 0.6 ml/kg/hr. Ibuprofen may displace bilirubin from binding sites, decrease platelet adhesion, or alter signs of infection. The drug may decrease efficacy of thiazide and loop diuretics, ACE inhibitors, and beta-blockers.

Shortages of ibuprofen may require alternative use of indomethacin. Dosing should follow product insert guidelines.

Treatment Failure

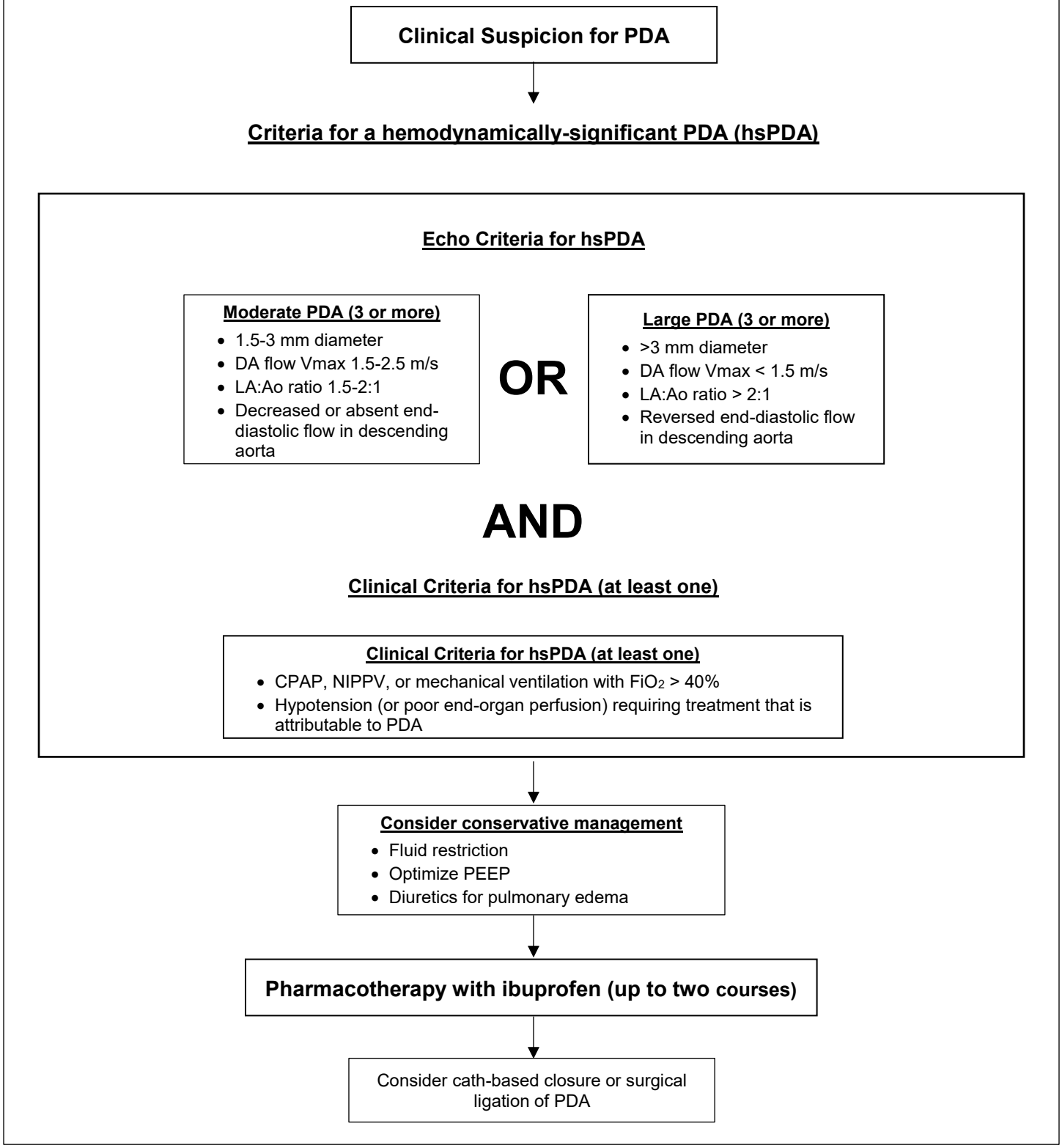
If the PDA fails to close or re-opens after the first 3 dose course, and remains symptomatic, options include:

- Administer one or more additional course(s) of ibuprofen
- Surgical ligation of PDA may be considered

Indomethacin Treatment

If ibuprofen is not available, indomethacin may be used. Recommended dosage depends upon age of infant at time of therapy. A course of therapy is defined as three IV doses given at 12-24 hour intervals, with careful attention to urine output. Consider 12-hour dosing interval if urine output is >1 mL/kg/hr and 24-hour dosing interval if urine output is <1 mL/kg/hr but

Figure 2-6. Approach to management of the PDA in the preterm infant



>0.6 mL/kg/hr. If anuria or marked oliguria (urine output < 0.6 ml/kg/hr) is evident at time of second or third dose, no additional doses should be given until renal function has returned to normal.

If PDA closes or is significantly reduced after an interval of 48 hours or more from completion of first course, no further doses are necessary.

Note: Acetaminophen (paracetamol) has also been used for treatment of a hemodynamically significant PDA if conservative measures are unsuccessful. A recent Cochrane Review (Ohlsson A and Shah PS, January 2020) suggests that acetaminophen may be as effective as ibuprofen (GRADE: moderate quality evidence). However, concerns exist of potential neurodevelopmental impairment associated with prenatal and postnatal acetaminophen administration. Thus, until further studies are completed, we do not recommend routine use of acetaminophen for closure of a hemodynamically significant PDA. Acetaminophen may be considered on a case-by-case basis.

Treatment Failure

If PDA fails to close or reopens after first 3 dose course and patient remains symptomatic options include:

- Administer a second course of 1-3 doses separated by 12-24 hour intervals. An echocardiogram is desirable before initiating a second course but may not be possible in some instances.
- Cath-based of surgical ligation of PDA

Surgical Treatment

PDA ligation may be required due to failure of medical management or clinical instability. Surgical ligation has been associated with adverse neurodevelopmental outcomes, although causality has not been established due to numerous confounding factors in this population. Changes in cardiopulmonary physiology may lead to a severe post ligation cardiac syndrome (PLCS) in up to 50% of preterm infants, characterized by oxygenation failure and systemic hypotension requiring cardiotropic support between 8-12 hours of surgery. Cardiac output is compromised as a result of changes in myocardial loading conditions with acute increase in afterload and decreased preload. Symptoms typically resolve by 24 hours post-intervention. Therapies aimed at lowering afterload, such as milrinone, may be beneficial. Other surgical morbidities may include vocal cord paralysis and thoracic duct trauma resulting in chylothorax.

Catheter Closure

In recent years, catheter device closure of PDA has begun to become more common in extremely premature neonates. Advances in available device technology have allowed this procedure to be performed in this population. Catheter closure of PDA is available at TCH in patients who providers believe not to be ideal candidates for medical or surgical treatment. Candidacy for catheter closure depends on clinical status of the patient including but not limited to need for high respiratory support and LA/ LV enlargement on echocardiogram. The procedure is performed via a venous approach and can be safely performed in infants <1000 grams if necessary. In a recent case series, the rate of PLCS appeared to be less than that seen in surgical ligation, however, further study is required. If primary team is considering catheter closure for a NICU patient, consultation with cardiology and the cath lab team should be initiated to determine candidacy. Discussion of post-catheterization monitoring and complications can be found in **Ch 2.4-Catheter-Based Interventions.**

2.4 Catheter-Based Interventions

Indications for cardiac catheterization can be broadly classified as diagnostic or therapeutic. While non-invasive modalities (echocardiography, MRI, CT) are often performed prior to catheterization to assist with procedural planning, advanced imaging can occasionally be bypassed to minimize radiation exposure or anesthetic risk. A common indication for diagnostic catheterization in infants is evaluation of pulmonary hypertension.

Common interventions include:

- **Atrial septostomy-** creation, dilation or stenting of an atrial septal defect (ASD) is required to maintain adequate atrial mixing in transposition of the great arteries (TGA) or left atrial decompression in hypoplastic left heart syndrome (HLHS); usually performed soon after delivery. In HLHS, absent or restrictive ASD is associated with high morbidity and mortality in utero and in the immediate postnatal period. Urgent septostomy and stenting is often performed immediately after the delivery to decompress the left atrium and prevent development of pulmonary hypertension. Atrial septal stenting is also performed as part of the hybrid palliation for HLHS either in conjunction with or soon after pulmonary artery banding.
- **Shunt closure-** ASD, VSD and PDAs are a source of pulmonary over-circulation and can cause significant respiratory compromise. Echo-guided cardiac catheterization, and sometimes bedside PDA closure, can be performed in extremely premature or critically ill neonates using venous access alone. Percutaneous closure can be considered in critically ill patients with large secundum ASD or muscular VSD, esp. the swiss cheese type VSDs, and can often allow weaning of respiratory support in a select few with chronic lung disease. Certain lesions associated with aortopulmonary shunts, like Scimitar syndrome, benefit from device closure to treat left ventricular volume load.
- **Valvuloplasty-** aortic and pulmonary valvuloplasty is performed soon after birth for severe and critical valve stenosis. Pulmonary valve perforation and valvuloplasty is performed in patients with pulmonary atresia with intact ventricular septum after confirming non-right ventricle dependent coronary perfusion, or in Tetralogy of Fallot with pulmonary atresia. In a select few that are otherwise unable to undergo complete repair due to associated comorbidities or low weight, severe valvar and/or subvalvar obstruction in Tetralogy of Fallot can also be addressed with balloon pulmonary valvuloplasty or right ventricular outflow tract stenting.
- **Ductal stenting-** performed to allow/augment pulmonary blood flow in pulmonary stenosis and atresia with persistent desaturation despite pulmonary valvuloplasty. It is also an integral part of the hybrid palliation for HLHS. If needed, alternative routes of access (e.g., percutaneous

axillary, carotid or umbilical artery access) can be performed to enhance the safety and efficacy of the procedure.

- **Branch pulmonary arteries or coarctation angioplasty-** angioplasty is performed in select patients with coarctation associated with severe ventricular dysfunction to allow stabilization of ventricular function prior to surgical repair. Similarly, pulmonary artery angioplasty can be performed for severe pulmonary artery stenosis, congenital or post-operative.
- **Pulmonary vein dilation and stenting-** pulmonary vein stenosis, associated with prematurity, can significantly worsen cardiorespiratory function. Angioplasty and stenting can be performed in those with multiple vein involvement and pulmonary hypertension. Efforts are made to recanalize atretic veins to maximize pulmonary flow.
- **Thrombectomy and dilation of occluded systemic veins and arteries-** symptomatic occlusion of central veins and arteries, often secondary to chronic line placement, can be treated by a combination of techniques including thrombectomy, angioplasty and/or stenting.
- **Pericardiocentesis-**Venous access is usually femoral vein with internal jugular approach used as an alternative. Umbilical access is preferred in newborns when accessible. Right and left heart structures can be accessed for hemodynamic and therapeutic procedures via the venous approach using an atrial communication (ASD or PFO). Arterial access is, however, needed for aortic valve and some ductal interventions and can be via the femoral, axillary, carotid or umbilical arteries. Patients are generally anticoagulated with heparin during the procedure to reduce the risk of thromboembolism. In order to minimize radiation, PDA closure is often performed under echocardiographic guidance in smaller infants.

Catheter-Related Arterial Thrombosis (CAT)

The reported incidence of CAT in infants ranges in the literature from 2 to 7.9%. Changes in equipment and techniques have decreased incidence over time. Risk factors include weight, use of larger sheaths and longer procedural time. Vascular complication rate increases from 0.9% in those between 2.5-3.5 kg to 6% in those < 2.5 kg. Although often asymptomatic, if left untreated, CAT can lead to loss of vascular access for future access and rarely leg-length discrepancy or loss of limb. Initial detection is reliant on careful observation of distal pulses, temperature and capillary refill, triggering further evaluation with Doppler ultrasound. **(Fig 2-7)** Timely detection and initiation of therapy (achieving and maintaining therapeutic levels within 1st 24 hours) is critical for successful treatment. While some degree of thrombus is often present after arterial access, treatment should be reserved for occlusive thrombi and treatment regimen should be based on whether it is limb threatening or not. Limb threatening lesions are treated with systemic or locally infused tissue plasminogen activator (t-PA) vs thrombectomy. Non-limb threatening thrombosis is usually treated with unfractionated heparin (UFH) and low molecular weight heparin (LMWH). LMWH tends to reach therapeutic levels earlier, requires less frequent monitoring during initiation and maintenance therapy, is administered subcutaneously, and can be administered at home by caregivers, and is therefore often preferred. Usual duration of therapy ranges between 6 weeks to 3 months. During maintenance phase, Hematology service will guide therapy until discharge or clot resolution whichever is earlier. Follow up with Hematology post discharge may be required.

Table 2-12. Risk stratification*

Low Risk	Non-occlusive and asymptomatic venous thrombus (CRT, PVT, unilateral RVT), chronic organized venous thrombus.
Moderate Risk	Any symptomatic or acute occlusive venous thrombus without ischemia or organ failure (CRT, RVT, PVT), Bilateral RVT, propagating venous thrombus on serial imaging, thrombus extending in to central vein (SVC, IVC). ,
High Risk	Any arterial thrombus, Any thrombus causing limb ischemia or organ injury (renal impairment, cardiac failure), occlusive central artery or vein (Aorta, SVC, IVC), symptomatic pulmonary embolism

*Cerebral sinus venous thrombosis and thrombosis related to congenital heart disease are excluded.

Therapy for CAT

Unfractionated heparin (UFH), **(Table 2-13)** and low molecular weight heparin (LMWH), **(Table 2-14)** at treatment dosing are the agents of choice for the management of CAT. Due to inherently low antithrombin levels, UFH and LMWH dosing may be higher depending on the age of the patient and should be taken into consideration. UFH has several advantages in that it can be used in patients with renal dysfunction, it can be fully reversed with protamine and therefore preferred if there are further invasive procedures needed, and can reach therapeutic levels within 4 hours of initiation if dosed appropriately. Before starting an unfractionated heparin drip, a baseline CBC, PT, PTT, fibrinogen, and D-dimer should be drawn if >4-8 hours post-catheterization. A heparin level (anti-Xa) and PTT should be obtained 4 hours after the loading dose and 4 hours after every infusion rate change. Correlation between the two lab values should be evaluated as well as potential confounding factors that may additionally prolong PTT and underestimate anticoagulation. Once stable, heparin level and PTT should be checked every 12 hours and platelet count at least every 3 days.

Conversely, LMWH requires less frequent monitoring once therapeutic, is administered subcutaneously, and can be administered at home by caregivers. Of note, LMWH is eliminated renally, therefore patients with renal dysfunction should not be managed with enoxaparin as first-line. In addition, enoxaparin may take multiple doses to reach true steady state which should be taken into consideration when interpreting levels. If initiating enoxaparin, anti-Xa (a.k.a. Lovenox level) should be obtained 4 hours after administration of enoxaparin to accurately assess laboratory values. A minimum of 2 doses of enoxaparin should be administered of each dosing regimen to allow for a steady-state concentration.

During maintenance phase, Hematology service will guide therapy until discharge or clot resolution whichever is earlier. Follow up with Hematology post discharge may be required.

2.5 Arrhythmias

The observation of an abnormally fast or slow heart rate may be the first sign of arrhythmia. The ideal method to calculate heart rate and diagnose arrhythmias is by an EKG. Count all QRS complexes in a period of 6 seconds and multiply by 10 to obtain beats/minute or measure the R-R interval in milliseconds and 60,000/RR (ms) = heart rate in bpm.

Supraventricular Tachycardia (SVT)

This is a group of mostly narrow-complex tachycardias caused by re-entry of electrical impulses through an accessory pathway between the atria and ventricles or the AV node.

Atrioventricular Reentrant Tachycardia (AVRT)

In neonates with pre-excitation/WPW, a delta wave, short PR, and wide QRS is seen on the baseline EKG in sinus rhythm as conduction occurs through the accessory pathway between the atria and ventricles. Those with concealed accessory pathways do not exhibit pre-excitation. In AVRT, the electrical impulse is conducted from the atria down the AV node, His-Purkinje system and then up the accessory pathway back to the atria to complete the reentrant circuit. Heart rate is typically 250-300 beats/min. On the EKG, P waves can fall between the QRS complexes or be superimposed on the T wave. There is little to no variation in the R-R intervals. In neonates, AVRT is the more common etiology for SVT.

Atrioventricular Nodal Reentrant Tachycardia (AVNRT)

AVNRT occurs due to the presence of dual pathways in the AV node: one pathway with fast conduction, generally with long effective refractory period and one pathway with slow conduction and a shorter effective refractory period. The re-entrant circuit is initiated when a premature atrial contraction (PAC) is blocked during the refractory period of the fast-conducting pathway, leading to conduction down the slow pathway and up the fast pathway, thereby establishing the reentrant circuit. On an EKG, the P waves may be difficult to discern as they are superimposed on the QRS complex. There is little to no variability in the R-R intervals. In neonates, AVNRT is less frequent.

Treatment

Any neonate with SVT should be assessed promptly for hemodynamic instability (e.g. change in activity, tachypnea, poor feeding, pallor, poor peripheral pulses, and perfusion). It is not uncommon to have neonates that are asymptomatic with short episodes of SVT. For hemodynamically compromised infants, synchronized electrical cardioversion with 0.5-1.0 J/kg is indicated. In both AVRT and AVNRT, the goal of initial therapy is blocking the AV node conduction, thereby

Figure 2-7. Suggested post catheterization management

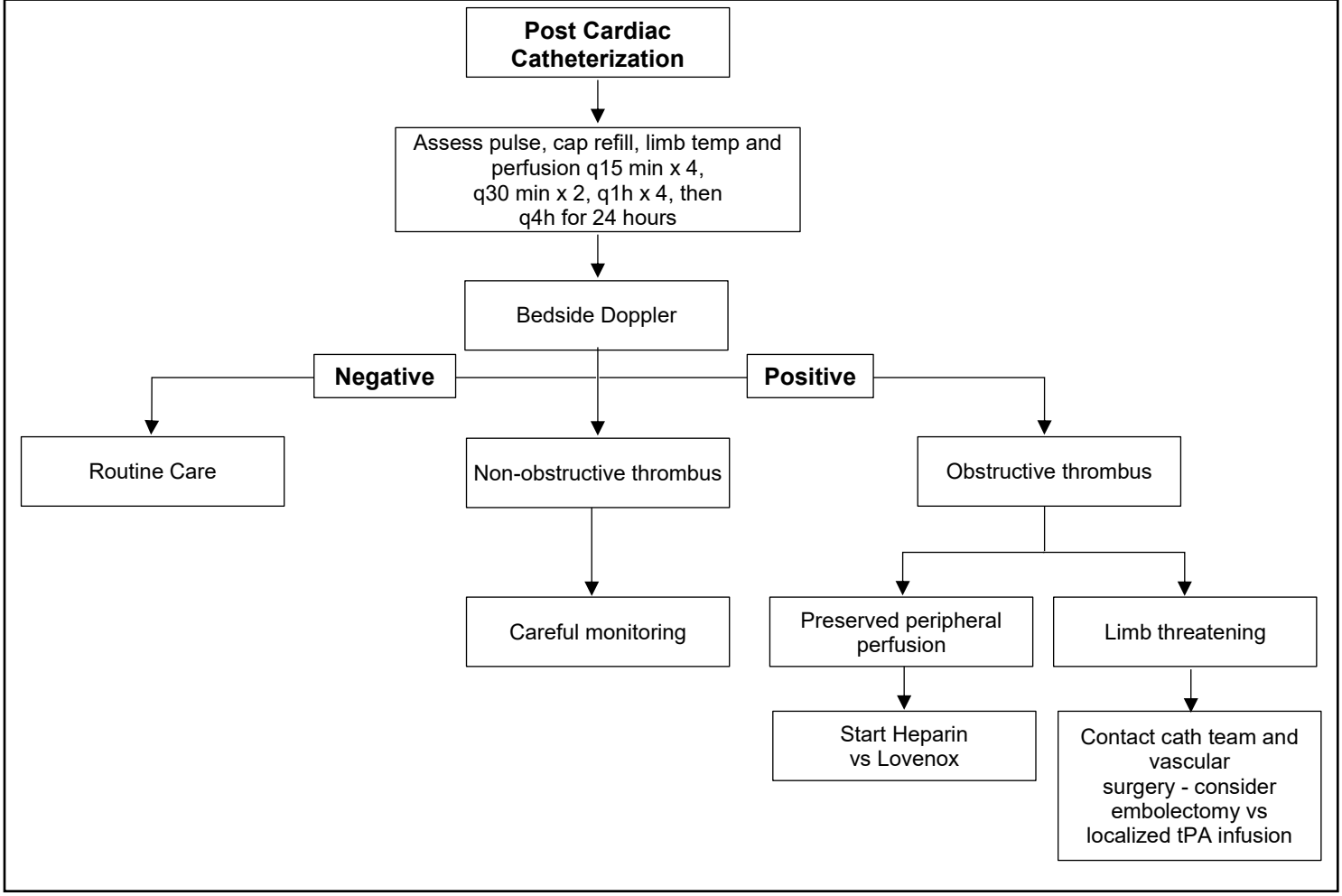


Table 2-13. Heparin dosage and titration

Initial dosing in patients < 1 year of age not currently on ECMO	75 units/kg administered over 10 minutes followed by a continuous infusion initiated at 28 units/kg/hr		
• Adjust dose according to heparin and PTT levels • Do not administer bolus in patients with stroke, active bleed, or high risk of bleed			
Heparin Level Goal 0.3-0.7 units/mL	**PTT Goal 70-101 seconds**	**Dose Adjustment**	**Time to Repeat Heparin Level and PTT**
< 0.2	< 60	Give 50 units/kg bolus and increase infusion rate by 10%	4 hours after rate change
0.2-0.29	60-69	Increase infusion rate by 10%	4 hours after rate change
0.3-0.7	70-101	Keep rate the same	Every 12 hours
0.71-0.8	102-112	Decrease infusion rate by 10%	4 hours after rate change
0.81-0.99	113-130	Hold infusion for 30 minutes and decrease infusion rate by 10%	4 hours after rate change
≥1	>130	Repeat heparin level; hold infusion for 60 minutes and decrease infusion rate by 10%	4 hours after rate change

Table 2-14. Enoxaparin dosage and titration

Enoxaparin			
Initial dose	< 2 months age	1.7 mg/kg/DOSE SubQ every 12H	
	> 2 months age	1 mg/kg/DOSE SubQ every 12H	
Rounding	Weight < 2.5 kg	Round to the nearest WHOLE mg	
	Weight > 2.5 kg	Round UP to nearest WHOLE mg	
Lovenox® Level (units/mL)			
Treatment Goal level 0.5-1	**Prophylaxis Goal level 0.2-0.4**	**Dose Titration**	**Time to Repeat Lovenox® Level**
<0.35	<0.15	Increase dose by 25%	4 hours after next dose
0.35-0.49	0.15-0.19	Increase dose by 10%	4 hours after next dose
0.5-1	0.2-0.4	Keep same dosage	Check level weekly (4 hrs after dose)
1.1-1.5	0.41-1	Decrease dose by 20%	4 hours after next dose
1.6-2	1.1-2	Decrease dose by 30% and hold dose for 3 hours from next due time	4 hours after next dose
>2	>2	Repeat Lovenox® level, hold all doses until level is 0.5, then decrease dose by 40%	Check level every 12 hours until level < 0.5 units/mL

interrupting the reentry circuit. This may be achieved by vagal maneuvers (e.g. elicit gag with NG tube or apply ice to the face) or rectal stimulation. When applying ice to the face, place the bag over the face and ears for 15 seconds. In ill neonates, vagal maneuvers should not be continued for more than 5 minutes before trying other modalities. If unsuccessful, IV adenosine should be administered by rapid infusion using the 2-syringe technique. Intravenous esmolol, sotalol, procainamide, or amiodarone may be used as alternatives if adenosine is unsuccessful. Long-term management of SVT depends on frequency, severity, and ease with which the episodes terminate. Treatment, when indicated, is usually with beta-blockers. Transcatheter ablation of accessory pathways is performed in older children.

Adenosine – This medication has a short half-life (6-10 seconds) and should be administered at 0.1 mg/kg via rapid IV push, followed by a rapid flush, through IV access that is closest to the heart to ensure adequate delivery of the drug to the myocardium before metabolism. Dose is increased to 0.2 mg/kg if patient is unresponsive to the first dose. Despite extensive experience with adenosine, adverse effects have been noted, including the generation of atrial and ventricular tachyarrhythmias, asystole, and bronchospasm. Therefore, the code cart should be readily available when administering adenosine.

Propranolol – This enteral β-blocker is first line therapy for uncomplicated SVT or atrial tachycardia in neonates and infants. Usual starting dose is 4 mg/kg/day divided q6 hours. Propranolol has been rarely associated with hypoglycemia, hyperkalemia, and increased airway resistance. For patients needing an intravenous β-blocker option, esmolol is the preferred agent due to its rapid onset and half-life.

Esmolol – This is a very useful pharmacologic agent in patients who experience recurrent or sustained SVT. This β-blocker has class II antiarrhythmic properties and can be used as a continuous infusion for treatment of supraventricular or ventricular arrhythmias. Esmolol is often used when a quick onset and short half-life of β-receptor blockade are beneficial. Adverse events are similar to those of other β-blockers and consist of bradycardia and hypotension.

Sotalol – This is a class III anti-arrhythmic with some weak beta-blocker properties. It is used as a second line agent in SVT patients that fail therapy with propranolol. Starting dose is

usually ~120-150 mg/m2/day divided every 8 hours enterally. Intravenous sotalol can also be used for termination of an active arrhythmia that is unresponsive to adenosine. Sotalol prolongs repolarization and can lead to QTc prolongation and arrhythmias. Patients should have daily ECGs to monitor QTc when initiating sotalol therapy.

Flecainide – This is a class Ic anti-arrhythmic that is used as a second line agent in the management of SVT and atrial tachycardias. Starting dose is usually 120-150 mg/m2/day divided every 8 hours enterally. Milk impairs the absorption of flecainide therefore it must be given consistently in regard to timing with feedings. If patient has a decreased intake of feeds, monitor for toxicities and obtain flecainide levels. Flecainide blocks sodium channels slowing the upstroke of the action potential. Daily ECGs should be performed during initiation and up-titration of flecainide to monitor QRS duration.

Amiodarone – For patients who are unresponsive to β-blockade, a class III antiarrhythmic may be successful in terminating SVT. IV bolus dose is 5 mg/kg for active arrhythmias infused over 20-60 minutes in a patient with a pulse. Given the long half-life, a loading dose of 20 mg/kg/day is given which is eventually decreased to a maintenance dose of 5-10 mg/kg/day. Many adverse effects are associated with amiodarone therapy, including pulmonary fibrosis, thyroid toxicity, corneal deposits, hepatotoxicity, decreased growth, developmental delay, dermatologic hypersensitivity, and arrhythmias (e.g., Torsades). A baseline evaluation for potentially affected organ system function is warranted.

Hypotension is a common adverse event after the intravenous administration of amiodarone. Intravenous amiodarone is incompatible with numerous solutions including heparin. Therefore, it is recommended that amiodarone be infused via a dedicated line and flushes with heparin in normal saline be avoided.

Atrial Flutter

Atrial flutter is a rapid heart rhythm caused by an extra electrical pathway in the atria (macroreentrant circuit). This leads to rapid regular atrial contractions (>250 per minute) with variable conduction. It is usually a narrow complex tachycardia. It often produces "sawtooth" waves in the electrocardiogram. In children, it is most commonly seen in association with CHD, but can also be seen in healthy neonates. The majority are asymptomatic and present in the first 48 hours of life. Treatment of choice is synchronized cardioversion (0.5-1 J/Kg). One can also consider trans-esophageal pacing or intravenous sotalol for conversion. In patients with structurally normal hearts, neonatal atrial flutter usually does not recur and no long-term medications are needed.

Congenital Complete AV Block

In congenital complete AV block, there is no electrical communication between the atria and the ventricles. The p-waves are completely dissociated from the QRS complexes. The atrial rate is usually in the 120-150 bpm range and the ventricular rate is in the 50-80 bpm range. The most common cause is maternal autoimmune disorders (lupus, Sjogren's syndrome) but one needs to also evaluate for CHD that can be associated with AV block (Heterotaxy syndrome, congenitally corrected transposition). Another cause that can mimic complete AV block is long QT syndrome, so it's important to always measure QTc interval in patients with suspected AV block. Treatment depends on hemodynamic status. Some patients have an adequate escape rate and are asymptomatic. For patients that require treatment, isoproterenol drip or epinephrine can provide temporary heart rate support. In emergencies, transcutaneous pacing can be used. Pacemaker placement is the permanent therapy for these patients.

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Section 3: Endocrinology

Editors: Catherine Gannon and Daniela Dinu

3.1 Approach to the Management of Disorders of Sexual Development

Definition

Disorders of sex development (DSD) is a broad term used to describe congenital conditions in which the development of the chromosomal, gonadal and anatomic sex is atypical.

DSDs are classified based on karyotype:

- 46, XX DSDs, which include disorders of gonadal (ovarian) development, and disorders of androgen excess, including congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency.
- 46, XY DSDs, which include disorders of gonadal (testicular) development, disorders of androgen synthesis or action and hypogonadotropic hypogonadism.
- Sex Chromosome DSDs, which include mixed gonadal dysgenesis (45, X/46, XY karyotypes) and mosaic and chimeric sex chromosome karyotypes.

DSDs occur in approximately 1 in 4,500 live births. Minor abnormalities may be more common. A comprehensive and prompt evaluation is required when the external genitalia are sufficiently ambiguous to hamper sex assignment, are inconsistent with prenatal results, or could potentially involve a life-threatening condition or comorbidity such as Congenital Adrenal Hyperplasia (CAH) or hypogonadotropic hypogonadism associated to hypopituitarism.

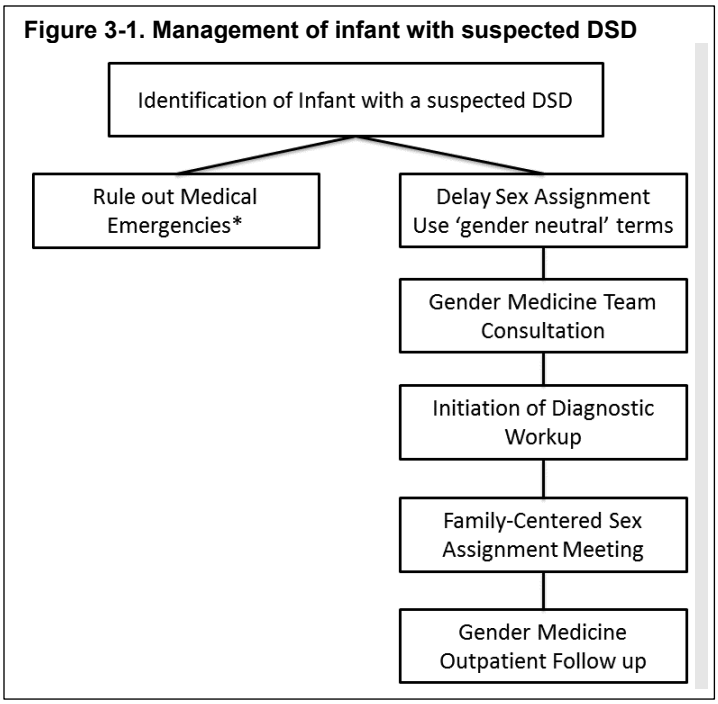
Clinical findings that should prompt an evaluation include:

- Micropenis, defined as penile length < 2.5 cm in a term infant,
- Clitoromegaly, defined as clitoral length > 0.9 cm in a term infant,
- Penoscrotal or perineal hypospadias,
- Hypospadias with unilateral or bilateral non-palpable testis
- Apparent female genitalia with an inguinal or labial mass,
- Non palpable testes in an apparent male with an abnormal CAH screen,
- Discrepancy between antenatal karyotype and postnatal phenotype.

General Concepts: The Multidisciplinary Team Approach

Management of an infant with a DSD is complex and requires a coordinated effort between multiple specialties. **(Fig 3-1)** Providers should support the family and encourage holding, feeding and interacting with the infant as normally as possible. Terms with negative connotations should be avoided. And most importantly, it is critical **NOT** to assign sex until a diagnosis is reached. Gender neutral terms such as "your baby", "Baby Smith", "gonads" (instead of testicles or ovaries), "genital folds" (instead of scrotum or labia), "genital tubercle" (instead of clitoris or penis) should be used when communicating with parents and between providers.

Figure 3-1. Management of infant with suspected DSD



All infants should be evaluated by the Gender Medicine Team, which is composed of pediatric endocrinologists, geneticists, urologists, gynecologists, neonatologists, psychologists, pathologists, social workers and ethicists. The team guides the diagnostic workup and, once results are available, meets with the family for sex assignment. The process of sex assignment is family-centered and involves a discussion of the different components of sex: chromosomes, genes, hormones, internal structures, external structures, reproductive function and societal values. In all cases, sex assignment should occur prior to discharge.

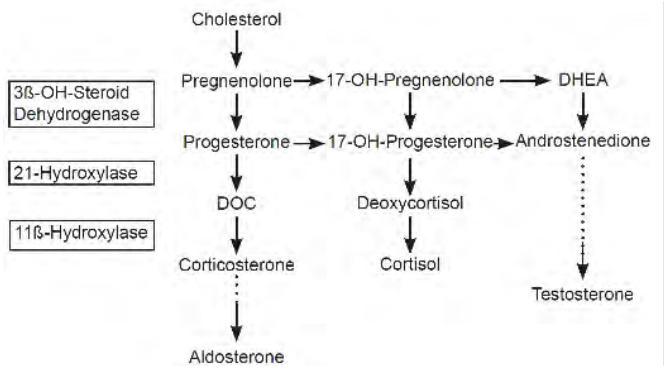
Parents should be continuously educated concerning the issues being assessed in their infant. Because of the complexity of the diagnoses of DSD, such education can be overwhelming to a parent who is already stressed due to lack of a sex assignment in their newborn. One member of the team, typically the primary neonatologist or the pediatrician should be the main source of information for the family in the early stages of the baby's evaluation. The final decision concerning gender assignment will rest with the parents. Thus, it is imperative that they understand the pros and cons of the recommendation of the multidisciplinary team. This typically requires several meetings of the specialists and family to help the parents reach an informed decision.

Medical Emergencies

Congenital Adrenal Hyperplasia (CAH)

CAH is a group of autosomal recessive disorders characterized by the inability to produce cortisol due to an enzyme deficiency in the steroid synthesis pathway (**Fig 3-2**). CAH is a medical emergency as it may be associated with cortisol and aldosterone deficiency. If untreated, the infants may develop a salt wasting crisis (e.g., hyponatremia, hyperkalemia, hypovolemia, and shock). CAH should be suspected in infants with frank genital ambiguity, apparent male genitalia with non-palpable gonads, clitoromegaly, or elevated 17-hydroxyprogesterone on the newborn screen.

Figure 3-2. Pathways of adrenal hormone synthesis



The most common form of CAH is caused by 21-hydroxylase deficiency. In this condition, cortisol precursors are diverted to adrenal androgen production and the external genitalia of a 46, XX fetus becomes virilized. Internal genitalia are unaffected.

The diagnosis is made by measuring the adrenal steroid precursors, including 17-hydroxyprogesterone before and after administering Cosyntropin (high dose ACTH stimulation test). Treatment involves the replacement of hydrocortisone, fludrocortisone, and sodium chloride. In clinically unstable patients or patients with a high clinical suspicion for CAH, hydrocortisone at 100 mg/m2 IV can be started after drawing the sample, while awaiting results.

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism is a group of conditions caused by deficient production of gonadotropins: LH and FSH. Fetal gonadotropins are required for androgen production, testicular descent and penile growth. Therefore, male neonates with congenital hypogonadotropic hypogonadism may present with micropenis and cryptorchidism. Hypogonadotropic hypogonadism should be suspected in infants with micropenis (usually without hypospadias) or cryptorchidism, particularly if associated with other midline defects or a history of hypoglycemia.

Hypogonadotropic hypogonadism may present isolated or in combination with other pituitary deficiencies such as ACTH, TSH and GH. In this case, it is considered a medical emergency as patients may develop adrenal crisis or hypoglycemia due to lack of cortisol and GH, respectively. Therefore, in infants in whom hypogonadotropic hypogonadism is suspected, all pituitary axes need to be evaluated and treated accordingly.

Evaluation of a Baby with Ambiguous Genitalia

As different conditions may result in the development of atypical genitalia, there is no single test that will lead to the diagnosis in all affected patients. To better utilize resources, diagnostic evaluation should start with a detailed history and physical exam, followed by genetic, hormonal and imaging studies.

History

- Maternal drug history (virilizing drugs, e.g., progestins, finasteride, or phenytoin), or Maternal virilization (androgen-secreting tumors in the adrenals or the ovary).
- Consanguinity of the parents
- Genital ambiguity in siblings or in the family
- Neonatal deaths
- History of infertility or amenorrhea

Physical Examination

General Examination

- Dysmorphic features suggest genetic syndromes (e.g., Smith-Lemli Opitz syndrome, Denys-Drash syndrome)
- Midline defects suggest hypothalamic-pituitary causes for hypogonadism.
- State of hydration and blood pressure must be assessed for congenital adrenal hyperplasia (CAH). In CAH, salt loss and cardiovascular collapse usually occur between the 4th and 15th days of age and should be considered in the differential diagnosis.
- Hyperbilirubinemia may be secondary to concomitant thyroid or cortisol deficiency.

External Genitalia

- Genital tubercle (penis/ clitoris). This structure should be measured on its dorsal surface from pubic ramus to the tip. A tubercle length <2.5 cm in a term male is considered a micropenis, while a tubercle length > 0.9 cm in a term female is considered clitoromegaly.
- Genital folds (scrotum/labia). Note the degree of labioscrotal fusion and its rugosity, and the presence or absence of a separate vaginal opening.
- Location of the urethral opening, presence and severity of hypospadias.
- Gonads (testes/ovaries), presence of uni- or bilateral cryptorchidism, inguinal masses that could represent gonads in the apparent female infant.
- Degree of Virilization. Prader's Staging can be used to describe increasing virilization in an infant with ambiguous genitalia:

  Stage I - a slightly virilized female, perhaps only exhibiting isolated clitoral hypertrophy.

  Stage II - a narrow vestibule at the end of which the vagina and the urethra open.

  Stage III - a single perineal orifice giving access to a urogenital sinus with the labia majora partially fused.

  Stage IV - a phenotypic male with hypospadias and micropenis.

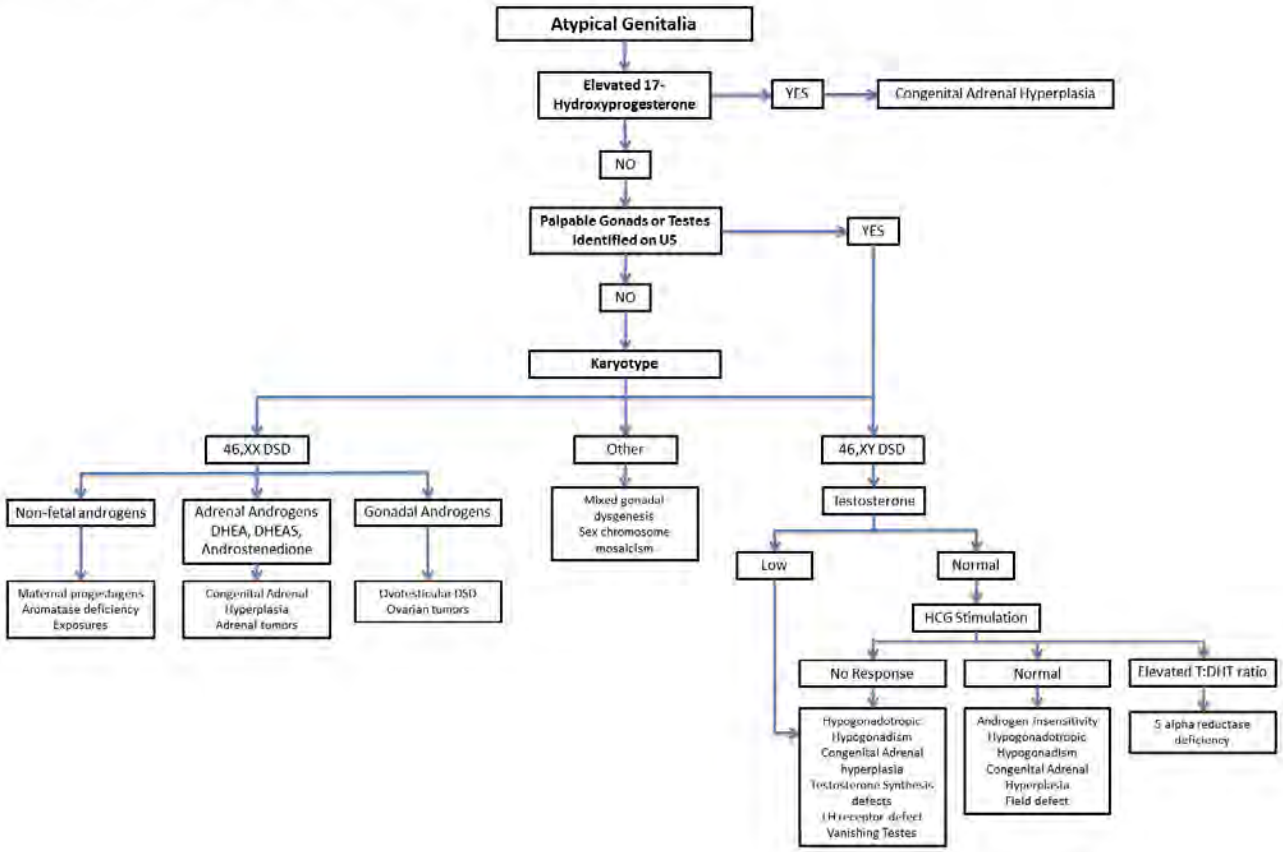
  Stage V - a cryptorchid boy.

Initial investigations

Genetics

- Karyotype. A karyotype should be obtained urgently, as it helps develop a differential diagnosis and to plan further investigations.
- FISH studies using probes, specific for X (DX 1) and the Y (SRY) chromosome should be obtained and mosaicism should be excluded.

Figure 3-3. Diagnostic Approach to Atypical Genitalia



- Comprehensive microarrays (CMA), Whole Exome Sequencing (WES) and other single gene analysis may be needed depending on the clinical situation.

Internal Genitalia Anatomy

- Pelvic ultrasound exam should be ordered to assess presence of Mullerian structures (uterus or uterine remnants), gonads, and to exclude renal anomalies
- Magnetic resonance imaging (MRI) of the abdomen and the pelvis, exploratory laparoscopy, evaluation under anesthesia, cystoscopy, and urogenital contrast studies may be necessary for complete evaluation.

Hormonal Tests

- **17-Hydroxyprogesterone** is useful to diagnose 21-OH hydroxylase deficiency (responsible for 90% of CAH). If the levels are non-diagnostic or if the infant needs to be started on steroids, perform a high dose ACTH stimulation test (250 mcg of Cosyntropin for infants > 3kg or 125 mcg for infants < 3kg). This will accentuate the block in the metabolic pathway. Stimulation test is followed by CAH panel test at 60 minutes.
- **Testosterone, dihydrotestosterone (DHT), and Anti-Mullerian Hormone (AMH**). Testosterone is produced by testicular Leydig cells and is converted to a more active form, DHT. AMH is produced by the Sertoli cells. Male levels of these hormones represent hormonally active testicular tissue. Adequate levels of DHT by mass spec rule out 5-alpha-reductase deficiency.
- **Gonadotropins (LH, FSH).** Raised basal levels are consistent with primary gonadal failure; low levels can be a sign of hypogonadotropic hypogonadism.
- Other tests such as inhibin B levels, estradiol, and human chorionic gonadotropin (HCG) stimulation tests may be necessary depending on the clinical situation.

3.2 Hypothyroxinemia of Prematurity

Introduction

Hypothyroxinemia is defined by the state screening program as a total thyroxine (T4) level <90% of samples screened on that day. In infants <32 weeks' gestation, hypothyroxinemia of prematurity with normal or low thyrotropin (TSH) levels is common. The serum levels of thyroid hormones in premature infants are considerably lower than those in term infants as both the thyroid gland hormone biosynthesis and the hypothalamic-pituitary axis (HPA) are immature and thyroid-binding globulin levels are low. The degree of hypothyroxinemia is also related to gestational age and the severity of neonatal disease. Further, pharmacologic agents may inhibit TSH secretion (e.g., glucocorticoids, dopamine). In these preterm infants, a period of approximately 6–8 weeks of hypothyroxinemia occurs, and is more severe at shorter gestational ages. Very low birth weight (VLBW) infants also have an 8-fold increased risk for development of transient primary hypothyroidism with low T4 levels and marked elevations in TSH. It is uncertain whether this condition contributes to adverse neurodevelopmental outcome or whether treatment with T4 during this period results in improved developmental outcome.

The prevalence of permanent hypothyroidism in preterm infants is comparable to that of term infants. It is important to distinguish transient hypothyroxinemia from primary or secondary hypothyroidism.

Epidemiology

The prevalence of hypothyroidism is 1 in 4,000, however, the prevalence of hypothyroxinemia is not known.

Diagnosis

Because levels of total and free T4 in premature infants are low, distinguishing physiologic hypothyroxinemia from true central (secondary hypothalamic or hypopituitary) hypothyroidism is often difficult. In extremely low birth weight infants, the first newborn screen (NBS) result often has low T4 and normal TSH.

In infants with low T4 and normal TSH who are asymptomatic, repeat the NBS (if the second screen has not yet been sent) and simultaneously measure free T4 and TSH in the hospital laboratory. If the thyroid function tests, or the repeat NBS, or both are abnormal, order a free T4 by equilibrium dialysis (remember that heparin, Lasix, high free fatty acid concentrations interfere with this determination by displacing T4 from binding proteins and falsely elevating free T4 concentrations) and then obtain an endocrinology consultation when the results of the T4 by ED are back.

Clinical findings that suggest central hypothyroidism include:

- micropenis
- cleft lip or cleft palate
- midline facial hypoplasia
- nystagmus
- hypoglycemia
- prolonged indirect hyperbilirubinemia
- evidence of abnormal adrenal function, deficiencies of growth hormone, prolactin, or gonadotropins
- central diabetes insipidus
- radiologic evidence of structural head abnormalities (hypothalamus, pituitary gland, IVH)

Treatment

True congenital hypothyroidism should be treated with replacement thyroxine (levothyroxine sodium, 8–10 mcg/kg per day, given orally; the IM or IV dose is 50% to 75% of the oral dose). Follow the infant's thyroid function (TSH, free T4, and total T4) 2 and 4 weeks after instituting replacement therapy. A pediatric endocrinologist should guide further therapy and follow-up. A Cochrane systematic review does not support the treatment of transient hypothyroxinemia of prematurity to reduce neonatal mortality, improve neurodevelopmental outcome, nor to reduce the severity of respiratory distress syndrome. This review's conclusions are limited by the small number of infants in the included trials.

Prognosis

In most patients, hypothyroxinemia is transient and resolves completely in 4–8 weeks. However, the frequency of follow-up thyroid function studies should be based on the clinical picture and the degree of hypothyroxinemia.

3.3 Steroid Therapy for Adrenal Insufficiency

Etiology

Maternal cortisol is converted to cortisone by the placenta during gestation, which prevents the suppressive effect on the fetal hypothalamic pituitary adrenal axis (HPA). At birth, a surge of fetal cortisol levels is seen, which is much higher in spontaneous labor compared to induced labor or cesarean delivery. Evidence suggests that the fetal adrenal cortex does not produce cortisol *de novo* until late in gestation (approximately 30 weeks' gestation) when increased levels of cortisol induce the maturation required for extrauterine life.

Factors predisposing neonates to adrenal insufficiency include developmental immaturity (i.e., in preterm infants) and relative adrenal insufficiency. Relative adrenal insufficiency is defined as the production of inadequate levels of cortisol in the setting of a severe illness or stressful condition. Proposed mechanisms for relative adrenal insufficiency have included cytokine-related suppression of ACTH or cortisol synthesis, cytokine-induced tissue resistance to cortisol effects, hypoperfusion or hemorrhage of the adrenal gland (i.e., which can occur with sepsis), or limited adrenocortical reserve.

Signs and Symptoms

Signs and symptoms of acute adrenal insufficiency include:

- Hypoglycemia
- Hyponatremia and hyperkalemia (seen in mineralocorticoid deficiency, e.g., aldosterone deficiency or congenital adrenal hyperplasia)
- Cardiovascular dysfunction resulting in hypotension and shock, often non-responsive to volume and ionotropic therapy

Evaluation of Hypothalamic-Pituitary-Adrenal Axis and Function

Evaluation should be performed 2–7 days after finishing a course of steroids >2 weeks. If the evaluation demonstrates a non-responsive result, the evaluation should be repeated in 6–8 weeks.

Laboratory Testing

The following laboratory testing should be sent:

- Perform adrenal gland stimulation test by administering 1 microgram of Cosyntropin IV (low dose testing) and check cortisol level at baseline, 30 and 60 minutes after administration of ACTH
- A baseline cortisol level >10 mcg/dL and total stimulated level >18 mcg/dL or a change from baseline of >10 mcg/dL indicates a normal response. If there is a question regarding adequacy of response, pediatric endocrinology consultation should be obtained.

Treatment

For acute adrenal insufficiency or for infants with adrenal suppression, hydrocortisone should be provided during a surgical procedure or when experiencing significant clinical illness (e.g., NEC, sepsis). Once infant's clinical status has stabilized, start to wean the hydrocortisone dose with the goal of tapering off steroids over the course of 5–10 days; faster if there are no blood pressure issues.

Table 3-1. Hydrocortisone for vasopressor resistant hypotension

Gestational Age	Hydrocortisone Dosing
GA < 32 weeks	• 1 mg/kg every 8 hours[1,2,3]
GA ≥ 32 weeks	• **Mild to moderate stress:** 20 to 50 mg/m^2/day divided every 6-8 hours; doses on the lower end of the range (20 to 30 mg/m^2/day) may be divided twice daily[4,5] • **Major stress or surgery:** 100 mg/m^2/day in divided doses every 6 hours[6]
For patients with known or suspected adrenal suppression: **Planned surgery:** Pre-anesthesia of 50 mg/m^2 IV or IM administered 30 to 60 minutes prior to surgery followed by 50 mg/m^2/day divided every 6-8 hours for at least 24 hours	

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[5] Shulman DI, Palmert MR, Kemp SF; Lawson Wilkins Drug and Therapeutics Committee. Adrenal insufficiency: still a cause of morbidity and death in childhood. *Pediatrics*. 2007;119(2):e484-e494

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3.4 Hypoglycemia

Neonatal hypoglycemia is common and diagnosis and appropriate management remain a subject of controversy. Important physiologic and prognostic differences exist between transient neonatal hypoglycemia (TNH) occurring during the first 24-48 hours of life and hypoglycemia persisting beyond that time period or presenting later.

Blood glucose (BG) values are lowest during the initial 48 hours of life and transient values ≤40 mg/dL are common. Current evidence does not identify a BG concentration or threshold that is "safe" or a level inevitably associated with irreversible brain injury. Individual BG values must be evaluated in conjunction with assessment of patient risk, neurologic behavior and presence of other contributing factors.

Point of care testing (POCT) and iStat-type devices are convenient for glucose screening and are used by most hospitals for bedside testing. However, they evaluate the whole BG value, with limited accuracy in the hypoglycemia range. It is essential to confirm low BG values with a clinical laboratory plasma glucose (PG) specimen. However, if a POCT value is low, appropriate intervention should not be delayed while awaiting confirmatory laboratory testing.

Whole BG values (POCT devices) are ~15% lower than PG (laboratory) values. The BG value also depends on the patient's hematocrit, and PG sent to the laboratory may be lower if not immediately tested due to metabolism of glucose by erythrocytes. "BG" will be used in this section and, unless specifically stated, can refer to either plasma glucose (laboratory method) or whole blood glucose (POCT method).

3.5 Transitional Neonatal Hypoglycemia (≤ 48 hours of life)

Fetal blood glucose (BG) values at term are about 10 mg/dL less than those of the mother. Fetal insulin is responsive to fetal glucose concentrations, but fetal glucose values are primarily determined by maternal concentrations. Fetal insulin functions to regulate fetal growth. Obligate cerebral glucose utilization is high in neonates, and the ability to utilize alternate fuels such as ketones and lactate for cerebral metabolism is limited in the first two days. Following birth, mean BG values in healthy term neonates diminish and reach a nadir of 50-60 mg/dL at 1-2 hours of age. Values subsequently increase over the next 2-3 days to a mean >70 mg/dL.

The most common cause of hypoglycemia in neonates is transient neonatal hypoglycemia (TNH), impairment of the metabolic transition from intrauterine to extrauterine life, which typically resolves by 48 hours.

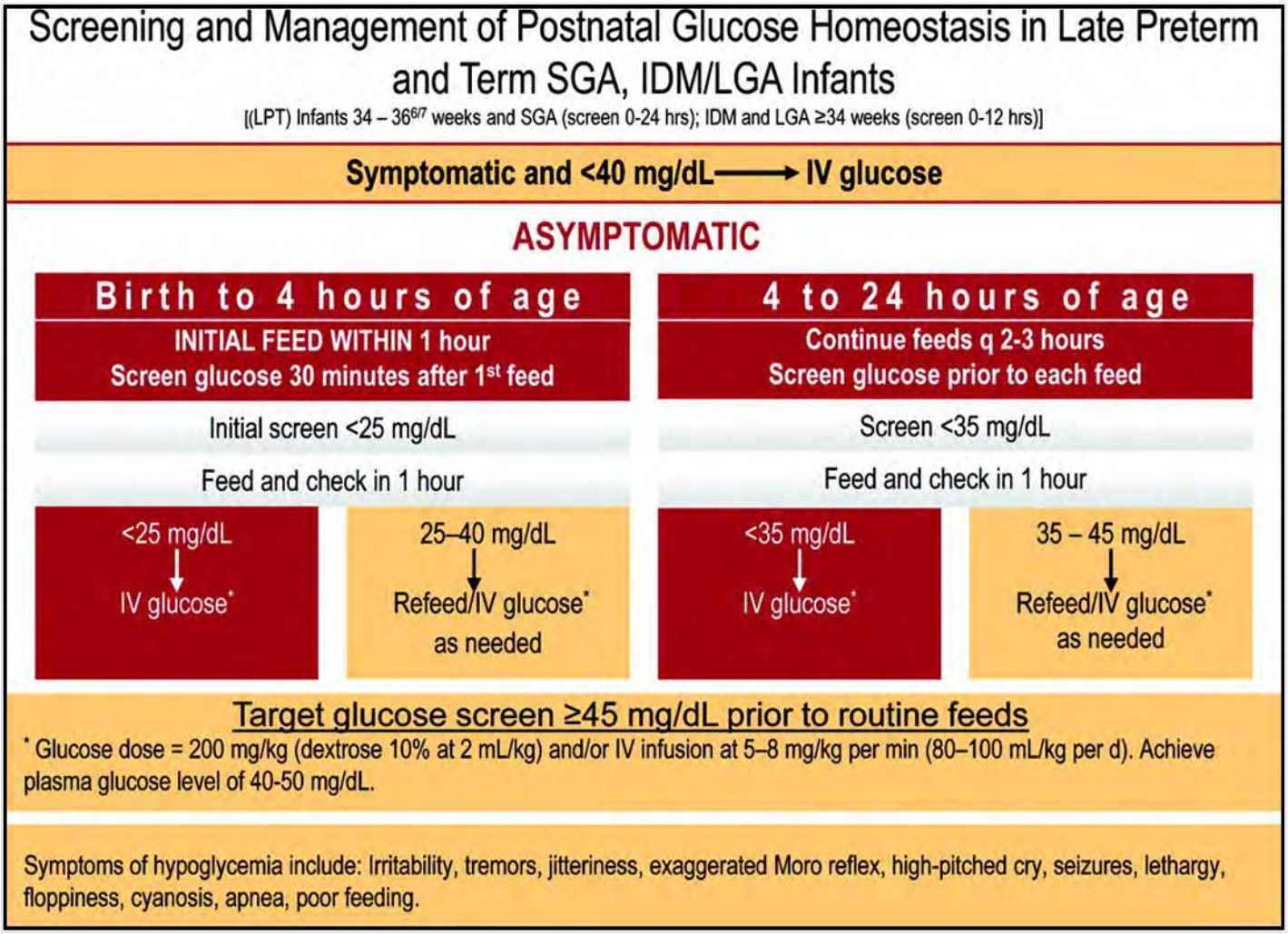
Infants at high risk for TNH include:

- Infants of diabetic mothers
- LGA infants
- Infants with fetal growth restriction (SGA infants)
- Preterm infants <37 weeks GA, especially those requiring NICU care.
- Other neonates with significant perinatal stress, unstable cardiopulmonary function, infection, polycythemia, or neurologic injury.

Approximately 50% of infants in these risk groups exhibit at least 1 BG value ≤47 mg/dL during the first 48 hours of life, and 19% have values ≤37 mg/dL. In one prospective study, recurring episodes occurred in 19%, and 6% had their initial episode after 24 hours of age. Eighty percent were asymptomatic, 15% were too lethargic to feed and 7% were jittery. Most symptomatic neonates have BG values <25 mg/dL, as do those with hyperinsulinism or genetic hypoglycemic disorders. Importantly, symptoms of hypoglycemia are non-specific and can occur with other neonatal conditions.

Evidence suggests that TNH is a disorder of insulin dysregulation. Transient immaturity exists in the suppression of insulin secretion as plasma glucose levels fall during the early hours following birth. This results in a state of "functional" hyperinsulinism in which insulin levels may be in the "normal" range but are not appropriate for the observed plasma glucose concentrations. This dysfunctional regulation of insulin suppresses production of free fatty acids and ketones, making them unavailable as alternate energy sources for cerebral metabolism.

Figure 3-4. Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34–36 6/7 weeks) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants.



Management of TNH

Evidence linking hypoglycemia and adverse neurologic outcome has been conflicting. Although some studies have associated asymptomatic hypoglycemia with developmental delay and poor academic achievement, current evidence does not identify a specific BG value or threshold below which cerebral injury will occur. Treatment studies have also reported conflicting outcomes. Maintaining BG in the normal range for age is important to prevent immediate and long-term neurodevelopmental consequences of hypoglycemia.

Glucose screening. Babies in the high-risk categories noted above should feed shortly after birth if able and receive glucose screening between 30 minutes to 2 hours of life. Some may require continued monitoring during the first 24 to 48 hours until BG values stabilize >60mg/dL. Several clinical scenarios occur among these high-risk patients. Management strategy must be individualized and depends upon BG value, risk and clinical findings. **Ch 12.10-Newborn Screening-Risk Based Screening: Glucose Screening**

Need for screening and/or intervention will usually involve one of the following clinical scenarios:

Symptomatic neonates. Symptomatic infants (seizures, temperature instability, respiratory distress, lethargy, apnea, inability to orally feed, or marked jitteriness) with a BG value <40 mg/dL should be given a bolus of 2 mL/kg of D10W followed by a continuous glucose infusion of 5-8 mg/kg/min, titrated to maintain BG >60mg/dL. Failure to provide the continuous infusion may result in recurrence of hypoglycemia. One should not wait for the results of laboratory PG levels to initiate management of symptomatic infants. The use of higher concentration dextrose (12.5% dextrose in water) allows the baby to continue to feed orally without giving excessive fluid. Dextrose concentrations higher than 12.5% require central venous access. Concentrated dextrose fluids via central line may need to be provided when volume overload for the infant is a concern. In general, due to concerns about osmolarity, our practice is to not exceed D30 concentration.

- **Late preterm (34-36 6/7 weeks) infants and term IDM, SGA or LGA infants who are stable and asymptomatic.** These infants should be offered feeds within one hour after birth (breastfeeding, oral or gavage feeding with human milk or formula) and have BG tested 30 minutes after the feed. Frequent feeding should continue every 2-3 hours with BG

monitoring prior to each feed. The initial treatment target is a progressive rise in BG value to >45 mg/dL in the first 4 hours of life. Monitoring of BG values should continue for 12-24 hours. **(Fig 3-4)** If BG values >45 mg/dL cannot be achieved with frequent feedings, supplementation with IV dextrose is necessary. When BG values are stable >60 mg/dL and oral feeding is established, weaning of dextrose-containing IV fluids can be attempted with BG checks after each wean.

- **At risk neonates who are NPO and asymptomatic**. Perinatal conditions requiring NICU care place infants at risk for hypoglycemia and delayed initiation of feedings. These include preterm infants <34 weeks, infants with cardiopulmonary disease, and other high-risk conditions that preclude successful enteral feeds. These infants should be started on an IV dextrose infusion providing 5-7 mg/kg/min and have BG checked by 30-60 minutes of life. Babies <25 weeks' gestation should be started at a GIR of 4-6 mg/kg/min. This GIR is effective in preventing hypoglycemia in most high-risk patients. However, if BG > 45 mg/dL cannot be maintained, administer an IV bolus of 2 mL/kg of D10W followed by an increase in GIR by 10-20%.

Glucose Calculations

Glucose Infusion Rate (GIR) = mg glucose/kg/min =
[% dextrose × fluid goal]/ 144

% Dextrose to order using Total Fluid Goal:

$$\left[\frac{\text{[GIR Goal (mg/kg/min)} \times 1.44\text{]}}{\text{Total fluid goal (ml/kg/day)}} \times 100\right]$$

GIR Goal (mg/kg/min) × 1.44 = gm glucose /kg/day
Then divide by fluid goal (ml/kg/day) =
Dextrose per mL × 100 = g/ 100 mL

Subsequent Management

TNH should resolve by 48 to 72 hours of life. Prior to discharge of an infant who required glucose supplementation as treatment for TNH, the clinician must be certain that infant can maintain normal BG values during several feeding cycles on a routine diet. This is particularly important if the infant required intervention with IV dextrose or was symptomatic. Those with symptoms, very low values, or need for high levels of IV dextrose supplementation (GIR >10-12mg/kg/min) are suspect for a persistent disorder of glucose metabolism and are candidates for further evaluation prior to discharge. A high index of suspicion is necessary to promote early diagnosis of hyperinsulinism and other persistent hypoglycemia disorders before severe, recurrent episodes occur, as these have been associated with developmental disabilities.

3.6 Persistent Hypoglycemia

Persistent hypoglycemia is defined as the need for glucose supplementation beyond 48-72 hours of life to maintain BG values > 60 mg/dL. A thorough diagnostic work up is essential.

Hyperinsulinism should be considered in neonates requiring a GIR > 10 mg/kg/min as well as any neonate with persistent and frequent hypoglycemic episodes. The diagnosis of hyperinsulinemic hypoglycemia cannot be made by solely measuring insulin concentrations at the time of a hypoglycemic episode. Identification of a specific etiology requires a battery of laboratory studies obtained during an episode of hypoglycemia.

It is critical to use history and physical examination, as well as the clinical picture, to narrow the differential diagnosis. Sending laboratory tests without guidance from the clinical picture may lead to a non-diagnostic evaluation. For example, a newborn with micropenis and undescended testicles will require a pituitary evaluation rather than an insulin or acyl carnitine concentrations. Lab tests should be obtained once persistent hypoglycemia is determined when the infant becomes hypoglycemic (plasma glucose < 50 mg/dL) either spontaneously or in concert with a planned weaning of the glucose infusion rate or monitored fasting. Pediatric Endocrinology Service consultation should be obtained after results of the initial testing as found in **Fig 3-5** are known, but before treatment begins.

Table 3-2. Proposed target glucose levels (PES recommendations) in late preterm and term infants admitted to NICU for hypoglycemia

Age	<48h	>48h
Goal (target) glucose	≥50	≥60*
Glucose level when GIR may be weaned	≥60	≥70*

* Unless there is an Endocrinology consult with specific recommendations or a critical sample drawn that confirms hyperinsulinism

Table 3-3. Suggested weaning protocol

Action	<48 HOL	>48HOL*
Wean GIR by 0.5-1	Glucose ≥60	Glucose ≥70
No change	Glucose 50-59	Glucose 60-69
Increase GIR by 0.5-1	Glucose 40-49	Glucose 45-59
Bolus with D10 2ml/kg and increase GIR by 1	Glucose ≤ 39	Glucose ≤ 44

***** Follow Endocrinology recommendations if consulted

Causes of persistent hypoglycemia are listed below to help determine the etiology. (**Fig 3-6**)

Causes of Persistent Hypoglycemia

Disorders of Insulin Secretion and Production

Persistent hyperinsulinemic hypoglycemia of infancy (congenital hyperinsulinism)

- Infants of diabetic mothers
- Perinatal stress
- Erythroblastosis fetalis
- Beckwith-Wiedemann Syndrome

Endocrine Abnormalities

- Hypothalamic/ Pituitary dysfunction
- Central adrenal insufficiency
- GH deficiency
- A combination GH and adrenal insufficiency as part of pan hypopituitarism
- Primary adrenal insufficiency
- Congenital adrenal hyperplasia
- Congenital adrenal hypoplasia
- Adrenal hemorrhage

Disorders of Ketogenesis and Fatty Acid Oxygenation

- Fatty acid oxidation disorders, MCAD being the most common
- Disorders of carnitine transport/carnitine deficiency

Defects in Amino Acid Metabolism:

- Maple syrup urine disease
- Propionic acidemia
- Methylmalonic acidemia

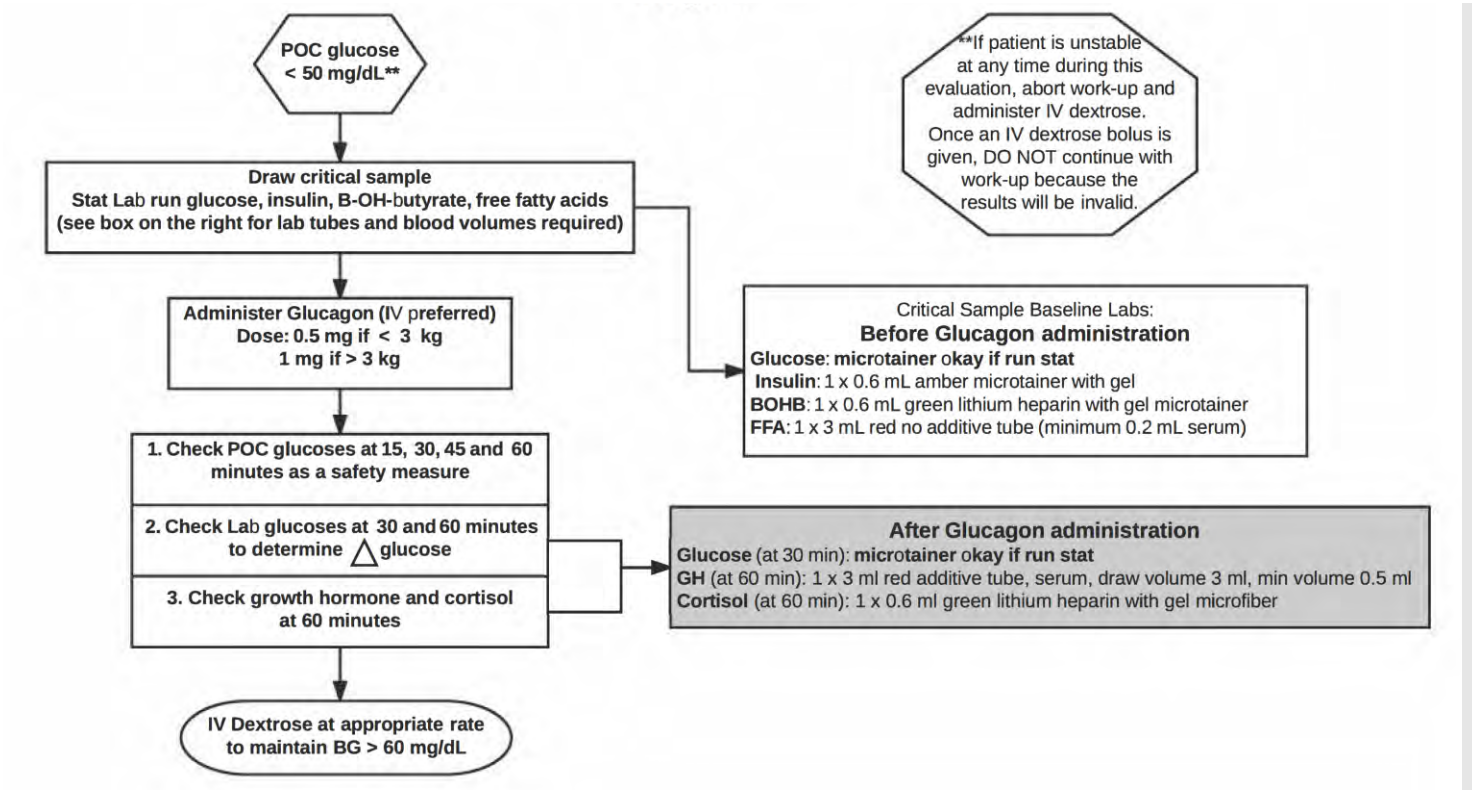
Inborn Errors of Glucose Production:

- Glycogen storage disease
- Disorders of gluconeogenesis - pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase
- Hereditary Fructose Intolerance

Evaluation of Persistent Hypoglycemia

Ongoing hypoglycemia beyond the first 48 hours of life, and particularly beyond the first week, increases the concern for an underlying hypoglycemia disorder. In these neonates, it is suggested to begin laboratory evaluation between 72 hours and 7 days for most, so that persistent hypoglycemia may be excluded before discharge home. Testing is performed when the BG is <50 mg/dL, either spontaneously or as part of a diagnostic fast because tests performed when the BG is normal are not generally helpful. (strong recommendation, high quality evidence)

Figure 3-5. Persistent hypoglycemia evaluation flow diagram



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In neonates suspected of having a congenital hypoglycemia disorder a treatment goal of BG >70 mg/dL is recommended. (strong recommendation, low quality evidence)

For high-risk neonates without a suspected congenital hypoglycemia disorder, a goal of >60 mg/dL is still suggested (i.e. SGA, IDM). (weak recommendation, very low quality)

Consultation with a specialist should be considered before planning discharge from the nursery for neonates with known genetic or other persistent forms of hypoglycemia. In these cases, "safety" fasting test may be recommended to ensure that BG can be maintained above 70 mg/dL if a feeding is missed (minimum 6 - 8 hours). (expert opinion)

Suggested Laboratory Evaluation for Persistent Hypoglycemia

- Check blood sugar every 3 hours
- When blood sugar < 60 mg/dL, check every 1 hour * Run glucose levels in the lab STAT rather than by POC alone.
- When blood sugar < 50 mg/dL, draw critical blood samples before treating hypoglycemia:
  - » Plasma glucose level
  - » Plasma insulin level
  - » Serum beta-hydroxybutyrate
  - » Free fatty acids
  - » Plasma cortisol and growth hormone

After drawing critical blood samples, treat with glucagon IM (**Fig 3-5** for dosing) and recheck serum glucose at 30 minutes and cortisol and growth hormone at 60 minutes. Start IV dextrose as appropriate to maintain blood sugar above 60 mg/dl. If patient is unstable while hypoglycemic, bolus with 2 mL/kg of $D_{10}W$.

Testing for non-endocrine causes of persistent hypoglycemia may include:

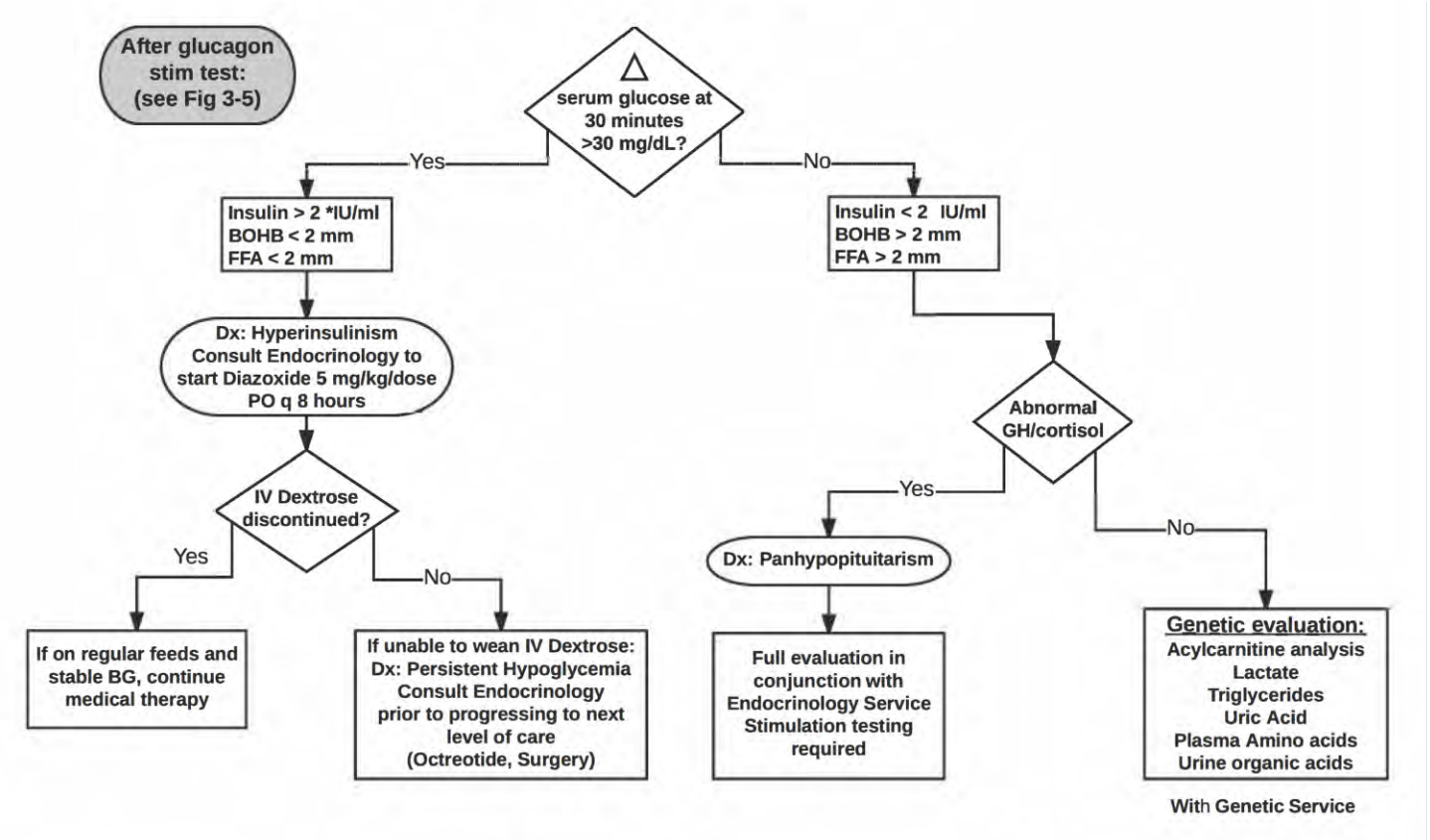
- C-peptide
- Acylcarnitine profile
- Plasma amino acids
- Pyruvic acid
- Serum ammonia and lactate
- Urine organic acids and ketones
- Targeted gene panel

Timing and state at which testing will yield the best information should be discussed as part of Genetics/Metabolic Consultation, but generally do not require the patient to be hypoglycemic at time of testing.

3.7 Hyperglycemia

Glucose values of 80-144 mg/dL fall between the 10th and 90th percentile in very low birth weight infants (VLBW) and the renal glucose threshold is between 150 and 180 mg/dL. However, during the first postnatal week, about one-third of VLBW infants have glucose concentrations of >180 mg/dL. While there is no

Figure 3-6. Persistent hypoglycemic diagnostic categories



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established definition of hyperglycemia, there is increasing evidence that glucose levels >180 mg/dl are associated with increased mortality in VLBW infants. Hyperglycemia has also been associated with higher risk of ROP, late onset sepsis, brain white matter injury, adverse neurologic outcomes, and reduced long-term growth. Possible reasons for this include limited insulin secretion capacity in preterm infants, increased secretion of catecholamines in growth restricted newborns and those exposed to hypoxia, increase in hepatic glucose production via increased secretion of cortisol, glucagon, and growth hormone, administration of catecholamines and glucocorticoids, and delayed/ slow advancement of enteral feeding.

The risk of hyperglycemia can be decreased by:

- Early initiation and advancement of enteral feeding.
- Optimizing protein intake to a goal of 3.5-4 gm/kg.
- Slow advance of glucose infusion rates. Two strategies have been employed to treat hyperglycemia reducing glucose infusion rates or administering exogenous insulin.

In infants with blood glucose values persistently greater than 150 mg/dL the glucose infusion rate should be reduced by decreasing the GIR by 1-2 (Do not use dextrose concentrations less than 5% given its hypoosmolality). The GIR should not be decreased below 3.5 with the goal of correcting hyperglycemia (low evidence). Although restricting glucose intake to avoid hyperglycemia for prolonged periods of time is undesirable for growth, this approach is preferable to insulin administration in the short term due to the associated higher risk of hypoglycemic episodes.

Use of insulin has been associated with lower mortality in extremely preterm infants, and improves utilization of infused glucose, permitting greater caloric intake. Insulin therapy should be considered for babies already receiving a low GIR with persistent BG values greater than 180 mg/dL with the goal of insulin therapy to maintain the BG value below 180 mg/dL while avoiding hypoglycemia.

An *initial bolus of regular insulin* at a dose of 0.05 to 0.1 units/kg infused over 15 minutes may be given without IV extension tubing, followed by a continuous infusion if acceptable blood glucose values are not achieved. Monitor blood glucose every 30-60 minutes following doses until stable, then as needed. Due to unpredictable absorption in neonates, subcutaneous injection of insulin should be avoided.

The usual *infusion starting dose* is 0.01 to 0.05 units/kg/hour, monitor blood glucose every 30 minutes and titrate in 0.01 units/kg/hour increments (usual range: 0.01 to 0.1 units/kg/hour) until goal blood glucose values of 130 to 180 mg/dL are obtained. To saturate insulin binding sites, the IV tubing should be flushed per unit protocol prior to starting the infusion. Due to differences in the dead space of tubing distal to the interface of the insulin infusion set and the primary IV line, the onset of insulin action is highly variable.

The initial dose required to achieve the desired BG values may be greater than the dose required to maintain them in the desired range. Insulin administration in premature infants is associated with significant risk of hypoglycemia and BG values must be monitored closely even when target BG values have been achieved. If the BG is rapidly declining, the insulin infusion rate should be decreased, and if BG values are less than 100 mg/dL, the insulin infusion should be discontinued and BG monitored closely until stable. Serum potassium levels also should be monitored frequently during insulin infusion. Once effective enteral feeds are established, glucose intolerance often resolves.

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Section 4: Environment

Editors: Rebeca Cavazos and George Mandy

4.1 NICU Environment

The NICU environment includes both inanimate and animate sources of stimulation. Inanimate stimulation includes sound, light, bedding, temperature, odor, and airflow. Animate stimulation comes from caregivers and parents. The short-term impact of environment on preterm and term infants has been well studied, but its role in brain development and developmental outcomes remains under investigation. Some amount of environmental stimulation is necessary for appropriate neurodevelopment in preterm infants, so avoiding both sensory deprivation and overstimulation is a good initial goal. Even more subtle than this is the challenge of providing the correct quantity and quality of stimuli for appropriate neurodevelopment.

Effects of Environment

Manipulating the perinatal sensory experience of the fetus and neonate through enhancement or deprivation alters patterns of early perceptual and behavioral development. These alterations depend on the type and amount of stimulation, as well as its timing relative to an infant's level of developmental maturity. Although research suggests that the NICU environment and experiences influence outcomes, many interventions do not have an accumulated evidence base to support use in the NICU. Prevention of harm takes precedence over the developmental and environmental stimulation of a neonate when the neonate is fragile or immature. Avoiding under-stimulation of a stable and more maturely functioning infant is encouraged. Child life and developmental pediatric specialists are available when needed.

The onset of function of sensory systems proceeds sequentially:

1. tactile
2. vestibular
3. chemical (gustatory-olfactory)
4. auditory
5. visual

The first four systems become functional in the protected intrauterine environment, while the visual system remains relatively unstimulated prenatally. The intrauterine environment is buffered for the fetus by reducing concurrent or multimodal stimulation; likewise, the NICU environment aims to offer low stimulation to the tactile, vestibular, gustatory, and olfactory systems. Unfortunately, the type, timing, and amount of stimulation is substantially increased outside of the womb, including unfiltered auditory and visual stimulation. These are dramatically different from what nature intended for a developing fetus. Observation of each individual infant's physiologic and behavioral responses to the environment may assist caregivers and parents in determining the appropriate modifications and adaptations that will support the infant's continued stability and maintain functioning.

Therapeutic Handling and Positioning

The tactile sense is the first sensory system to develop in utero and is functional for pain, temperature, and pressure by of the time a fetus reaches viability. Tactile sensation forms the basis for early communication and is a powerful emotional exchange between infants and parents. Handling and positioning techniques promote comfort, minimize stress, and prevent deformities while creating a balance between nurturing care and necessary interventions. Touch, individualized to an infant's tolerance and thresholds, initiates the bond between the newborn and family. Balancing routine or adverse tactile stimulation such as procedures and tests with pleasurable or benign touch is essential. The type, timing, and amount of stimulation must be considered individually according to an infant's stability and medical condition.

Partnering with Families

The extent of handling can affect changes in infants. Premature infants demonstrate cry expression, grimacing, and knee and leg flexion during total reposition changes. Physiologic alterations in blood pressure, heart rate, and respiratory rhythm and rate occur with touch and handling. Hypoxemia can occur with non-painful or routine caregiving activities such as suctioning, repositioning, taking vital signs, diaper changes, and electrode removal. Those changes can be minimized with some handling techniques, including:

- Avoiding sudden postural changes by slowly turning an infant while containing extremities in a gently tucked, midline position.
- Use of blanket swaddling and hand containment to decrease physiologic and behavioral distress during routine care procedures such as bathing, weighing, and heel lance.
- Immediately returning infants to supportive positioning or swaddling after exams, tests, or procedures to avoid prolonged arousal, fluctuating vital signs, or both.

Skin-to-skin holding, also known as Kangaroo care (KC), stimulates all of the early developing senses. It provides warmth and the sensation of skin against skin (tactile), rhythmic rise and fall of chest (vestibular), scent of mother and breast milk if lactating (olfactory), and quiet parent speech and heartbeat (auditory). KC is appropriate as soon as an infant is stable enough to transfer to the parent's chest.

Benefits of Kangaroo care include:

- improved state organization including increased frequency and duration of sleep and less crying
- increased weight gain
- decreased nosocomial infection
- increased maternal milk volume and increased breast feeding at discharge
- maintenance of skin temperature
- less variability in heart rate and transcutaneous oxygen
- decreased apnea and/or bradycardia

Mothers who provide skin to skin holding or Kangaroo care (KC) report less depression and perceive their infants more positively than non-KC mothers. KC mothers are more responsive to infant cues, and their infants demonstrate more alerting and longer eye gaze with their mothers. KC is associated with increase in successful breast feeding. At 6 months, KC infants are more socially engaging and score

significantly higher on the Bayley Motor and Psychomotor developmental indices.

Kangaroo care practice can sometimes raise concerns of impairing cerebral blood flow during maneuvers from a resting position to a kangaroo care position. Cerebral monitoring of stable preterm infants showed a 2-5% decrease in cerebral oxygenation during maneuvers, however, the percentage did not reach statistical significance. A more recent study identified that kangaroo care actually improves cerebral blood flow in stable preterm infants after the infant was held for 30 minutes or longer. If a patient is unstable to transfer for kangaroo care, or if short visits are anticipated, it is recommended to encourage/teach parents "containment" or "hand hugs" to promote bonding.

Acuity, maturation, and behavioral responses of each infant change over time requiring continual reassessment of the amount, type, and timing of tactile interventions during the hospital course. Since touch can be disruptive to maturing sleep-wake states, avoid touching a sleeping infant for care or nurturing unless absolutely necessary.

Positioning

Prolonged immobility and decreased spontaneous movement increase the risk of position-related deformities. Factors associated with short- and long-term postural and motor abnormalities include illness, weakness, low muscle tone, immature motor control, and treatments such as ECMO and sedation.

Common malpositions include:

- abduction and external rotation of the hips
- shoulder retraction
- scapular adduction
- neck extension
- postural arching
- abnormal molding of the head

Primary goals for positioning are comfort, stability of physiologic systems, and functional posture and movement. Before birth, the uterus provides a flexible, circumferential boundary that facilitates physiologic flexion as the uterine space becomes limited during advancing pregnancy. In comparison, in the NICU infants may lie flat in an extended posture with extremities abducted and externally rotated while their heads are frequently positioned toward the right. In time, muscle contractures and repetitive postures can lead to abnormal posture and movement. Therapeutic positioning promotes neurobehavioral organization, musculoskeletal formation, and neuromotor functioning.

Containment

Infants who are unable to maintain a gently flexed position may benefit from containment using a blanket (or blankets) or commercial products to provide boundaries strategically placed to achieve a tucked, flexed position. Gentle, flexible boundaries contain while allowing controlled movements that promote flexor–extensor balance without the disorganization or stress of uncontrolled movement. Use of boundaries does not ensure appropriate positioning, and an infant's appearance and comfort are more important than commercial products or many blankets in a bed. Physical and occupational therapists are available to assist with appropriate positioning.

Just as in the womb, a newborn's postnatal resting posture is predisposed to physiologic flexion with some limited range of motion in knees, hips, elbows, and shoulders to support muscle strength and normal flexor–extensor balance over time. Daily physical activity of low birth weight preterm infants improves bone growth and development. Infants who are restless or who fight containment and who are able to maintain flexed postures unassisted are ready to gradually transition out of positioning aids and boundaries. Older infants with chronic cardiorespiratory or other prolonged health problems may need to keep their boundaries.

Correct Positioning

Correct positioning includes:

- neutral or slight flexion of the neck
- rounded shoulders
- flexed elbows and knees
- hands to face or in midline
- tucked body or trunk
- partial flexion of hips adducted to near midline
- lower boundary for foot-bracing or complete circumferential boundary that supports position and calms infants.

Each position has advantages and disadvantages.

Prone position - improves oxygenation and ventilation. Reflux is decreased when the head of the bed is raised about 30 degrees. Prone positioning places an infant at risk for flattened posture unless a prone roll is used.

Side lying - is the least studied position. It encourages midline orientation, hand-to-mouth activity, calming, and, with appropriate boundaries, a flexed, tucked position. Although some suggest that side lying may contribute to atelectasis of the dependent lung, no evidence supports this hypothesis.

Supine positioning - appears to be the least comfortable and most disorganizing position for preterm infants, with decreased arterial oxygen tension, lung compliance, and tidal volume compared to prone. However, since the supine position reduces the risk of SIDS, it is recommended for infants close to discharge and at home.

Proper Positioning Techniques

Proper positioning techniques can prevent the formation of positional deformities including:

- **Plagiocephaly** - abnormal molding of an infant's head shape due to external forces applied either pre- or postnatally.
- **Dolichocephaly** - lateral flattening or narrow, elongated head shape of preterm infants that occurs over time due to their soft, thin skulls.
- **Brachycephaly** - flattened occiput, alopecia (bald spot), and deformation of the ipsilateral ear and forehead.

- **Torticollis** ("twisted neck") - with limited movement and head tilted to one side due to shortening of the sternocleidomastoid muscle.

These conditions may be prevented by:

- using bedding with decreased interface pressure to reduce external forces against the vulnerable preterm head
- varying positions
- providing care and stimulation to infants from both sides of the bed

Products - Foam mattress overlays and gel products, including mattresses and pillows, exhibit the lowest interface pressures. Memory foam bedding accentuates preterm head molding. One goal of these products is to prevent brachycephaly (recommended by the American Academy of Pediatrics through the "tummy to play" program). Once brachycephaly occurs, physical therapy, helmets, or both are required for progressive head reshaping. Surgery is not usually required unless the scalp deformation includes craniosynostosis.

Multidisciplinary Team - The team concept that underlies neonatal care also extends to developmental care.

- Child life specialists and clinical nurse specialists facilitate therapeutic positioning and handling, create individual positioning and handling plans, teach staff and parents general principles of positioning and handling, and teach parents infant massage. Music therapy is available through the child life department.
- Occupational and physical therapists facilitate therapeutic positioning and therapeutic touch, increase handling tolerance of sensitive infants, improve oral-motor function, enhance movement and equilibrium, support improved motor patterns, foster relaxation and sensory integration, create or order appropriate assistive devices (e.g., kid cart, tumble form chair), and teach parents infant massage.
- Speech and language therapists may advise regarding speaker valve use in infants who have tracheostomies and early language/communication needs.
- Developmental assessment provides individualized risk, neurodevelopmental and behavioral evaluations, evidence-based recommendations, parent/family counseling support and multidisciplinary collaboration.
- Department of Physical Medicine and Rehabilitation consults may be helpful in cases with persistent tone/mobility issues.
- Social workers provide psychosocial family and community resource support.

Environmental Factors

Tastes and Odors

Infants frequently are exposed to unpleasant scents such as alcohol and povidone iodine. Taste rarely is stimulated prior to oral feeding. Some evidence suggests that:

- olfactory and gustatory learning begins in utero
- preterm infants around 26 weeks' gestational age prefer sweet to bitter taste
- maternal odor reduces crying and increases mouthing behaviors
- the sweetness of sucrose modulates pain response in term and preterm infants

Exposure to biologically meaningful odors and tastes such as maternal scent, colostrum, and breastmilk eventually might prove beneficial as a means of fostering parent recognition, calming, and pleasurable experience. Even infants who are not yet orally fed might enjoy the scent of milk or a small taste of breast milk applied to the lips.

Sound

The acoustic environment of the NICU has not been implicated in hearing loss but might influence auditory processing and language development of NICU graduates. Acoustic stimulation results in physiologic responses in a fetus as early as 23 to 25 weeks' gestation. In the womb, exposure to sound is primarily to maternal sounds, the most important being the mother's voice. In the NICU, sound is unpredictable and does not reflect the intrauterine or normal home environment that is important for auditory and language development.

Effects of Sound

Sudden loud sounds in the NICU cause physiologic and behavioral responses in term and preterm infants including sleep disruption, agitation, crying, avoidance behaviors, tachycardia/bradycardia, tachypnea, irregular respiration/apnea, decreased oxygen saturations, mottled skin, peripheral vasoconstriction or increased systemic blood pressure. Such disruptions can interfere with an infant's clinical progress and stable behavioral functioning. It has not been established whether sounds in the NICU are related, directly or indirectly, to delays in speech and language development and problems in articulation and auditory processing, which are observed in higher rates in preterm infants than in full term infants.

Concerns include the potential disruption of developing auditory and communication pathways by sound distortion, irrelevant noise, and interference with maternal and paternal sounds during critical periods of development. Infants' sensitivity to environmental noise is demonstrated by how easily sleep is disrupted. Noise levels from 70 to 75 dB disrupt sleep states in one half of healthy term infants after only 3 minutes and in all infants after 12 minutes. Many infants wake from light sleep after exposure to just 55 to 65 dB. Preterm infants are in light sleep for almost 70% of the day, causing them to be particularly vulnerable to fluctuating sound levels.

Interventions

The best available evidence suggests that a background noise level of 50 dB is desirable, with noise exceeding 55 dB only 10% of the time and noise never exceeding 70 dB. An ongoing sound measurement program is an essential component of this approach including consideration of the following:

- An infant's exposure to sound should include time with parents in a quiet, ambient environment that does not interfere with normal speech.
- Although earphones or earplugs are not recommended, brief use of neonatal ear protection devices might be necessary during tests such as magnetic resonance imaging or other procedures known to produce loud noises.

- Personnel are a main source of sound in the NICU. Practical sound limitation measures include:
  - » speak in low to moderate volumes
  - » conduct rounds and report away from the bedside of sleeping or sound sensitive infants
  - » keep pagers and phones on vibrate mode
  - » avoid placing equipment on top of incubators
- Rouse infants gently with soft speech or gentle touch to prevent rapid state changes before examination or other tactile procedures.
- Encourage parent-infant time together.
- Limit time when musical mobiles or tapes are used until older pre-term or term infants demonstrate ongoing physiologic and behavioral stability during auditory supplementation.

All NICU staff must work together toward minimizing the potential detrimental influence of the sound environment while promoting natural parent involvement to support opportunities for auditory development.

Light, Vision, and Biologic Rhythms

The visual system receives little stimulation in the uterus. As a result, preterm infants, in particular, are ill-prepared for the intense visual stimulation of the NICU because maturation and differentiation of retinal connections to the visual cortex develop in the NICU rather than during the last trimester in utero. Early stimulation of the immature visual system in animal models alters development of the visual system as well as other sensory systems.

Effects of Light

Light has not been implicated in the development of retinopathy of prematurity. Studies that recommend reduced lighting or cycled lighting have not included long-term follow-up on the impact of either strategy on the developing visual system or other sensory systems, other ophthalmic sequelae, or disturbances in visual processing. Although studies using reduced lighting for preterm infants demonstrate no short- term negative effect on vision or medical outcomes, abrupt increases in lighting can result in decreased oxygen saturation in preterm infants. Evidence is insufficient to show that day-to-night cycling of light supports earlier development of circadian rhythm in preterm infants.

For acutely ill and preterm infants, reduced lighting appears to be a safe alternative to continuous, bright lighting in the NICU. Providing cycled lighting from 34 weeks may be beneficial. Development of circadian rhythm is more likely to be supported by infant maturation, cycled lighting, and decreased nighttime disruptions for care.

Preterm infants demonstrate brief alerting and attention around 30 to 32 weeks but can easily become stressed and disorganized by the effort. Careful attention to physiologic and behavioral manifestations of each infant, term or preterm, provides information concerning individual tolerance for light and visual stimulation.

Parents: The Natural Environment

The most natural environment possible for any infant includes the touch of the mother or father's chest, the gentle motion of rocking or of parents' breathing, the odor and taste of breast milk, and the scents, tender vocalizations, and heartbeats of the parents. The case for providing these experiences as early and as often as possible is compelling.

When a visit to the hospital is impossible, difficult, or inconvenient, parents of infants born at certain outlying hospitals may use Family Vision. This is a program offered by Neonatal Telemedicine, using videoconferencing technologies to enable families to see their infants and speak to their nurses. This option, especially appealing to mothers who have just delivered, remains available after mothers are discharged. Family members, including siblings, may participate. Residents, fellows, nurse practitioners, and attending physicians are notified by text page of a visit scheduled to one of their patients; as with an actual bedside visit, participation is welcome and encouraged but is not necessary. Members of the medical team may initiate a visit if doing so would aid in communication with the family. We are systematically evaluating how family participation in this program affects bonding, stress, and trust.

Infection Control

Please refer to **Ch 8.1-Infection Control and Prevention**.

4.2 Thermal Regulation

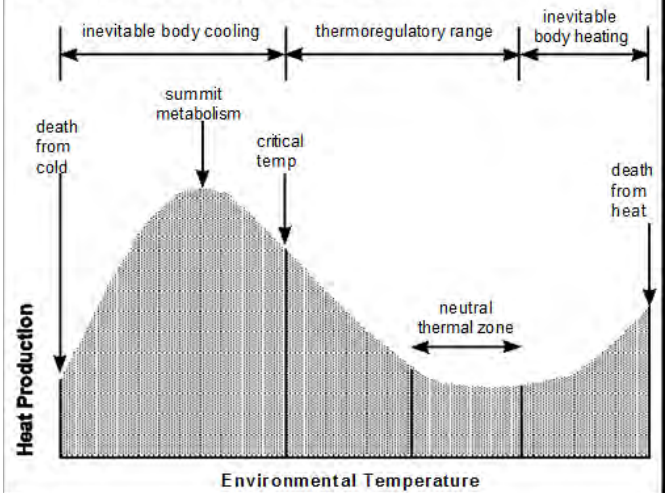
Large surface area and increased thermal conductance (poor insulation) accelerate heat loss in infants. This is exacerbated by immature skin development, and an overall thinner epidermal layer in preterm newborns. Evaporative heat loss is increased by bathing or failure to dry off amniotic fluid. Heat loss by radiation to cold incubator walls or objects in a cold delivery room is a major cause of thermal stress in babies. Estimated heat loss by infants in the delivery room may be as high as 200 kcal/kg per minute, which far exceeds their maximal heat production. Core temperature may fall 2°C (3.6°F) within 15 minutes after delivery **(Table 4–1).**

Placement of the baby away from a window and the use of warmth maintaining hats provide additional protection against excess heat loss.

Table 4-1. Sources of heat loss in infant

Type of heat loss	Environmental temperature		
	30°C (86°F)	33°C (91°F)	36°C (97°F)
Radiation: cool room and walls	43%	40%	34%
Convection: breezy air currents	37%	33%	19%
Evaporation: not dried quickly	16%	24%	56%
Conduction: cold blankets on warmer	5%	3%	1%

Figure 4-1. Effects of environmental temperature on oxygen consumption and body temperature



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Responses to Cold Environment

Shivering - involuntary muscular activity.

Voluntary muscular activity - not very important in babies.

Non-shivering thermogenesis - a major mechanism of heat production in infancy, which is under CNS control (mediated by the hypothalamus). This mechanism is induced by epinephrine via oxidation of fat (especially active in brown fat deposits). Temperature receptors in the trigeminal nerve distribution of the face are particularly sensitive to cold mist or oxygen. Measured oxygen consumption is the best indicator of heat loss and heat production. Oxygen consumption may increase up to 2.5 times basal levels at air temperature 28° to 29°C (82° to 84°F). In a cold environment, first a rise in oxygen consumption and endogenous heat production occurs then a fall in skin and core temperature if heat loss continues to exceed heat production **(Fig 4-1)**. Hypoxia inhibits the metabolic response to cold.

Consequences of Thermal Stress

- Increased oxygen consumption and carbon dioxide production. Oxygen uptake and carbon dioxide excretion already may be impaired if respiratory disease is present.
- Acidemia.
- Increased norepinephrine secretion causing pulmonary vasoconstriction.
- Increased affinity of hemoglobin for oxygen, which causes impaired release at tissue level.
- Increased free fatty acids, which compete with bilirubin for albumin binding.

Preterm infants are especially vulnerable and severe hypothermia is directly correlated with preterm mortality. Hypothermia is also associated with serious morbidities, such as increased respiratory issues, hypoglycemia, and late-onset sepsis. Because of this, admission temperature should be recorded as a predictor of outcomes as well as a quality indicator (Class I, LOE B-NR).

Hypothermia implies heat loss exceeding heat production. The response varies among infants of different size and gestational age, but cooling may trigger a hypermetabolic response leading to agitation, tachypnea, tachycardia and acidosis. Slow rewarming (0.5°C/h) of unintentionally hypothermic newborns (temperature less than 36°C) may be prudent at hospital admission. The simplest approach is to place infant under a radiant warmer with servo control of anterior abdominal wall skin temperature and set point at 36.5°C. Monitor infant temperature closely. Apnea or hypoglycemia may occur during rewarming, even in more mature infants. Remember: hypothermia may be a subtle sign of sepsis, especially in preterm infants.

Normal Temperature Ranges

Axillary temperatures: 36.5-37.4 °C (97.7-99.3 °F) for term and preterm infants in open crib. **(AAP/ACOG 2012)** It is recommended that the temperature of newly born non-asphyxiated infants be maintained between 36.5°C and 37.5°C after birth through admission and stabilization.

Core temperatures: 36.5-37.5°C (97.7-99.5°F) for term and preterm infants. (Ranges reported in numerous oxygen consumption studies when O_2 consumption minimal)

Recommended room temperature for neonatal care units - 22-26°C (72-78°F). **(AAP/ACOG 2007)**

Management

Delivery Room

Recommended DR air temperature:

- NRP 7th edition – 23-25°C (74-77°F)
- The goal is an axillary temperature between 36.5°C and 37.5°C (97.7°F -99.5°F).

Dry off amniotic fluid thoroughly and remove any wet linens. Perform resuscitation and stabilization under a preheated radiant warmer. Minimize evaporative and radiant losses in neonates born at less than 32 weeks gestation by covering infant or swaddling in a plastic bag or with plastic wrap blanket.

The addition of a thermal mattress, warmed humidified gases, and increased room temperature were all effective in reducing hypothermia. For all the studies, hyperthermia was a concern, but harm was not shown. Hyperthermia (greater than 38.0°C) should be avoided due to the potential associated risks

Early skin-to-skin contact should be the normal initial practice for healthy newborns including those born by cesarean delivery at 35 weeks gestation or more.

Transport

Use a transport incubator with air temperature initially adjusted according to **Table 4–2**. Plastic bags and stocking caps can be additional measures to minimize heat loss. Gel warming pads may also be used to prevent hypothermia when the infant is removed from its heated environment. Thermal environment should be adequate to keep axillary temperature in the range of 97.7° to 99.5°F.

NICU Admission

- Place infant < 32 weeks and/or < 1250 grams in a pre-warmed convertible incubator (e.g. Giraffe Omnibed®).

Table 4-2. Neutral thermal environmental temperatures: Suggested starting incubator air temperature for clinical approximation of a neutral thermal environment

Age and Weight		Temperature (°C)	
		Starting	Range
0-6 h	<1200 g	35.0	34-35.4
	1200-1500 g	34.1	33.9-34.4
	1500-2500 g	33.4	32.8-33.8
	>2500 g[1]	32.9	32-33.8
6-12 h	<1200 g	35.0	34-35.4
	1200-1500 g	34.0	33.5-34.3
	1500-2500 g	33.1	32.2-33.8
	>2500 g[1]	32.8	31.4-33.8
12-24 h	<1200 g	34.0	34-35.4
	1200-1500 g	33.8	33.9-34.3
	1500-2500 g	32.8	31.8-33.8
	>2500 g[1]	32.4	31-33.7
24-36 h	<1200 g	34.0	34-35
	1200-1500 g	33.6	33.1-34.2
	1500-2500 g	32.8	31.6-33.6
	>2500 g[1]	32.1	30.7-33.5
36-48 h	<1200 g	34.0	34-35
	1200-1500 g	33.5	33-34.1
	1500-2500 g	32.5	34.1-33.5
	>2500 g[1]	31.9	32.5-33.3
48-72 h	<1200 g	34.0	34-35
	1200-1500 g	33.5	33-34
	1500-2500 g	32.3	31.2-33.4
	>2500 g[1]	31.7	30.1-33.2
72-96 h	<1200 g	34.0	34-35
	1200-1500 g	33.5	32-34
	1500-2500 g	32.3	31.1-33.2
	>2500 g[1]	31.3	29.8-32.8
4-12 d	<1500 g	33.5	33-34
	1500-2500 g	32.1	31-33.2
	>2500 g[1]		
	4-5 d	31.0	29.5-32.6
	5-6 d	30.9	29.4-32.3
	6-8 d	30.6	29-32.2
	8-10 d	30.3	29-31.8
	10-12 d	30.1	29-31.4
12-14 d	<1500 g	33.5	32.6-34
	1500-2500 g	32.1	31-33.2
	>2500 g[1]	29.8	29-30.8
2-3 wk	<1500 g	33.1	32.2-34
	1500-2500 g	31.7	30.5-33
3-4 wk	<1500 g	32.6	31.6-33.6
	1500-2500 g	30.9	30-32.7
4-5 wk	<1500 g	32.0	31.2-33
	1500-2500 g	30.9	29.5-32.2
5-6 wk	<1500 g	31.4	30.6-32.3
	1500-2500 g	30.4	29-31.8

[1]as well as >36 weeks' corrected gestation

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These devices can be operated in either the closed incubator mode or open radiant warmer mode. For ELBW babies the incubator mode is often combined with a high humidity (80%) environment during the first 7 days of life.

- It is recommended to keep the plastic wrap over the preterm infant until goal humidity level is attained in the incubator to reduce insensible water losses.
- Place infants between 32 and 35 weeks and > 1250 grams in a pre-warmed standard incubator.
- Place infants > 35 weeks and/or 1700 grams on a pre-warmed radiant warmer or open crib.
- For infants who are medically stable, consider kangaroo care with parents as a tool for thermoregulation.

Incubators

Recent model incubators provide two options for control of heater output:

1. Servo control of skin temperature ("Baby Control") or
2. Automated control of incubator air temperature ("Air Control").

Automatic control of incubator air temperature - In this mode the incubator can be programmed to automatically maintain air temperature at a value pre-selected by the user. Initial air temperature setting is selected from a temperature data set such as **Table 4-2** or that contained in the incubator computer. Infant axillary temperature is monitored periodically and the desired air temperature setting is progressively reduced as the infant matures. This mode is appropriate for larger, more mature and stable infants. This should not be confused with servo control of skin temperature as discussed below.

Servo control of skin surface temperature - used for smaller, younger, less stable infants or those with significant apnea. Provides the most rigid control of environmental temperature and produces the lowest, most consistent metabolic rate. Set the servo control to maintain anterior abdominal wall skin temperature between 36.2°C and 36.5°C, which clinically approximates the neutral thermal environment with minimal oxygen consumption. Axillary temperature usually is maintained in the 97.7° to 99.5°F range. If the servo set point must be below 36.2°C to keep axillary temperature below 99.5° F and equipment is functioning properly with no evidence of infection, the infant may be too mature for the servo control environment. Consider switching to a manual control incubator or open crib.

Hybrid incubators (Giraffe Omnibed® or similar model) - hybrid incubators of this type are preferred for infants less than 32 weeks' gestational age or 1250 grams at birth. This incubator may be used either as a radiant warmer or an incubator. When used as an incubator, the Omnibed® allows humidification of the environment, which can significantly decrease insensible water/heat losses, and radiant heat loss by the baby. An in-bed scale makes it easier to obtain frequent weights on the baby for assistance in fluid and nutritional management.

Radiant Warmers

Manual temperature control - avoid using this mode because of dangers of severe overheating If used to pre-warm the bed, heater power should not be set above 75% maximum.

Servo control of skin temperature - use for all infants requiring open access care under a radiant warmer. Radiant warmers do little to decrease heat loss but provide powerful heat replacement at the expense of increased evaporative water loss. Set servo control to maintain anterior abdominal skin temperature at 36.2° to 36.5°C to minimize metabolic rate and apnea. Under such circumstances, axillary temperature usually is in the range of 97.7° to 99.5° F. If temperature falls out of this range, care provider should evaluate carefully for evidence of equipment malfunction, excessive sources of heat loss or gain or possible infection.

Weaning

Weaning Incubator Servo Control Mode to Automatic Air Control Mode

Begin weaning from skin temperature servo control to air control mode when infant is clinically stable, heat requirements are decreasing and infant weighs at least 1250 grams. Place infant on air control mode while dressed in clothes, hat, diaper and/or blanket. Some babies who are stable and maturing rapidly may not require this step, since their incubator air operating temperature may have already been decreased to the range of 28.5°C by the skin temperature servo control mechanism.

Weaning Incubator Air Control to Open Crib

Weaning should begin when the following criteria have been met:

- Infant is > 1500 grams or > 34 weeks gestation
- Tolerance of enteral feeds
- Five (5) days of consistent weight gain
  - » (< 38 weeks: 10-20 g/kg/day)
  - » (> 38 weeks: 20-30 g/kg/day)
- Only occasional brief apnea/bradycardia episodes
- Physiologically stable
- Minimal incubator air temperature of < 28ºC for at least 8 hours
- Consider the size of the infant: LGA, SGA, the mature preterm infant, and the IUGR patients when weaning external heat source.

Delay in weaning preterm infants to an open crib is associated with prolongation of hospitalization and delay in achieving full oral feeding. Current evidence suggests incubator weaning can begin when most infants reach 1500g or 34 weeks. When infant can maintain axillary temperature in the normal range with incubator air temperature of approximately 28-28.5ºC, infant may be placed in an open crib with frequent temperature monitoring initially

Ancillary Measures

Swaddling - decreases heat loss in open cribs or standard incubators by increasing insulation at skin surface. Stocking caps should be used also.

Plastic Wrap Blanket - decreases evaporative water loss under radiant warmers and, therefore, reduces evaporative heat loss. Can also be used to reduce radiant heat loss in an incubator. Infants less than 1250 grams should be admitted directly into a hybrid incubator when available**.** Humidification of the environment obviates the need for a plastic wrap blanket. It is recommended to keep the plastic wrap over the preterm infant until goal humidity level is attained in the incubator to reduce insensible water losses.

Humidity - decreased transepidermal water loss and minimizes evaporative heat loss. Increased humidity (80%) is recommended for all infants < 29 weeks and/ or < 1250 grams for the first 7 days of life.

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Section 5: Gastroenterology

Editors: Amy Hair and Muralidhar Premkumar

5.1 Spontaneous Intestinal Perforation (SIP) and Necrotizing Enterocolitis (NEC)

Spontaneous Intestinal Perforation (SIP)

SIP is an abdominal emergency most commonly seen within the first 10 days of life and the prevalence is 2% in VLBW and 3% in ELBW infants. Median gestational age of affected neonates is 26 weeks, with a male predominance. SIP typically occurs in the terminal ileum but unlike NEC the perforation is isolated with well-defined margins and focal hemorrhage.

Risk Factors

Prematurity, chorioamnionitis, early exposure (<8 days of age) to postnatal dexamethasone, and concurrent use of both indomethacin and hydrocortisone increase the risk of SIP. The correlation between SIP and either postnatal hydrocortisone or indomethacin exposure alone is not clear. Infection with coagulase-negative *Staphylococcus* or *Candida albicans* have been described in SIP but whether these infections occur before or after SIP is unknown.

Presentation

Acute onset abdominal distension with hypotension in the first week (range 0-15 days) of life should raise the concern for SIP. The abdominal wall can often have a blue-black discoloration, which differs from the typical erythema seen in NEC.

Diagnosis

SIP should be strongly suspected based on clinical findings in an infant in the first 10 days of life. Definitive diagnosis is based on operative findings of an isolated perforation with otherwise normal bowel.

Abdominal radiograph in the supine and left lateral decubitus position should be obtained in evaluation of an infant with suspected SIP. Findings may include pneumoperitoneum or a gasless abdomen without evidence of pneumatosis intestinalis or portal venous gas. Ultrasound may show echogenic free fluid. Laboratory studies may indicate leukocytosis, anemia, thrombocytopenia and elevated serum bilirubin and alkaline phosphatase.

Treatment

Initial management of infants affected by SIP includes cessation of enteral feedings, nasogastric decompression, intravenous antibiotics, appropriate parenteral nutrition, stabilization with fluid resuscitation and use of inotropic medication if clinically indicated. IV antibiotics including ampicillin, gentamicin, and metronidazole should be administered as suggested in **Table 5-1.** Pediatric surgery should be consulted immediately. The definitive treatment for SIP is surgery.

Surgical options consist of:

- Placing a percutaneous peritoneal drain (PPD), or
- Performing an exploratory laparotomy with bowel resection

Percutaneous peritoneal drain (PPD) is a bedside procedure that avoids the risks of anesthesia and laparotomy in severely ill infants. Once inserted, the drain should be monitored closely and gradually backed out once drainage has ceased. Laparotomy is often reserved in cases of re-accumulation of free air in the abdomen, ongoing sepsis, fistula formation, or bowel obstruction. Long-term survival is comparable in both the surgical techniques. Pending the results of the recently concluded randomized control trials, currently there is no strong evidence to suggest that one surgical approach is superior. However, 50-60% of those infants who undergo PPD do not require subsequent laparotomies.

After return of normal bowel function, enteral feedings may be reinitiated gradually. Contrast studies may be required if gastrointestinal tract patency is uncertain, as these patients can develop bowel obstructions later in life due to strictures.

Long-term mortality of SIP is lower than that of NEC. When compared to surgical NEC, infants affected by SIP have similar risks of combined death or neurodevelopmental impairment, but greater risks of ROP, IVH and white matter injury.

Necrotizing Enterocolitis (NEC)

NEC is the most common abdominal emergency in preterm infants. It occurs in 3% to 10% of VLBW infants and occasionally occurs in late preterm or full-term infants with

Table 5-1. Consensus-based guidelines for antibiotic therapy in gastrointestinal patients

Diagnosis	Suggested Treatment Regimen	Alternate Treatment Regimen	Maximum Duration of Therapy
Medical NEC without evidence of pneumatosis	Ampicillin, Amikacin	Piperacillin and Tazobactam (Zosyn®)[1]	7 days
Medical NEC with evidence of pneumatosis	Ampicillin, Amikacin, and Metronidazole	Piperacillin and Tazobactam (Zosyn®)[1]	7 days
Surgical NEC or spontaneous intestinal perforation or post-abdominal drain placement or post-laparotomy	Ampicillin, Amikacin, and Metronidazole	Piperacillin and Tazobactam (Zosyn®)[1]	10 days
Small bowel atresia repair or gastroschisis abdominal closure	Cefazolin for perioperative coverage or Cefoxitin for patients needing anaerobic coverage	n/a	Until skin closure only

[1] Should only be used in select cases when routine antibiotic coverage is deemed to be indadequate based on antibiotic susceptibility patterns or failure to improve on the standard regimen.

predisposing conditions (congenital heart disease, gastroschisis and severe IUGR). Mortality can be as high as 30% with a high rate of intestinal and neurodevelopmental sequelae.

Prevention

There are no absolute methods for preventing NEC. In VLBW infants, use of an exclusive human milk diet and adherence to feeding protocols can reduce the overall incidence of NEC to < 5% and NEC requiring surgery within 2 weeks of onset to about 1%. Whether these strategies may successfully be used in other high-risk groups, including babies with some forms of congenital heart disease or abdominal wall defects is unknown.

Early attention to clinical symptoms of feeding intolerance including abdominal distension, bloody stools, and emesis is essential. However, reliance on occult blood measurement is not effective in identifying developing NEC.

Presentation

Infants who have NEC can present with abdominal distension, feeding intolerance, emesis, bilious residuals, gross rectal bleeding, diarrhea, and/or abdominal wall erythema with or without crepitus or induration of the abdominal skin. Systemic manifestations are like those of sepsis. Symptoms may progress to frank apnea and bradycardia followed by cardiovascular collapse.

Diagnosis

The differential diagnoses include ileus secondary to sepsis, spontaneous intestinal perforation (SIP), meconium peritonitis, Hirschsprung-associated enterocolitis, cow's milk protein intolerance, malrotation with volvulus and acute intestinal obstruction.

The clear presence of pneumatosis intestinalis is diagnostic in the presence of other clinical symptoms, especially bloody stools. Other laboratory data that support NEC include thrombocytopenia, neutropenia, disseminated intravascular coagulation (DIC), elevated lactic acid levels, and electrolyte abnormalities including hyperkalemia and hyponatremia.

Laboratory evaluation often includes:

- Cultures of blood, cerebrospinal fluid, and urine, (catheterized urine sample in infants > 1500 g, no bladder taps should be done)
- CBC, electrolytes, BUN, and creatinine
- Blood gas
- Lactic acid level

Serial AP abdominal films, with or without left lateral decubitus film, are performed approximately every 6 to 12 hours to monitor for pneumatosis intestinalis, portal venous gas, perforation, fixed dilated loops of bowel or worsening bowel gas pattern.

Treatment

For suspected or proven cases of NEC, enteral feeding is discontinued, and parenteral nutrition (PN) is initiated. A Replogle tube should be placed to low intermittent suction for decompression of GI tract. Usually, suction is continued until clinical symptoms such as ileus and pneumatosis resolve.

Parenteral antibiotic therapy is initiated and continued based on the severity of NEC as suggested in **Table 5-1**.

Pediatric surgery should be consulted early in the disease course. Patients with suspected NEC who have resolution of radiographic findings and return of a normal clinical exam and bowel function within 48 to 72 hours may be candidates for early re-feeding at 5 days after the initial presentation. The most common indication for surgery is pneumoperitoneum. Other indications may include rapid clinical deterioration, development of intestinal mass or obstruction, or radiographic appearance of a fixed loop of bowel.

Surgical choices consist of:

- Performing an exploratory laparotomy with or without staged resection and enterostomy, or
- Placing a primary peritoneal drain (PPD).

Despite the potential interventions and optimal medical management, the mortality rate remains between 10% and 30%.

Complications that can occur after NEC include short bowel syndrome with malabsorption, intestinal stricture formation, intestinal failure, intestinal failure-associated liver disease, growth failure, and long-term neuromorbidity.

5.2 Intestinal Failure and Intestinal Rehabilitation

Intestinal failure (IF) is a condition of malabsorption that results from small bowel resection, congenital anatomical defect, or functional dysmotility that requires prolonged parenteral nutrition (PN).

Currently, infants with very short remaining bowel segments are candidates for long-term intestinal rehabilitation. Normal bowel length for a term infant is approximately 200 to 250 cm and is generally half that length in premature infants born less than 30 weeks gestation. With multi-disciplinary care, newer generation lipid injectable emulsions (ILE), and better infection control measures, the survival in infants with short bowel syndrome at our institution is 95-100% irrespective of the residual bowel length (RBL). However, the likelihood of achieving enteral autonomy (EA) is dependent on RBL

- In infants with RBL > 30 cm, 70-95% achieved EA by age of 4-14 months.
- In infants with RBL < 30 cm, only 50% achieved EA by median follow up age of 18-30 months.

Importance

The management of infants with IF is clinically challenging. Close monitoring is needed to ensure proper growth and nutrition as well as to recognize and treat associated complications. Although the survival of these patients has improved with the advent of PN, there is still significant morbidity associated with this form of nutrition including prolonged hospitalization, dependency on central venous catheters for PN, bloodstream infections, and intestinal failure-associated liver disease (IFALD). IFALD is defined as elevation of conjugated bilirubin ≥ 2 mg/dL with prolonged dependence on parenteral nutrition (≥14 days) in the absence

of other causes of cholestasis. An important goal is to promote intestinal adaptation as early as possible in order to transition patients to full enteral nutrition while maintaining adequate nutrition and growth velocity. A multidisciplinary approach with coordinated efforts from the neonatology, nutrition, gastroenterology, and surgical teams is key to successful intestinal rehabilitation.

Goals

The primary goal is to identify patients at high-risk for the development of IF and subsequent complications in order to formulate a multidisciplinary management plan early in the clinical course to maximize intestinal rehabilitation and provide liver protection from IFALD.

Short-term Goals

Short-term goals include early initiation of minimal enteral nutrition to begin the bowel adaptive process. Human milk, either mother's own milk or donor milk, is the preferred choice for these feedings because of the immunoglobulins and trophic factors it contains. However, if malabsorption and feeding intolerance persist, an amino acid-based formula may be necessary. Bottle or breast feedings, even in small volumes, should be considered if the infant is deemed ready to tolerate enteral nutrition (EN). This proactive approach to initiate oral feeding can potentially reduce oral aversion and aid in the rehabilitative process.

Long-term Goals

Intestinal growth and adaptation is a slow and progressive process, and advances in EN need to be undertaken with this in mind. In severe cases of IF, the goal of EA might not be achieved during hospitalization. Such infants will require home PN until that goal is achieved. Frequent re-evaluation of progress in EN intake and careful monitoring for IFALD must be undertaken. Discharge planning, including cycling of PN and initiation of post-discharge teaching, should be initiated well in advance of planned discharge if home PN is to be used.

Patient Population at Texas Children's Hospital

High-Risk Conditions

In the conditions listed below, the intestinal rehabilitation attending will approach the primary neonatologist, regardless of formal consult status, and offer to participate in the care of the infant with IF.

The conditions under the high-risk group include the following:

- Short bowel syndrome (SBS) defined as < 60 cm of remaining intestine
- Ultra-short bowel syndrome defined as < 30 cm of remaining intestine
- Necrotizing enterocolitis: surgical NEC
- Complex gastroschisis and large omphalocele
- Parenteral nutrition dependence for more than 4 weeks with intestinal failure (anatomic or functional)
- Intestinal failure (anatomic or functional) with history of multiple failed feeding attempts and PN dependence
- Infant with IFALD (conjugated bilirubin ≥ 2 mg/dL) and PN dependence (these infants benefit from Omegaven®).

Low-Risk Conditions

The consultation will be initiated only at the request of the primary team.

The conditions under the low-risk group include the following but are not limited to:

- Necrotizing enterocolitis: medical NEC Stage 2 or greater (not requiring surgical resection)
- Existing or anticipated parental nutrition dependence for 2 or more weeks following any of the following:
- Acquired
  - » Spontaneous intestinal perforation
  - » Malrotation with volvulus
- Congenital
  - » Simple Gastroschisis
  - » Small Omphalocele
  - » Any intestinal atresia
  - » Bowel malformations (i.e. meconium ileus)
- Persistence of growth failure for more than 4 weeks on EN.
- Removal of any length of intestines following any of the above conditions

Consult to NICU Intestinal Rehabilitation Team

- To consult the NICU Intestinal Rehabilitation team, under the order tab search for "NICU IR".
- The consult name is "IP Consult to Intestinal Rehabilitation (NICU)" and the Px Code is CON304825.
- Complete the required fields and accept and sign the order.

Initiation of Parenteral Nutrition

Place a central line for PN at time of diagnosis (or as soon as medically able if undergoing sepsis evaluation) in infants with the following diagnoses:

- Abdominal wall defects (gastroschisis, omphalocele)
- Major bowel defects (malrotation, volvulus, atresias)
- Medical NEC - Stage 2 or greater
- Intestinal perforations
- Significant growth failure on full fortified enteral feedings

In general, start with Neo PICC by the Vascular Access Team (VAT) and reserve Interventional Radiology (IR)/surgically placed lines for long-term PN (and home PN) or if unable to obtain peripheral PICC line by VAT.

- Central lines at discharge for home PN
- Generally placed by interventional radiology
- Specify upper extremity *"Internal Jugular Approach"* IR line-tunneled, cuffed, single lumen; also called the "*NICU Intestinal Rehabilitation Protocol for IR lines."*

Initiate PN as per nutrition guidelines and advance as tolerated to provide 90 -100 kcal/kg/day and 3.5-4 g protein/kg/day (preterm infants) and 2-3 g protein/kg/day (term infants). Higher macronutrient intakes may be required to promote adequate growth in this population. SMOFlipid ® is recommended as the ILE of choice in infants with IF to provide nutrition and prevent IFALD. (weak recommendation, low to very low quality of evidence)

Initiation of Enteral Nutrition

After evidence of bowel function, when medically feasible, start trophic feedings at 10-20 mL/kg/day of preferably mother's own milk (maternal EBM), donor human milk (donor EBM) if maternal EBM is not available, or appropriate formula (typically elemental formula).

- In the presence of cholestasis (conjugated bilirubin ≥ 2.0 mg/dL), may consider use of elemental formula for initial feedings rather than donor EBM if maternal EBM not available.
- Feedings should be provided via continuous infusion for infants with short bowel syndrome, complex gastroschisis, or with previously demonstrated intolerance to bolus/oral feedings.
- Some infants may tolerate initiation of enteral feedings with bolus feedings.
- For infants with simple gastroschisis or small omphalocele that are greater than 34 weeks post-menstrual age, may consider providing oral feedings as tolerated and medically appropriate.

If unable to start EN, after discussion with surgery and NICU Intestinal Rehabilitation Team, the team may consider contrast studies as medically appropriate to rule out anatomic or functional dysmotility.

Advancement of Enteral Nutrition

Feeding Advancement Protocols are categorized into High, Medium, and Low Risk by level of concern for intolerance of EN based on surgical history, RBL, and clinical course (**Table 5-2**). EN should provide 110-130 kcal/kg/day and 3.5-4.5 g protein/kg/day (preterm infants) and 2-3 g protein/kg/day (term infants). For older infants, nutrient needs to maintain appropriate growth velocity may be less. Monitor growth and adjust estimated needs accordingly. Infants should demonstrate appropriate growth on home nutrition regimen prior to discharge.

Fortification Strategies

Fortification strategies should be individualized and are dependent on the infant's gestational age, weight, gastrointestinal history, previous feeding history, and the presence of cholestasis. Strategies utilized may include donor human milk-based fortifier, bovine milk-based fortifier, elemental formula, preterm formula, and transitional or term

Table 5-2. Feeding advancement protocols

	High Risk	Medium Risk	Low Risk
Definition	• Ultra-Short Bowel infants (Typically defined as < 30 cm of remaining intestine)	• Infants with previous intolerance to bolus/oral feedings or anticipated need for partial long-term PN support	• Infants without history of short-term feeding intolerance that are expected to reach full EN during admission
Initiation[1]	• Initiate continuous feedings at approximately 10 ml/kg/day or 0.5 ml/hr.	• Maintain trophic feedings for a minimum of 3 days for infants <1250 g at birth. • May consider providing trophic feedings in larger infants to establish tolerance prior to advancement.	• Maintain trophic feedings for a minimum of 3 days for infants <1250 g at birth. • May consider providing trophic feedings in larger infants to establish tolerance prior to advancement.
Advancement[2]	• Advancement interval will be individualized and determined after a collaborative discussion with NICU Intestinal Rehabilitation Team.	• Advance by 10 mL/kg every 2-3 days as tolerated. • Twice weekly volume advancements typically occur on Mondays and Thursdays. • If anticipated or proven inability to maintain age-appropriate weight gain and linear growth velocity, regardless of feeding tolerance, some infants may require partial PN in conjunction with EN for an extended period of time. • Typically partial PN volume of at least 50 mL/kg/day is required to meet the need for additional nutritional intake.	• Advance feedings as tolerated by 10-20 mL/kg/day (20 mL/kg/day should be standard for most babies).

[1] Consider initiation of enteral nutrition if gastrointestinal output (Replogle, g-tube or ostomy) is stable and approximately 20 mL/kg/day or less.
[2] Ensure EN provided at an appropriate caloric density (fortify as needed) prior to the discontinuation of PN.

Table 5-3. Laboratory monitoring for patients requiring parenteral nutrition[1]	
Frequency of Monitoring	**Laboratory Test**
Weekly	Electrolyes[2], BUN, Creatinine, Glucose, Conjugated bilirubin, Triglyceride
Every 2 weeks	ALT, AST, GGT, Alkaline Phosphatase, Calcium, Phosphorous, Hemoglobin, Hematocrit[3]
Every 4 weeks	Zinc, Copper, Selenium[4]

[1]For monitoring guidelines during initiation of PN, see **Table 13-15**

[2]Increased gastrointestinal output (Replogle and/or ostomy) may warrant more frequent monitoring.

[3]Monitor the week of discharge as clinically indicated.

[4]If medically feasible, obtain on admission in patients transferred from outside hospital with IF.

formulas when appropriate. Fortification strategies for each patient will be discussed between the primary team and the NICU Intestinal Rehabilitation Team. If fortification is indicated, this should typically occur when EN volume is approximately 80 mL/kg/day to continue meeting estimated needs while weaning PN volume below 40-50 mL/kg/day. Elemental formulas are generally not concentrated greater than 24 kcal/ounce due to concerns of the high osmolality provided by the formula.

Lab Monitoring

In addition to routine nutrition labs, the labs in **Table 5-3** may be monitored:

Weaning of Parenteral Nutrition

If infants are advancing well on EN, central lines may be removed when infant is receiving approximately 100-120 mL/kg/day of EN. Exceptions are infants with high or medium risk conditions as well as those with a history of feeding intolerance followed by the NICU Intestinal Rehabilitation Team. These infants should demonstrate adequate growth and tolerance to EN and fortification prior to removing central lines as they can exhibit inadequate growth and might require PN in conjunction with EN for additional caloric intake for a period of time. A thoughtful discussion with the NICU Intestinal Rehabilitation Team regarding the benefit: risk ratio of prolonging the central line duration should occur and be documented in the medical record.

Bacterial Overgrowth

Bacterial overgrowth is a common complication of IF. Areas of dysmotility and bowel dilation offer an ideal environment for abnormal bacterial propagation. The adverse effects of bacterial overgrowth may include abdominal pain, worsening intestinal motility, changes in stool frequency and/or consistency, mucosal ulceration with bleeding, deconjugation of bile acids, and the generation of toxic byproducts such as D-lactic acid. Bacterial overgrowth is thought to enhance bacterial translocation, which may lead to systemic complications. A strategy for either prophylaxis or treatment of bacterial overgrowth is the administration of enteral/oral Metronidazole (Flagyl®) at 10 mg/kg/dose given twice daily for one week each month (weak recommendation, low quality evidence). In rare instances, the duration of this regimen can be extended. Bacterial overgrowth prophylaxis or treatment is typically not administered in patients that are kept NPO. Initiation of bacterial overgrowth prophylaxis or treatment should be discussed with the NICU Intestinal Rehabilitation Team.

Replacement Fluids for Losses- Combined Replogle and Ostomy Output

0.9% normal saline (NS) without any additives is the preferred replacement fluid for Replogle and other ostomy losses. 0.45% NS, or 0.9% NS with dextrose or electrolyte additives are not recommended except in special circumstances. If additional electrolyte supplementation is required, adjustments should be made to PN based on laboratory values. When the combined Replogle and ostomy output exceeds 20 mL/kg/day, the entire amount of output should be replaced. Based on the volume of output, the frequency and amount of replacement fluids for losses should be increased based on **Table 5-4**.

Feeding Infants with Ostomies

Achievement of full EN prior to re-anastomosis may be an appropriate strategy for some infants with IF due to SBS and

Table 5-4. Replacement fluids for losses (combined replogle and ostomy output)[1]			
Combined Output (replogle and ostomy)	**Replacement Fluids[2,3]**	**Timeframe for Re assessment**	**Lab Monitoring**
<20 mL/kg/day	No replacement	Every 24 hours	Routine labs
20-30 mL/kg/day	0.5 mL NS for each 1 mL output over 12-24 hrs	Every 12-24 hours	Routine labs
30-40 mL/kg/day	0.5 mL NS for 1 mL output over 12 hrs	Every 12 hours	Daily electrolytes[3]
>40 mL/kg/day	0.5 mL NS for 1 mL output over 4 hours	Every 4 hours	Daily electrolytes[3]

[1] Replacement fluids not indicated with mucous fistula refeeding. (see Mucous Fistula Refeeding)

[2] Replace the full volume of output at 0.5 mL NS to each 1 mL output.

[3] If serum sodium greater than 140 mmol/L, may consider the use of 0.45% NS. Close monitoring of clinical status including urine output, and laboratory evaluation of these patients should frequently be done, since very high volume outputs might warrant 1:1 replacement.

ostomy with or without a mucous fistula (weak recommendation, low quality evidence). Some benefits include a reduction in PN days and lower peak conjugated bilirubin levels. Successful attainment of sustained EA prior to re-anastomosis may be influenced by post-menstrual age at time of ostomy creation, presence of a mucous fistula, and location (proximal versus distal) of ostomy. Mucous fistula refeeding should be attempted where feasible. However, attempts to achieve EA requires close monitoring for growth failure.

Mucous Fistula Refeeding

Infants requiring resection of bowel and enterostomy formation are at increased risk for fluid and electrolyte imbalances, malabsorption, nutrient deficiencies, growth failure, and IFALD. Infants with an ostomy and mucous fistula may benefit from refeeding of the mucous fistula. This involves collecting the ostomy output and infusing it into the distal small bowel through the mucous fistula. Mucous fistula refeeding helps mimic the digestion that would happen if bowel were in continuity including resorption of bile salts and other nutrients. Consultation with the NICU Intestinal Rehabilitation Team is indicated to identify candidates for mucous fistula refeeding prior to initiation. Once initiated, the goal is to refeed ostomy output volume via the mucous fistula in a 1:1 ratio and to monitor stool output from rectum and other clinical symptoms for signs of feeding intolerance. (strong recommendation, low quality evidence). **(Ch 16.1-Perioperative Management)**

Iron therapy

Infants with limited absorptive capacity may require intravenous iron. Since iron is not provided in PN, infants who have been on PN for more than six weeks are at increased risk for iron deficiency. Several newer formulations of parenteral iron have become available in recent years, including ferric carboxymaltose. This drug has an improved safety profile compared to other forms of IV iron, including iron dextran. The NICU Intestinal Rehabilitation team should be consulted to consider maintenance iron therapy in infants receiving minimal EN with anticipated prolonged need for PN.

Sucrose Oral Solution

The use of sucrose oral solution for procedure/pain events in patients with intestinal failure is discouraged and not recommended due to concerns for increased osmotic load in the gastrointestinal tract.

Discharge Coordination

If an infant is to be discharged on PN, interdisciplinary planning is essential and should be initiated at least 3 weeks prior to the anticipated discharge date. The Intestinal Rehabilitation Team will provide a discharge checklist to facilitate planning.

Cycling of Parenteral Nutrition

To promote age-appropriate development and in preparation for discharge, cycling of PN may be considered in infants discharging on PN. Cycling of PN is achieved with heparin-lock flush of the central venous catheter. Typically, infants are cycled off PN and lipid emulsion for four hours per day (typically cycled off from 1200-1600 daily). Initiation of heparin-lock flush should be discussed with the NICU Intestinal Rehabilitation team and initiated according to the protocol developed collaboratively with the VAT and nursing leadership.

Small Bowel/Multi-visceral Transplantation

The need for small bowel/multi-visceral transplantation in infants with SBS has decreased in recent years given improvements in medical and surgical management. The perceived need for referral for transplantation should be discussed with the NICU Intestinal Rehabilitation Team prior to initiating discussion with the patient's family.

5.3 Cholestasis

Introduction

Neonatal cholestasis is defined as impairment in the formation, flow, or excretion of bile. Biochemically, neonatal cholestasis is defined as conjugated hyperbilirubinemia that is present at birth or develops in the first few months of life. Cholestasis often develops well before the infant appears clinically jaundiced. As a result, elevated conjugated bilirubin levels are used to make the diagnosis. Conjugated bilirubin levels are measured using two different assays: "direct bilirubin (DB)" and "conjugated bilirubin (CB)" measurements. DB measurements are used at many hospitals (including Ben Taub General Hospital and most of the referring hospitals), whereas only CB measurements are performed at TCH. DB levels often are higher because they also measure the "delta" bilirubin fraction. As a result, CB measurements are preferred for management decisions. In infants with IFALD, usually a serum CB $\geq$2.0 mg/dL is used for defining cholestasis.

Significance

Unlike unconjugated bilirubin, conjugated bilirubin is not directly toxic to tissues, but can be a sign of significant, potentially fatal, underlying liver disease. It can be caused by diseases that need prompt surgical intervention, such as biliary atresia, or diseases that need immediate medical intervention, such as certain metabolic diseases or infection. Hence, it is important to reach a diagnosis in a timely manner.

Screening

All infants admitted to either well-baby or special care nurseries who are less than 4 months of age should have a screening conjugated or direct bilirubin when feasible. In newborns, this should occur within 48 hours of age. For infants discharged prior to two weeks of life, if the initial level exceeds the laboratory's normal range, the level should be rechecked at the 2 weeks well child check. If the level remains abnormal, the infant should be referred to the pediatric liver service. For infants that remain hospitalized, if the initial level exceeds the laboratory's normal range, a repeat test should occur at one week of life. If the level remains abnormal, pediatric liver service should be consulted and a stepwise approach to diagnosis as suggested under "investigations" section should be performed.

Etiology

The common causes of conjugated hyperbilirubinemia include biliary atresia (BA), neonatal hepatitis, Alagille syndrome, choledochal cysts, sepsis, intestinal failure-associated liver disease (IFALD), drug-induced liver injury, and genetic or metabolic liver diseases (e.g., galactosemia, tyrosinemia, hypothyroidism, alpha-1 antitrypsin deficiency, and neonatal hemochromatosis).

Table 5-5. Laboratory investigations	
Tests	**Rationale**
Specific cultures and or serologies	Viral Hepatitis
Initial testing: Plasma amino acids, urine organic acids, acylcarnitine profile, ammonia, lactate, pyruvate. **Specific testing:** Urine reducing substances, urine succinyl acetone, AAT concentration and phenotype deficiency.	Metabolic disorders Galactosemia, Tyrosinemia, AAT deficiency
Serum and urine bile acids	Bile acid synthesis disorders
Free T4 and TSH	Hypothyroidism
Sweat chloride and mutation analysis	Cystic fibrosis
Ferritin, transferrin saturation	Neonatal hemochromatosis
Peripheral smear for red cell morphology, blood typing (maternal and infant), and Coombs test	Mixed causes of unconjugated and conjugated hyperbilirubinemia
Hepatobiliary scintigraphy	Assess bile duct patency
Liver biopsy	Distinguishes biliary atresia from neonatal hepatitis

IFALD is one of the most common etiologies of cholestasis encountered in the NICU population. This condition typically presents in infants who are on prolonged parenteral nutrition (2 weeks or more) with elevated CB. Major risk factors are prematurity, the absence of enteral feeds and sources of inflammation including, surgeries, infections, small intestinal bacterial overgrowth and illness such as SIP and NEC.

Assessment

A thorough history should be taken, including any complications that occurred during pregnancy such as infection. A family history and detailed history of prior pregnancies should also be obtained.

Clinical assessment should include a detailed examination for dysmorphic features, hepatosplenomegaly, bleeding, cardiac murmurs, and any signs and symptoms of sepsis. In addition, assess the color of the stools and urine (pale stools and dark urine suggest cholestasis).

Investigations and Consultations

A Liver Team consult should be requested when a diagnosis other than sepsis or IFALD is suspected. The Liver Team will help guide the evaluation, including determining whether a liver biopsy is indicated. In addition, the Liver Team will help coordinate potential surgical or medical therapies. Many of these therapies are most effective when started earlier. Early evaluation should include an abdominal Ultrasound (USG), CBC, PT/INR and blood culture. If USG is concerning for BA or other obstructive etiology, the Pediatric Liver Team should be consulted. If USG is normal, focused investigations could be ordered per **Table 5-5** based on the clinical scenario and in consultation with the Pediatric Liver Team.

A Genetics consult should be considered if any of the following is present: a) family history of conjugated hyperbilirubinemia or liver disease, b) dysmorphic features, c) cardiac murmur.

Treatment

The treatment of cholestasis should primarily be directed toward the underlying condition.

Other supportive treatments include:

- **Feeding -** Treatment of IFALD includes the reestablishment of enteral nutrition as tolerated. Feeding human milk, premature infant formula, or both can be appropriate for VLBW infants with cholestasis. Premature infant formulas and amino acid-based formulas contain relatively high amounts of medium-chain triglycerides. An amino acid-based formula or a protein hydrolysate formula is commonly used for these infants when human milk is not available or well tolerated.
- **Ursodiol -** (ursodeoxycholic acid [UDCA]). This bile acid of animal origin is a potent choleretic and is indicated in the management of cystic fibrosis, primary biliary cirrhosis, and dissolution of cholesterol gallstones. It is given orally and appears moderately safe. It is potentially beneficial for infants who have an intact ileocecal valve and are tolerating feeds ≥ 20-40 mL/kg/day. If the terminal ileum has been resected, UDCA will not be efficiently absorbed, and bile acid-induced diarrhea may occur. The dose ranges from 15 to 45 mg/kg per day divided into two or three doses. It should be considered in infants who are enterally fed and have significant evidence of cholestasis (conjugated bilirubin level ≥ 1.5 mg/dL). Therapy should continue as long as cholestasis is evident, either in laboratory tests (elevated serum indices in the liver panel), low fat-soluble vitamin levels, or elevated serum bile acid levels. Infants discharged home on Ursodiol, should be followed by the TCH Liver team (if not followed by the TCH Intestinal Rehabilitation Clinic). If the patient is being evaluated for a bile acid synthesis defect, then UDCA treatment should be withheld until the evaluation has been completed. The use of UDCA in the prevention and treatment of IFALD has yielded conflicting results. Some studies have shown that UDCA may decrease the level of liver enzymes in IFALD patients whereas others have shown no benefit (weak recommendation, low quality evidence).
- **Fat-soluble vitamins** – Parenteral nutrition (PN) should provide sufficient vitamins A, D, and E (largely irrespective of volume). If bleeding occurs and INR is elevated, additional vitamin K can be given parenterally at a dose of 1 mg/day. Infants on enteral nutrition usually only require standard multivitamins, although the use of fat-soluble vitamins (in a water-soluble formulation) may be considered.

- **Trace Minerals** - Since trace minerals such as copper and manganese are excreted in the bile, in cholestasis they may accumulate in the liver and exacerbate hepatic dysfunction. Therefore, in the presence of cholestasis (conjugated bilirubin ≥ 2 mg/dL), it is recommended to reduce trace minerals in the PN. However, infants have a requirement for copper and will ultimately develop a copper deficiency in the absence of adequate copper provision. In the presence of cholestasis (conjugated bilirubin ≥ 2 mg/dL) without either jejunostomy or ileostomy, trace minerals should be provided 3 times per week (Monday, Wednesday and Friday) rather than daily. Parenteral zinc should be provided at maintenance levels daily. In infants where cholestasis is present with either jejunostomy or ileostomy, additional zinc may be provided to compensate for gastrointestinal losses. Copper, zinc, and selenium levels should be monitored every four weeks or as medically feasible in infants with cholestasis while on PN. Lab monitoring of trace mineral levels may indicate the need for further adjustments to supplementation.
- **Discontinuation of lipid limiting strategy OR lipid minimization strategy for prevention of IFALD -** Lipid limiting or minimization is a strategy whereby Intralipid® is limited to prevent IFALD. This strategy has been shown to be suboptimal in prevention of IFALD. Hence, the practice of restricting Intralipid® to 1 g/kg/d when conjugated bilirubin (CB) reaches ≥1.5 mg/dL is being discontinued. In infants with ongoing need for PN and rising conjugated bilirubin levels, consider the use of SMOFlipid® for prevention of IFALD based on recommendations below. Lipid limiting with SMOFlipid® is associated with essential fatty acid deficiency and is strongly discouraged (strong recommendation, very low-quality evidence). In situations where limiting ILE might be warranted (e.g. hypertriglyceridemia, fluid restriction, CDH either preoperative state or on ECMO with high conjugated bilirubin, cholestasis within 14 days after birth) please consult the Nutrition Team to institute safe ways of limiting ILE. Any lipid limiting should only be done in consultation with the Nutrition Team.
- **SMOFlipid® and Omegaven® -** Refer to **Ch 5.4-Lipid Injectable Emulsions** below.

5.4 Lipid Injectable Emulsions (ILE)

Historically, Intralipid® has been the standard ILE in all infants at Texas Children's Hospital units. However, Intralipid® has been linked to cholestasis and other poor outcomes with prolonged use. Newer generation ILEs such as SMOFlipid® and Omegaven® have better anti-inflammatory profile compared to Intralipid®. However, the proposed benefits of SMOFlipid® in clinical practice have not matched the promise shown by its apparently better biochemical profile. The effect of SMOFlipid® in prevention and treatment of cholestasis is modest. There is paucity of long-term neurodevelopmental outcomes data with SMOFlipid®. Use of SMOFlipid® in ECMO or states of anti-coagulation is not studied.

The beneficial effect of Omegaven® in treatment of cholestasis has been shown in several observational studies, but not in randomized control trials. Though the quality of evidence to support the use of Omegaven® in the treatment of cholestasis is very low (due to lack of randomized control trials), it comes with a strong recommendation.

Lipid limiting or minimization is a strategy whereby Intralipid® is limited to prevent IFALD. This strategy has been shown to be suboptimal in prevention of IFALD. Therefore, the practice of restricting Intralipid ® to 1 g/kg/d or less when conjugated bilirubin (CB) reaches 1.5 mg/dL or greater is no longer recommended.

There are no studies regarding the safety or efficacy of limiting the dose of SMOFlipid®. Limiting SMOFlipid® has been shown to be associated with essential fatty acid deficiency (EFAD) and is strongly discouraged.

Considering the above-mentioned evidence, the use of ILE at Texas Children's Hospital NICU is as follows:

a. Intralipid® is the ILE of choice for all infants, except those who are at risk for IFALD or who have IFALD (see b. and c. below).

b. In infants who are at risk for IFALD, SMOFlipid® is the recommended ILE to provide nutrition and prevent IFALD (weak recommendation, low to very low quality of evidence). See below for eligibility for SMOFlipid®.

c. In infants who have IFALD, Omegaven® is the recommended ILE as a source of nutrition and for treatment of IFALD® (strong recommendation, very low quality of evidence). See below for eligibility for Omegaven®.

Use of ILE in special patient populations:

1. Congenital diaphragmatic hernia (CDH): Intralipid® is the initial ILE of choice. Pre-operative use of SMOFlipid® is discouraged. Post-operatively, SMOFlipid® is recommended for prevention of IFALD if EN <50 mL/kg/day at14 days of age and a prolonged need for PN is anticipated.
2. Congenital heart disease: Intralipid® is the initial ILE of choice. SMOFlipid® is recommended for prevention of IFALD if EN <50 mL/kg/day at 14 days of age and a prolonged need for PN is anticipated.

Intralipid® (Omega-6 Fatty Acids Rich Lipid Emulsion)

Intralipid® is a soybean oil-based ILE rich in omega-6 fatty acids. It was approved for use in the US in 1972. There is a strong association between higher doses of Intralipid® and IFALD, which is thought to be due to the higher content of phytosterols, a high omega-6: omega-3 ratio, and lower content of antioxidants (vitamin E).

Omegaven® (Omega-3 Fatty Acids Rich Lipid Emulsion)

Omegaven® (Fresenius Kabi, Germany) is a fish oil-based ILE rich in omega-3 fatty acids. In 2018, Omegaven® was approved by the FDA as a source of nutrition in children with IFALD. Omegaven® is solely used as an intervention in the treatment of IFALD and has been shown to facilitate faster resolution of cholestasis, reduction in both the rate of liver transplants and mortality in these patients (strong recommendation, very low-

quality evidence). The etiopathogenesis of IFALD is multifactorial. The presence of phytosterols and high omega-6 to omega-3 fatty acids in the conventional soy-based lipid emulsion (Intralipid®) is thought to be an important factor. The beneficial effects of Omegaven® have been attributed to several factors including the high content of omega-3 fatty acid (FA) and their anti-inflammatory effects, the absence of phytosterols, high content of vitamin E and decreased de novo lipogenesis. Following the initiation of Omegaven® the level of conjugated bilirubin is usually noted to increase over the first week followed by a gradual decline resulting in complete resolution over a period of about 7 ± 2 weeks. The use of Omegaven® has so far proven to be safe with no known short-term side effects. Essential fatty acid deficiency and increased risk of bleeding, though theoretical concerns have not been described with the use of Omegaven®.

Eligibility Criteria for use of Omegaven®

- Greater than 14 days of age
- Conjugated bilirubin ≥2 mg/dL
- Expected prolonged need for PN

Exclusion Criteria

- Evidence of viral hepatitis or primary liver disease as the primary etiology of their cholestasis
- Clinically severe bleeding not able to be managed with routine measures

Use of Omegaven®

Once an infant meets eligibility for Omegaven®, Intralipid® or SMOFlipid® is discontinued and Omegaven® is initiated at 1 g/kg/day by continuous infusion over 24 hours/day. Omegaven® may be given over 16-22 hours/day if PN is cycled in preparation for discharge. Providing more than 1 g/kg/day is not encouraged by the FDA under this indication. Omegaven® can be provided via a central or peripheral line. Since Omegaven® is provided at 1g/kg/day, the glucose infusion rate in the PN may need to be increased as tolerated to 14-17 mg dextrose/kg/minute to provide sufficient calories for growth.

Duration of Treatment

Patients are considered to have resolved cholestasis when the conjugated bilirubin is < 2 mg/dL, which typically requires 6-10 weeks of therapy. Omegaven® is continued until enteral nutrition is tolerated at ≥ 80 mL/kg/day, even if cholestasis resolves sooner. There is no evidence to support treatment with Omegaven® for IFALD after EA is attained.

If a patient who has received Omegaven® in the past needs to resume PN for any reason (e.g., post-operative course), the patient may be considered for further use of Omegaven®, even if the conjugated bilirubin is < 2 mg/dL. Cases should be individually discussed with the NICU Intestinal Rehabilitation team, as in some cases resumption of Intralipid® or SMOFlipid® may be appropriate. In addition, patients who are readmitted to any unit at TCH after being on Omegaven® in the NICU may resume Omegaven®. This is done because the liver function tests may remain abnormal for several months despite normalization of conjugated bilirubin levels and the infant would likely benefit from the anti-inflammatory effects of omega-3 FA.

Monitoring

Conjugated bilirubin and serum triglycerides are measured just prior to the initiation of Omegaven®. Serum triglycerides should be measured again within 48 hours after initiation. Conjugated bilirubin and serum triglycerides are measured once a week thereafter until discontinuation of Omegaven®. Liver function tests (AST, ALT, and GGT) are also monitored every other week. **(Table 5-3)**

SMOFlipid® (Multi Component Lipid Emulsion)

SMOFlipid® is a new generation ILE comprised of 30% soybean oil, 30% MCT (coconut oil), 25% Olive oil and 15% Fish oil. SMOFlipid® was approved by the FDA for use in adults in 2016. The current evidence suggests that the use of SMOFlipid® in infants is safe. The biochemical profile of SMOFlipid® is associated with a more anti-inflammatory profile compared to Intralipid®. The proposed benefits of SMOFlipid® in clinical practice have not matched the promise shown by its apparently better biochemical profile. The effect of SMOFlipid® in prevention and treatment of cholestasis is modest. There is paucity of long-term neurodevelopmental outcomes data with SMOFlipid®. Use of SMOFlipid® in ECMO or states of anti-coagulation is not studied. Based on the current evidence, SMOFlipid® is perhaps a better ILE compared to Intralipid® only in prevention of IFALD in infants with prolonged need for PN (weak recommendation, low to very low quality of evidence).

Eligibility Criteria for use of SMOFlipid®

- By Diagnosis:
  - » Surgical gastrointestinal conditions:
    - o Diagnosis at birth: gastroschisis, omphalocele, atresia
    - o Post-natal diagnosis: volvulus, spontaneous intestinal perforation, necrotizing enterocolitis (stage 2 or greater), any surgical resection of intestine.
- By Duration of PN:
  - » EN < 50 mL/kg/day at 14 days of age AND expected prolonged need for PN.

Use of SMOFlipid®

Once an infant meets eligibility for SMOFlipid®, Intralipid® should be discontinued if already infusing. If SMOFlipid® is initiated at birth, SMOFlipid® is initiated at 1 g/kg/day by continuous infusion over 24 hours/day on day 1, increased to 2g/kg/day on day 2, and 3g/kg/day on day 3. When SMOFlipid® replaces Intralipid® initial dose of SMOFlipid® should match that of Intralipid®, usually a dose of 3 g/kg/day. Limiting SMOFlipid® has been associated with essential fatty acid deficiencies and is strongly discouraged. In clinical situations where lipid limiting is warranted, Nutrition Team should be consulted for safer options.

SMOFlipid® can be provided via a central or peripheral line. Currently, compatibility data with medications for SMOFlipid® and Omegaven® products are lacking. TCH practice is to utilize Intralipid® medication compatibility data until more specific data for SMOFlipid® and Omegaven® are available.

Monitoring

Conjugated bilirubin and serum triglycerides are measured just prior to the initiation of SMOFlipid®. Conjugated bilirubin and serum triglycerides are measured once a week thereafter until discontinuation of SMOFlipid®. Liver function tests (AST, ALT, and GGT) are also monitored every other week. **(Table 5-3)**

Recognizing Underlying End-Stage Liver Disease

Premature infants with hepatomegaly, splenomegaly, elevated liver panel indices, or evidence of liver functional impairments may have an underlying liver disease and should be considered for Liver Team consultation. In neonates who are unable to advance enteral nutrition, IFALD warrants concern. Findings of worsening conjugated hyperbilirubinemia, elevated PT, glucose instability, worsening hepatosplenomegaly, caput medusa, ascites, and GI bleeding from portal hypertension suggest the development of an irreversible liver disease. In these infants, the Liver Team should be consulted as early as possible after failure to advance enteral nutrition is recognized. This consultation will help determine if the infant is a candidate for transplantation of the liver and/or intestine.

5.5 Gastroesophageal Reflux (GER)

Gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus. GER commonly occurs during infancy and does not require medical intervention. Not all spitting is due to reflux and the differential diagnosis can include gastrointestinal anatomic abnormalities, metabolic disorders, or renal dysfunction. Although preterm infants frequently have GER, in most cases there is no temporal relationship between GER and apnea of prematurity.

The clinical findings that indicate GER should be documented in the medical record before instituting medical management. Attempt non-pharmacologic approaches, such as positioning and, if appropriate, changes to the duration and rate of the feeding. The use of prokinetic agents in healthy preterm infants is strongly discouraged. Adverse events have been associated with thickened feedings, therefore this intervention is not recommended in routine management of GER. The neonatology section of BCM recommends that no infant in any of our Level 2, 3 or 4 nurseries be provided any commercial thickening agent (Simply Thick® and similar products) designed to be added to infant formula or human milk. Consideration of the use of such agents should only be done in the context of an IRB-approved research protocol. The use of such commercial thickening agents is contraindicated in preterm infants, or former preterm infants, both during the hospitalization and after discharge due to the risk of NEC.

GER disease (GERD) is defined as symptoms or complications of GER. Certain infants may be at increased risk of GERD including those with congenital diaphragmatic hernia, tracheoesophageal fistula, esophageal atresia repairs **(see GER treatment in Ch. 16.3-Specific Surgical Conditions),** abdominal wall defects, and intestinal failure. GERD can present with symptoms of anorexia, dysphagia, odynophagia (pain on swallowing), arching of the back during feeding, irritability, hematemesis, anemia, or failure to thrive. These infants often display true esophageal and GI dysmotility, leading to increased risk of esophagitis and gastritis. In this subset of infants, treatment with proton pump inhibitors (PPIs) and H_2 receptor antagonists as an adjunctive therapy produce relief of symptoms and promote esophageal healing. Recent pharmacokinetic studies of at least one PPI have shown them to be well tolerated and provide dose related acid suppression in infants 1-24 months of age. Transpyloric feedings or fundoplication may need to be considered in the most severe cases to prevent long-term sequelae.

Note: Use of H_2 receptor antagonists in the neonatal population is associated with increased risk for NEC and gram-negative bacteremia. Though this level of evidence is not available for the proton pump inhibitors (PPIs), the same degree of caution should be extended to the PPIs due to the same end use result of increased gastric pH.

Famotidine (Pepcid) - a H_2 receptor antagonist (oral and intravenous forms available) and is compatible as an additive with parenteral nutrition.

Lansoprazole (Prevacid) - proton pump inhibitor (PPI) (available as oral suspension, capsule, and disintegrating oral tablets). Patients should receive the oral suspension while admitted in the NICU if possible and it is the preferred option in the outpatient setting. Alternative formulations may be used if an oral suspension is not available.

Pantoprazole (Protonix) - proton pump inhibitor (PPI) (available intravenously at TCH). Not compatible with parenteral nutrition.

Metoclopramide (Reglan) - a prokinetic agent that has been used, although data do not support efficacy in infants. The FDA has placed a Black Box warning on the chronic use of metoclopramide, as it has been linked to tardive dyskinesia even after the drug has been discontinued. The symptoms are rarely reversible and there is no known treatment. The use of this agent in our population is strongly discouraged under all circumstances.

Bethanecol (Urecholine) - a cholinergenic agent that has been used, although data do not support efficacy in infants. Routine use of this agent in our population is discouraged. Its potential use should be discussed with the intestinal rehabilitation team.

5.6 Promotility Agents

Erythromycin

Erythromycin has been used as a prokinetic agent to treat feeding intolerance and reflux in infants. Erythromycin activates the motilin receptors in the antrum of the stomach. There is insufficient evidence to recommend the use of Erythromycin to treat feeding intolerance in preterm infants as shown in a meta-analysis of 10 randomized controlled studies evaluating the efficacy of erythromycin in the prevention and treatment of feeding intolerance in preterm infants. The use of Erythromycin could be considered after 14 days of life in an infant with significant feeding intolerance due to moderate to severe GI dysmotility (weak recommendation, low-quality evidence) (see dosing below). Its potential use should be discussed with the Intestinal Rehabilitation Team.

Erythromycin Dosing for Infants - Erythromycin ethylsuccinate orally 5 to 10 mg/kg/dose every 6 hours; start at lower dose and assess for efficacy. Caution should be used with prolonged use due to the possibility of developing pyloric stenosis. Clinical judgment should be used with long-term use.

Augmentin (Amoxicillin/Clavulanate)

Augmentin can improve gastrointestinal motility by propagation of phase III migrating motor complexes in the intestine and has been used in infants with significant dysmotility (usually anatomic or functional intestinal failure) unresponsive the Erythromycin therapy. The formulation that has been studied for pro-motility purposes is the 80 mg-11.4 mg/mL suspension. Literature is limited to a case series. Its potential use should be discussed with the intestinal rehabilitation team (weak recommendation, very low-quality evidence).

Augmentin Dosing for Infants – Augmentin orally 10-20 mg/kg/dose every 12 hours.

Duration of Therapy

The duration of therapy for promotility agents will be based on symptoms, growth, adverse effects, and other factors. Any infant discharged home on a promotility agent should have follow-up either with TCH Intestinal Rehabilitation Clinic or Gastroenterology.

5.7 Probiotics

Intestinal dysbiosis has been shown to contribute to the risk of NEC and using probiotics to optimize intestinal microbiota is a promising option. Sharif et al in Cochrane systematic review summarized current evidence regarding the use of probiotics in very preterm infants. Probiotics administration in preterm neonates decreased NEC by 46% and by 30% if only high-quality trials are included (low certainty evidence). Probiotics also decreased mortality by 24% and late-onset sepsis by 11% (moderate certainty evidence) A clinical report from AAP Committee of the Fetus and Newborn published in May 2021 recommends against the routine use of probiotics in preterm infants because of an absence of a pharmaceutical grade probiotic product in the United States. At present, we do not use probiotics in the NICU at Texas Children's Hospital.

Suggested Reading

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Section 6: Genetics

Editors: Charleta Guillory and Mohan Pammi

6.1 Inborn Errors of Metabolism

Introduction

Genetic biochemical abnormalities in newborns comprise a large group of individually rare disorders with a number of stereotypic presentations. More than 1000 distinct metabolic disorders are recognized and novel entities continue to be described.

Metabolic disorders may be undetected (overlooked) or misdiagnosed because of their rarity and non-specific symptomatology. In acute disease, inborn errors of metabolism (IEM) are frequently not considered until more common conditions, such as sepsis, are excluded. Since newborns have a limited set of responses to severe overwhelming illness—with such non-specific findings as lethargy, poor feeding, and vomiting—clinical assessment is difficult. In general, the clinical context needs to influence the decision to carry out a metabolic evaluation and the breadth of the investigation. For example, a sepsis workup of a clinically ill newborn should lead to consideration, not the exclusion, of a metabolic evaluation. For example, E. coli sepsis is one complication of newborns with classic Galactosemia. The high-risk patient is a full-term infant with no risk factors for sepsis who develops lethargy and poor feeding. In addition, diagnostic testing of blood and urine may be informative only if collected at the proper time relative to the acute presentation. Novel biochemical technologies—such as tandem mass spectrometry and untargeted metabolomics that allow for the simultaneous analysis of hundreds of small molecules—enhance the ability to arrive at specific diagnoses.

Thus, a need remains for a high clinical suspicion in the appropriate diagnosis and treatment of metabolic disorders. While it is important to inquire whether others in the family have been similarly affected, since most of these conditions exhibit autosomal recessive inheritance, frequently the family history does not reveal prior affected individuals.

Increasingly, syndromic diseases are recognized as being caused by IEM, e.g., Smith-Lemli-Opitz syndrome, due to a defect in cholesterol biosynthesis; Zellweger syndrome, due to defects in peroxisomal biogenesis; serine synthesis defects causing Neu-Laxova syndrome, and neuronal migration abnormalities and related cerebral malformations caused by a variety of disorders of energy metabolism.

Screening for metabolic disease does not require a long list of tests; simply assessing the acid/base balance, ammonia and lactate levels, and a urinalysis can provide enough information in the acute setting to direct further testing. Infants diagnosed with IEM should receive Developmental referral and ECI (Early Childhood Intervention) referral.

Categories of IEM

In the overall assessment of a clinical scenario, two general categories of IEM can be considered:

- disorders that involve only one physiologic system, e.g., isolated hemolytic anemia due to disorders of glycolysis, and
- more generalized defects in a metabolic pathway common to more than one organ system or secondarily affecting more than one organ system. For example, hyperammonemia reflects a liver-specific abnormality of ureagenesis but secondarily affects central nervous system function.

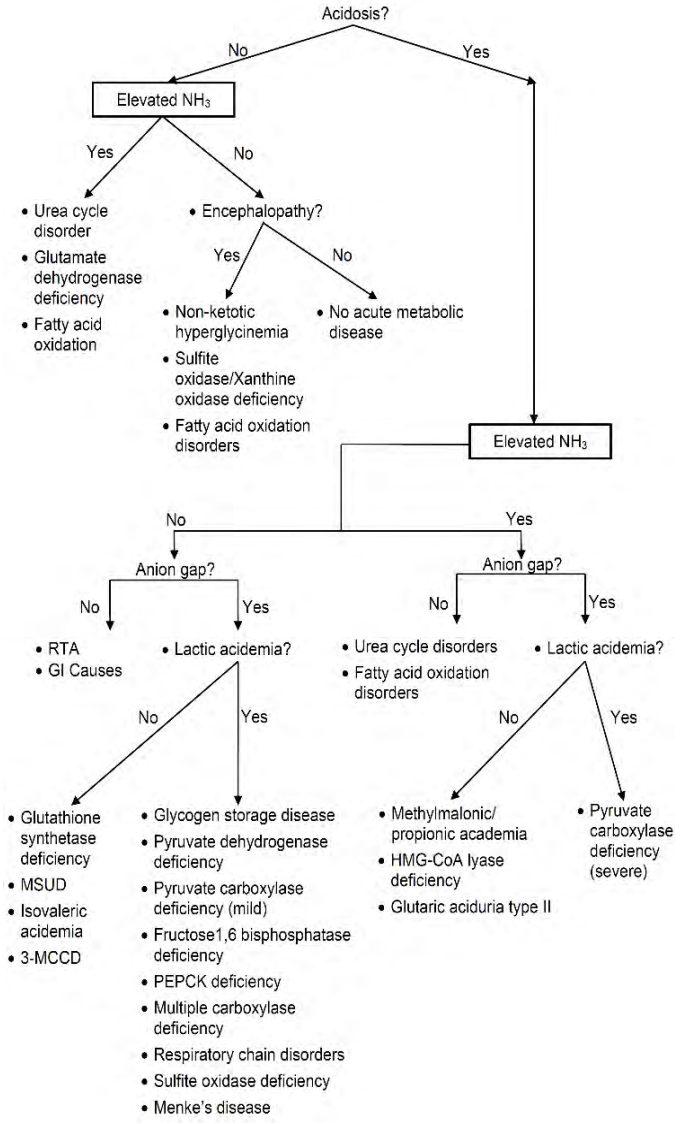
This second category can be further divided into three distinct clinical scenarios:

- **Disorders that affect the synthesis or breakdown of complex molecules (e.g., the lysosomal storage disorders) -** this group of disorders tends to have a progressive, somewhat fixed course independent of dietary intake or intercurrent events such as infection. While this class of disorders can present in the newborn period (e.g., fetal hydrops secondary to lysosomal storage disorder or fulminant hepatitis associated with alpha1-antitrypsin deficiency), diagnoses typically are made later in infancy or childhood. This group of disorders will not be discussed in detail, however since these disorders are increasingly amenable to treatments such as enzyme replacement therapy, the use of newborn screening for the identification of lysosomal disorders is expanding rapidly.
- **Systemic disorders that lead to acute intoxication from accumulation of toxic compounds preceding the metabolic block** - Early diagnosis and prompt treatment can significantly improve the clinical outcome. This category includes urea cycle defects, organic acidemias, and other aminoacidopathies, such as maple syrup urine disease. Many of the conditions in this group of disorders exhibit clinical similarities, which may include a symptom-free interval that ranges from hours to weeks followed by clinical evidence of intoxication (e.g., encephalopathy, vomiting, seizures, or liver failure). This group of disorders also tends to have a recurrent pattern with the waxing and waning of the offending metabolites. Treatment of these disorders requires the reduction or elimination of the offending compounds either through hemodialysis, a special diet, cofactor supplementation, or provision of a diversionary metabolic pathway.
- **Systemic disorders that result from a deficiency in energy production or utilization** - Since the brain, heart, skeletal muscle, and liver depend heavily on energy metabolism, these organs tend to be the primary site of pathology. This category includes a broad array of metabolic pathways, such as the mitochondrial respiratory chain, glycogen synthesis or breakdown, gluconeogenesis defects, and fatty acid oxidation defects. Signs and symptoms in this group reflect the specific organ systems involved, such as hypoglycemia, elevated lactic acid, liver failure, myopathy, cardiac failure, failure to thrive, and sudden death, or some combination of features.

Clinical Presentation

Clinical presentations may depend in part on the underlying biochemical defect but also on environmental effects such as infections and choice of nutritional source **(Fig 6–1).** Suspect an IEM when a child has a well period followed by a precipitous or more insidious decline in neurologic status. Presentation may be acute with potential for stroke–like sequelae, or progressive where development changes from normal to slower progress and skill loss. Onset of a disorder may precede birth followed by further neurological deterioration post-birth. IEM may be categorized by their most prominent neurological, behavioral or other clinical characteristics.

Figure 6-1. Presentations of metabolic disorders



In the intoxication type of disorders, the typical pattern is one of an apparently healthy infant who becomes increasingly fussy and disinterested in feeding. This may be accompanied by vomiting, which can be so severe as to be mistaken for pyloric stenosis.

Most metabolic disorders will have encephalopathy as a component of the clinical picture. Encephalopathy typically is a consequence of hyperammonemia, but also may be due to cerebral toxicity of particular fatty acids, as seen in certain defects in fatty acid oxidation such as medium-chain acyl-CoA dehydrogenase deficiency (MCAD), organic acids such as glutaric aciduria, or an accumulation of unusual highly reactive compounds such as sulfites and sulfocysteine in sulfite oxidase deficiency. In addition, particular amino acids have direct toxic effects via distinct mechanisms, such as glycine, which is elevated in the CSF of patients with non-ketotic hyperglycinemia (NKHG; glycine encephalopathy), or branched chain amino acids, which are increased in maple syrup urine disease.

In contrast, the alert but hypotonic infant suggests a different set of disorders, both syndromic, such as Prader-Willi syndrome or spinal muscular atrophy, and metabolic, such as Pompe disease (glycogen-storage disease type II [GSD2]).

Hyperammonemia

Hyperammonemia must be considered in encephalopathic patients since no other biochemical abnormalities (with the exception of plasma amino acid analysis) reliably suggest the presence of hyperammonemia, although early in the course a respiratory alkalosis may be seen. Prompt recognition of hyperammonemia is imperative for a good outcome; the correlation is clear between length of time that a patient is hyperammonemic and degree of neurologic damage.

Hyperammonemia may be:

- the only biochemical abnormality, as in the urea cycle disorders, or
- part of a broader biochemical perturbation such as profound acidosis (as seen in various organic acidurias) or hypoglycemia (as seen in hyperinsulinism associated with over activity of the enzyme glutamate dehydrogenase as a result of a gain of function mutation).

Hypoglycemia

Hypoglycemia can be a prominent feature in IEM and may be associated with encephalopathy, seizures or both.

Abnormalities associated with hypoglycemia in neonates include:

- glycogen-storage disease (GSD), in particular GSD1A due to glucose-6-phosphatase deficiency,
- GSD1B caused by glucose-6-phosphate translocase deficiency, and
- GSD3 due to debrancher deficiency.

GSD1A and 1B patients typically have signs and symptoms in the neonatal period, while GSD3 tends to come to attention later in the first year. The X-linked GSD9A form is more typically mild but can be associated with neonatal hypoglycemia. Abnormalities in blood chemistries that support the diagnosis of GSD1 include hyperlipidemia, uric acidemia, and lactic acidemia, while patients with GSD3 exhibit even greater elevations ALT and AST, along with hyperlipidemia and elevated CPK in most patients. DNA testing can establish the diagnosis of GSD1A and preclude the need for liver biopsy.

Other IEM in which hypoglycemia is a prominent feature include:

- fatty acid oxidation disorders (especially MCAD and SCHAD deficiency),
- gluconeogenesis defects (severe pyruvate carboxylase)
- mitochondrial respiratory chain disorders

Disorders of Fatty Acid Oxidation

Although disorders of fatty acid oxidation may be associated with hypoglycemia and can be clinically apparent in the newborn period, e.g., MCAD, SCHAD (causing hyperinsulinism), VLCAD, or CPT2, the typical patient is older. Such hypoglycemia is usually observed late in the course of the disease and hence is an ominous sign. Over 20 different enzyme defects are associated with fatty acid metabolism, the most common being MCAD and VLCAD deficiency, and the clinical scenario varies considerably.

Some patients will have a myopathic presentation that may be associated with rhabdomyolysis and cardiomyopathy; others will have a hepatic phenotype with features of hepatitis, hypoglycemia, and hyperammonemia.

Screen for these disorders with a plasma acyl-carnitine profile, urine acyl-glycine analysis, and urine organic acid analysis, which identify accumulated intermediates of fatty acid oxidation. Treatment is directed at avoiding the mobilization of fats, treating any secondary carnitine deficiency, and possibly bypassing any block in long-chain fatty acid oxidation (depending on the enzyme step involved) by providing medium-chain fats in the diet. A recently FDA-approved compound triheptanoin (Dojolvi), a seven carbon triglyceride, appears to be superior for certain long chain fatty acid disorders.

Although disorders with obvious systemic features usually significantly affect neurologic status, on rare occasions this is not the case. For example, an inborn error in glutathione synthesis (pyroglutamic aciduria) is associated with profound neonatal acidosis and hemolysis, yet neurologic problems typically are absent or mild.

An abnormal odor is apparent in various metabolic disorders, including sweaty feet in isovaleric acidemia or glutaric aciduria type 2, and an aroma of maple syrup in maple syrup urine disease (MSUD).

Maternal-Fetal Interactions

Some maternal-fetal interactions can affect either the mother or the infant or both. While the placenta often will detoxify the fetus in urea cycle disorders or organic acidurias, a number of disorders, such as those that affect energy production, have an in utero onset.

Likewise, an affected fetus can have a toxic effect on the mother. For example, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency has been unequivocally associated with the development of hemolysis, elevated liver function tests, low platelets (HELLP) syndrome, and fatty liver of pregnancy in some carrier (heterozygous) mothers. Several other disorders of fatty acid metabolism have been similarly linked to maternal disease.

Conversely, mothers who have poorly controlled phenylketonuria (PKU) are at high risk of delivering infants with microcephaly and congenital heart disease from in utero exposure to elevated circulating phenylalanine, despite the fetus being genotypically unaffected.

Finally, the metabolic stress of childbirth can precipitate a metabolic crisis in a mother who has not been previously identified as affected (e.g., post-partum hyperammonemia and death have been reported in mothers who are heterozygous for X-linked ornithine transcarbamylase deficiency, whether or not the fetus is affected).

Clinical Features

Fetal Hydrops

Fetal hydrops can be a manifestation of a large number of IEM, in particular various lysosomal storage disorders. A list of genetic disorders that have been associated with hydrops is provided **(Table 6–1).**

Table 6–1. Metabolic disorders, chromosomal abnormalities, and syndromes associated with nonimmune fetal hydrops

Lysosomal storage disorders

- sialidosis
- Hurler syndrome (MPS type I)
- Morquio syndrome (MPS type IV)
- Sly syndrome (MPS type VII)
- I-cell disease
- galactosialidosis disease
- multiple sulfatase deficiency
- infantile sialic acid/Salla disease
- Niemann-Pick disease types A and C
- Wolman disease/acid lipase deficiency
- Farber lipogranulomatosis/ceramidase deficiency
- GM1 gangliosidosis/beta galactosidase deficiency
- Gaucher disease/glucocerebrosidase deficiency

Other metabolic disorders

- fumarase deficiency
- primary carnitine deficiency
- neonatal hemochromatosis
- glycogen storage disease type IV
- Smith-Lemli-Opitz syndrome congenital disorders of glycosylation
- respiratory chain defects
- peroxisomal disorders

Hematologic disorders (associated with hemolysis)

- alpha-thalassemia
- pyruvate kinase deficiency
- glucose-6-phosphate dehydrogenase deficiency
- glucose-phosphate isomerase deficiency
- Glutathione synthetase deficiency

Chromosome abnormalities

- Turner syndrome (45,X)
- triploidy
- other chromosomal rearrangements
- trisomy 21
- trisomy 13
- trisomy 18

Other genetic disorders/syndromes

- Noonan syndrome
- McKusik-Kaufman syndrome
- Neu-Laxova syndrome
- Kippel-Trenaunay-Weber syndrome
- Diamond-Blackfan syndrome
- tuberous sclerosis
- skeletal dysplasias
- myotonic dystrophy
- nemaline myopathy
- recurrent isolated hydrops

Disorders of fetal movement

- arthrogryposis
- Pena-Shokeir sequence (fetal akinesia)

Neurologic Manifestations

Tone - In a variety of metabolic disorders, tone frequently is abnormal; most commonly hypotonia is seen. In addition to encephalopathy, posturing or stereotyped movements, as seen in MSUD or hyperammonemia, may give the impression of peripheral hypertonia. Infants with MSUD in particular may exhibit opisthotonus. Dystonia may be an early finding in a subset of disorders, in particular glutaric aciduria type 1 (glutaryl-CoA dehydrogenase deficiency), with selective injury to the basal ganglia, and in disorders of neurotransmitter synthesis such as L-amino acid decarboxylase deficiency, where autonomic instability is quite prominent.

Lethargy - in the intoxication disorders, lethargy becomes more prominent and seizures may be apparent as the infant is increasingly obtunded.

Tachypnea - the development of tachypnea may reflect a central effect of hyperammonemia early in its course. Tachypnea may also be a response to progressive metabolic acidosis.

Apnea - In contrast, infants with NKHG often present with apnea as the initial clinical feature, only later developing seizures.

Posturing - Posturing associated with intoxication is perceived as seizure activity, although, with rare exception, true convulsions are an inconsistent feature of IEM. Seizures dominate the clinical picture in pyridoxine-dependent and folinic-acid–responsive seizures (both due to ALDH7A1 deficiency). Also associated with seizures are sulfite oxidase deficiency, the related disorder molybdenum cofactor deficiency, and peroxisomal biogenesis disorders such as Zellweger syndrome. Likewise, the glucose transporter defect (GLUT 1) can be considered in infants with seizures, and a CSF glucose determination is diagnostic.

Ophthalmological features/examination - Cataracts may develop when metabolites accumulate (e.g., Galactosemia) or can be part of an energy disorder (e.g., Sengers syndrome; mitochondrial DNA depletion). Corneal clouding may occur in storage disorders.

Disorders of energy production - These disorders have a more variable neurologic picture.

- Often the infant has no well interval and typically is hypotonic.
- Hypertrophic cardiomyopathy is a frequent feature and dysmorphism and malformations, especially of the brain, can be attendant findings.
- While neurologic signs are prominent, coma rarely is a feature.
- Dystonia has been noted in a number of children with respiratory chain disorders, in particular complex I deficiency.
- Lactic acidemia with or without metabolic acidemia is a frequent, although not invariable, finding.

Liver Disease

Liver disease may be a prominent feature in a number of disorders. Hepatomegaly associated with hypoglycemia suggests GSD1 or GSD3, defects in gluconeogenesis, or fatty acid oxidation disorders. Evidence of liver failure (with jaundice, a coagulopathy, hepatocellular necrosis, hypoglycemia and ascites) suggests galactosemia, tyrosinemia type 1, respiratory chain disorders, disorders of glycoprotein glycosylation, or, in infants exposed to fructose-containing formula, hereditary fructose intolerance. Significant hepatic dysfunction and liver failure can also be observed in urea cycle disorders such as ornithine transcarbamylase (OTC) deficiency.

While deficiency of LCHAD, fatty acid transport, the carnitine palmitoyltransferases (CPTI/CPTII) and carnitine acylcarnitine translocase may lead to liver failure, most other disorders of fatty acid oxidation do not. Cholestatic jaundice without liver failure is a feature of the fatty acid oxidation disorders, disorders of bile acid metabolism and transport, Niemann-Pick type C, citrin deficiency (a partial urea cycle disorder), peroxisomal biogenesis disorders, and alpha1-antitrypsin deficiency. Distinguishing liver failure as a manifestation of an IEM from non-genetic etiologies can be quite challenging. Biochemical tests for IEM can be very abnormal secondary to hepatic insufficiency. For example, elevated plasma tyrosine and methionine is a frequent finding in liver failure. Depletion of mtDNA (e.g., Alpers syndrome, DGUOK or MPV17 deficiency) often leads to infantile liver failure, as does other forms of mitochondrial disease such as MTU1 deficiency that do not exhibit depletion.

Cardiac Disease

Functional cardiac disease is one manifestation of energy disorders. Both dilated and hypertrophic cardiomyopathy can be seen, occasionally in the same patient over time. An echocardiographic finding of left ventricular non-compaction may accompany a respiratory chain disorder or may be associated with the X-linked disorder, Barth syndrome, in which skeletal myopathy, 3-methylglutaconic aciduria, and episodic neutropenia co-exist. Fatty acid oxidation disorders such as LCHAD, VLCAD, or CPT2 can often lead to infantile cardiomyopathy. While Pompe disease has infantile, adolescent, and adult variants, it typically is several weeks to months of life before the infantile form exhibits the full clinical picture of severe hypotonia, mild hepatomegaly (without hypoglycemia) and hypertrophic cardiomyopathy (with giant QRS complexes). Pompe disease is now a target of newborn screening in selected States. Conduction abnormalities may accompany several disorders of fatty acid metabolism. In contrast to infant with sepsis, blood pressure is typically normal in IEM.

Laboratory Evaluation

In any infant with a suspected IEM, initial laboratory evaluation should include electrolytes, glucose, lactate, ammonia, blood pH, complete blood count, and urinalysis. Screening tests that detect a large number of IEM can be distinguished from tests that address a single specific entity, the former being of more value in the initial evaluation. It is important to draw the labs when the infant is acutely ill in order to obtain the most accurate results possible. When evaluating a sick infant, certain features direct the testing.

Blood ammonia level - should be determined promptly in encephalopathic infants. Draw the sample from a free-flowing vein or artery, place it on ice, and immediately assay in the laboratory. Values less than 100 micromolar/L are of little significance in newborns and do not provide an explanation for the

encephalopathy. However, ammonia values can change rapidly and repeated determinations may be indicated depending on the clinical circumstances. Ammonia levels also may be elevated in instances of severe hepatic disease due to other causes (e.g., neonatal herpes infection) or in vascular anomalies such as persistent ductus venosus.

Plasma amino acid analysis - This is an excellent screening test for a number of amino acidopathies and some organic acidurias. When ammonia is elevated, plasma glutamine and plasma alanine are often increased. Elevated alanine also is seen in the face of lactic acidosis, whether due to a genetic disorder or not (e.g., hypoxic injury). Glycine typically is increased in a disorder of glycine breakdown—NKHG, and certain organic acidurias such as propionic or methylmalonic acidemia (historically referred to as ketotic hyperglycinemias).

Urea cycle disorders often can be distinguished by plasma amino acid analysis. Elevated citrulline can be observed in 4 disorders:

- citrullinemia type 1 (argininosuccinate synthetase deficiency),
- citrullinemia type 2 (citrin deficiency),
- argininosuccinate lyase deficiency, and
- severe pyruvate carboxylase deficiency (a defect in gluconeogenesis).

In addition to modest elevation of citrulline, identifying argininosuccinic acid in plasma or urine is diagnostic for argininosuccinate lyase deficiency. Citrulline may also be elevated in renal failure. Elevated arginine is a constant finding in untreated arginase deficiency, although these patients generally are not symptomatic in the newborn period and the arginine level may be transiently normal and hence may be missed by newborn screening.

Several urea cycle disorders cannot be reliably distinguished by plasma amino acid analysis and require additional tests, including urine orotic acid, which accumulates in OTC, ASS1, ASL, and arginase defiency. The branched-chain amino acids leucine, valine, and isoleucine are elevated in MSUD, with leucine values typically 10- to 20-fold elevated. The finding of alloisoleucine is diagnostic for MSUD. Defects in serine biosynthesis are reflected in low plasma and CSF serine levels. These infants have a neurologic presentation, as manifested by seizures and microcephaly, and may exhibit IUGR, cataracts, skin anomalies and contractures (Neu-Laxova syndrome). CSF amino acid analysis is required to establish the diagnosis of NKHG but otherwise is of limited value. Combined increases in lactate and glycine may point to a group of disorders causing lipoic acid deficiency.

Determining the acid/base status of an infant and the presence or absence of an anion gap helps to distinguish organic acidurias and related disorders from urea cycle disorders, the latter typically not exhibiting metabolic acidemia. The level of lactic acid in blood is influenced by several factors, including adequacy of perfusion and whether a fasting or post- prandial sample was used. If the sample is drawn incorrectly, or is not assayed promptly, lactic acid levels often are spuriously elevated. Truly elevated (greater than 2 mM) venous lactic acid should prompt a search for an underlying cause; the higher the level, the greater the urgency. Moderate elevations (<6 mM) in lactic acid may not be accompanied by changes in blood pH.

Elevated lactic acid can accompany a number of inherited conditions, including:

- a variety of organic acidurias,
- disorders of glycogen breakdown,
- pyruvate dehydrogenase deficiency,
- respiratory chain disorders,
- gluconeogenic defects, and
- vitamin cofactor transport or metabolism such as biotin or thiamine.

The finding of lactic acidemia should, at a minimum, prompt a complete metabolic evaluation. On occasion, severe lactic acidosis may resolve spontaneously later in infancy without explanation.

For certain organic acidurias such as propionic aciduria, glutaric aciduria type 2, or methylmalonic aciduria, hyperammonemia is a frequent, but not constant, finding. Combined hyperammonemia and lactic acidosis is also a feature of Carbonic Anhydrase 5A, where impaired mitochondrial bicarbonate production affects both ureagenesis and pyruvate metabolism. While lactic acid may increase modestly in organic acidurias, the often profound acidosis, and very prominent anion gap, is attributable to accumulation of the offending organic acid. Because of bone marrow suppression by the organic acid, severe leukopenia and thrombocytopenia may present, mimicking features of sepsis. Likewise, the finding of urine ketosis in a newborn should prompt a search for an IEM. With MSUD or defects in ketolysis (e.g., 3-ketothiolase deficiency or succinyl-CoA transferase deficiency), large amounts of ketones may be present in the urine and, conversely, defects in fatty acid oxidation typically demonstrate a hypoketotic state. Since carnitine is an important component of fatty acid metabolism, analyzing acylcarnitines in plasma (acylcarnitine profile) is a sensitive screen for many but not all of these disorders, and often is diagnostic for other organic acidurias. This is a major component of newborn screening.

Urine organic acid analysis – This is an excellent screening test for a large number of IEM. Since some diagnostic compounds are short– lived and volatile, urine collected in the acute phase of the illness and processed immediately yields the best diagnostic sensitivity. Determining urine orotic acid can be quite helpful in distinguishing the different urea cycle disorders. More recently, it was recognized that disturbed mitochondrial function, as seen in respiratory chain disorders, also may lead to an elevation in orotic acid due to the role of mitochondria in pyrimidine metabolism. Other pyrimidines such as uracil can be detected by urine organic acid analysis in symptomatic OTC deficiency.

Urine-reducing substance - detects galactosemia and related disorders. However, false-positive results occur following certain antibiotics, and elevated galactose can be seen in several other conditions in which the liver is not clearing galactose, including:

- tyrosinemia type 1,
- citrin deficiency,

- Fanconi-Bickel syndrome (GLUT2 deficiency),
- disorders of bile acid metabolism, and
- vascular shunts such as persistent ductus venosus.

Total plasma homocysteine - can be helpful in distinguishing several IEM. Since most plasma homocysteine is bound to protein, routine amino acid analysis may not detect significant elevations in homocysteine. Homocysteine may be elevated both in acquired and inherited abnormalities of vitamin B12 metabolism, including maternal B12 deficiency. It may be an isolated finding or may be elevated in concert with methylmalonic acid. Hence, obtaining a B12 level in an infant with a suspected organic aciduria can be useful to sort out these possibilities before administering 1 mg of hydroxycobalamin IM. Disorders of B12 metabolism may require considerably more B12 to improve homocysteine levels, while maternal deficiency (pernicious anemia) is corrected almost immediately with a single dose.

Homocystinuria is a rare disorder that typically escapes detection in infancy, and therapy with pyridoxine can be curative. Since homocysteine is prothombotic, it should be measured when investigating vascular events in infants and children. As newborn screening is expanded to include a large number of other conditions, homocystinuria should be routinely detected in newborns. The distinguishing feature between homocystinuria caused by deficiency of cystathionine beta synthase and homocystinemia associated with B12 metabolism is the presence of very elevated methionine in the former case. Low homocysteine values can be seen in patients with sulfite oxidase or molybdenum cofactor deficiency. Sulfocysteine is found in both conditions, while certain urine purines will be elevated in the latter condition.

Muscle biopsy - when the clinical picture and plasma lactate measurements suggest a mitochondrial or respiratory chain disorder, a muscle biopsy may be recommended in consultation with the Genetics team. The muscle biopsy is analyzed for histologic or histochemical evidence of mitochondrial disease and may lead to recommendations of more genetic tests for specific mitochondrial diseases. Respiratory chain complex studies are then usually carried out on skeletal muscle or skin fibroblasts. DNA sequencing or quantitation of mtDNA in affected tissues may be indicated, and use of exome or genome next generation sequencing is supplanting the need for the more invasive muscle biopsy.

Online Resources

Several websites, including **genereviews.org**, provide information on specific disorders, tests currently available, and references to laboratories performing specific testing; online references such as The Metabolic and Molecular Basis of Inherited Disease and UptoDate are widely used in practice. Specialist Metabolic-Genetic consultation may helpfully guide investigation.

Treatment

Initial treatment of an infant with a suspected IEM depends in part on the initial laboratory evaluation, including electrolytes, glucose, lactate, ammonia, blood pH, complete blood count, and urinalysis. In general, plasma amino acid and urine organic acid analyses may be obtained within 24 hours, while an acylcarnitine profile may take 48 to 72 hours. However, treatment can begin before the diagnosis of a specific disorder is established and should not be delayed while awaiting specialized laboratory results. Aggressive correction of acidosis with bicarbonate, infusion of glucose for hypoglycemia, and provision of vitamin cofactors all can be done while a specific diagnosis is pursued.

Cystic Fibrosis

A newborn screen for cystic fibrosis may be normal, return a result of an elevated immunoreactive trypsinogen (IRT), or a very elevated IRT. IRT is an exocrine pancreatic protein which is elevated in CF and other GI diseases. If a baby's initial newborn screen at 24 to 48 hours of life has an elevated IRT, the newborn screen should be repeated at 1 to 2 weeks of age. If the repeat newborn screen is then negative, no further action is necessary.

However, if the IRT remains elevated, the State of Texas will automatically carry out a DNA analysis on the sample. This DNA analysis is a 60 + 4 panel and identifies one or more variants in up to 90% of patients in Texas, depending on ethnicity. The DNA analysis takes up to 5 days and may return no mutations, 1 mutation, or 2 mutations. If there are no mutations identified, no sweat testing is required but the patient should be carefully watched for the development of any respiratory symptoms. If there are 1 or 2 mutations identified, the patient should be referred for sweat testing. The baby must be a minimum weight of 2 kg, a minimum gestational age of 36 weeks, and a minimum chronological age of 2 weeks to qualify for a sweat test. If any newborn screen returns a result of a very elevated IRT, that baby's screen is immediately referred by the State for DNA analysis. It is important to note that an elevated IRT may also be caused by the stress of critical illness. In addition, a baby may have a false negative result as well if s/he has received multiple blood transfusions.

Infants with a positive newborn screen can undergo testing as early as 2 days of life. However, the Cystic Fibrosis Foundation recommends waiting until the child is 10 days old. For premature infants, testing should wait until they are 2 kg in size and greater than 36 weeks corrected gestational age, if possible. Infants with positive sweat tests and 2 mutations require a Pulmonary Medicine consultation. Patients with clinical indications of CF (e.g., meconium ileus) should receive evaluation with sweat test irrespective of the newborn screen result and should also be evaluated by Pulmonary Medicine. Should further gene sequencing be necessary, a full genetic panel through BCM is able to sequence the majority of the >1500 possible mutations for the disease.
For further information, please contact **Pam Tuley, CF center coordinator at 832-822-1348, patuley@texaschildrens.org**

Galactosemia

Infants with classical galactosemia frequently develop signs and symptoms of galactose toxicity before the results of newborn screening are available, requiring that pediatricians remain vigilant when persistent jaundice, coagulopathy, cataracts, or sepsis—particularly caused by E. coli is found.

Treatment is supportive in addition to substitution of the offending galactose-containing formula with a soy formula. Despite good dietary compliance two thirds of children with classic galactosemia exhibit neurologic sequelae including developmental delay, dysarthria, tremor and, rarely, ataxia.

GSD1

GSD1 can be managed acutely by glucose infusion and bicarbonate. Unlike cases of hyperinsulinism, the glucose requirements should not be greater than those of fasting infants. A nighttime milk drip using a soy based formula and addition of polycose to daytime feeds usually prevents hypoglycemia. Older children can be treated with cornstarch (1.5 to 2 gm/kg per dose, 4 to 6 times per day) to maintain blood glucose, and a more slowly digested modified cornstarch branded Gycosade for night time use.

In older children, treatment of hyperuricemia is needed, and in patients with GSD1B, chronic neutropenia requires treatment with G-CSF and other biologics.

MSUD

MSUD, a defect in the branched chain ketoacid dehydrogenase leading to elevated leucine, valine and isoleucine, can be a diagnostic challenge in that most common metabolic parameters are not very disturbed and, given the prominent neurologic features, other etiologies (such as herpes encephalitis, intracerebral hemorrhage, or epilepsy) are first sought. Modest acidosis and, when present, mild hyperammonemia are the rule, as is hypoglycemia due to leucine-mediated insulin release, however, urine ketones are typically notably increased. Brain edema, especially of the cerebellum and brain stem, frequently is observed. Because of this, excessive fluid resuscitation can be catastrophic in older children.

Provision of non-protein calories and insulin can help improve the metabolic abnormalities and providing a branched-chain amino-acid–free formula allows protein synthesis to proceed, reducing the levels of the toxic branched-chain amino acids.

Careful monitoring of amino acid levels in the plasma is required since valine and isoleucine supplementation usually is needed to reduce leucine levels.

Depending on the clinical severity, dietary management with a branched chain amino acid free formula or hemodialysis can be used to rapidly reduce leucine levels. Long term treatment may require liver transplantation.

Organic Aciduria

A newborn who is hyperammonemic and severely acidotic can be assumed to have an organic aciduria. In this setting, intravenous administration of L-carnitine (100 mg/kg per day divided t.i.d.) can relieve secondary carnitine deficiency and help to remove the offending organic acid. In addition to bicarbonate, providing calories in the form of glucose and insulin can reverse the catabolic state that contributes to metabolic perturbations. Administration of the vitamins thiamine (100 mg), biotin (10 mg), and hydroxycobalamin (1 mg) will address vitamin- responsive forms of organic acidurias. Frequently the hyperammonemia will respond to these therapies promptly, avoiding the need to dialyze the infant. Carbaglu (carglumic acid) can improve the hyperammonemia associated with organic acidurias.

PKU

Infants with PKU or milder hyperphenylalaninemia have no acute metabolic decompensation and treatment should be initiated by 2 to 3 weeks of life. Treatment involves a low-phenylalanine diet (in infancy, a phenylalanine-free formula supplemented with regular formula to provide the prescribed amount of phenylalanine) for life with frequent monitoring of plasma phenylalanine levels. With good dietary compliance, developmental outcomes are very good. A subset of children respond to enzyme cofactor supplementation (tetrahydrobiopterin), and novel therapies such as subcutaneous enzyme replacement therapy are now commercially available for older patients.

Urea Cycle Disorders

An infant with a urea cycle disorder, if identified early in the course, may not have secondary metabolic consequences, such as respiratory acidosis, found in those infants diagnosed later. The acid/base status tends to respond much more readily to bicarbonate than in the organic acidurias, and hydration and glucose alone improves the biochemical parameters. Infants with ornithine transcarbamylase deficiency frequently present with respiratory symptoms and hypotonia shortly after birth.

Severe hyperammonemia typically requires hemodialysis; other treatment options using medications to provide alternative pathways for excess nitrogen excretion (phenylacetate and benzoate; Ammonul) are available.

Surgical placement of dialysis catheters of appropriate size is essential for effective dialysis. While dialysis is being orchestrated, a priming infusion of sodium phenylacetate, and sodium benzoate (250 mg/kg of each) along with 200 to 600 mg/kg of arginine in 25 to 35 mL/kg of 10% dextrose can be administered over 90 minutes. The same doses then are given over 24 hours.

While the availability of Ammonul is typically limited to tertiary care hospitals, arginine is widely available. The dose of arginine depends on which urea cycle disorder is suspected but until a diagnosis is established 600 mg/kg is recommended. The arginine replenishes intermediate molecules of the urea cycle and replaces the arginine normally generated by the kidney via the urea cycle for protein synthesis to reverse protein catabolism. In conjunction with a protein restricted diet, administration of arginine alone is effectively curative in argininosuccinate lyase deficiency. While it would not be indicated for Arginase deficiency, this condition is generally not symptomatic in neonates.

Again, glucose and insulin infusion can help treat urea cycle disorders and, for the most common urea cycle disorder (X-linked ornithine transcarbamylase deficiency), oral citrulline (200 mg/kg per day) can help reduce ammonia levels. Administration of any of these medications should be done in consultation with the Genetics Service.

Newborn Screening

Currently, the state of Texas requires that all newborns be screened twice. The first screen is obtained between 24 and 48 hours of age and the second between the first and second week of life. Using highly sensitive, high throughput technology (tandem mass spectrometry), enhanced newborn screening detects a large number of additional IEM (e.g., many of the disorders of fatty acid oxidation, organic acidurias, and amino acidopathies), often before the onset of symptoms. Expanded newborn screening in Texas includes 32 core disorders (including hearing screen and critical congenital heart disease

[CCHD] screen) and 24 secondary disorders (**Table 6–2**). Expanding testing to include lysosomal storage disorders is anticipated. Spinal muscle atrophy (SMA) affects about 100 children in Texas each year. SMA is a debilitating condition, however, if detected early it is treatable. The Texas Department of State Health Services will begin SMA newborn screening in early summer of 2021.

Ideally, the first test should follow a protein- containing meal to detect elevated phenylalanine. Accurate quantitation depends on the blood spot filter paper being adequately saturated. Testing is performed by the Texas Department of State Health Services which, for the detection of galactosemia, currently measure only GALT (galactose-1- phosphate uridyl transferase) activity directly. This fails to detect those infants with elevated galactose from other causes such as galactokinase deficiency.

Expanded testing is also available commercially in Texas. Information regarding additional metabolic screening is available upon request from the Genetics Service. Patients with Downs's syndrome have a high risk for hypothyroidism (1%), which can be missed by the T4-based state newborn screening. Thyroid function testing is recommended for babies with confirmed Down syndrome.

Table 6–2. Newborn screening program in Texas

Disorder group	
Amino acid disorders	• Argininosuccinic Acidemia (ASA) • Citrullinemia (CIT) • Homocystinuria (HCY) • Maple syrup urine disease (MSUD) • Phenylketonuria (PKU) • Tyrosinemia (TYR 1)
Fatty acid oxidation disorders	• Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD) • Very Long Chain Acyl-CoA Dehydrogenase deficiency (VLCAD) • Long Chain Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD) • Trifunctional Protein Deficiency (TFP) • Carnitine Uptake Defect (CUD)
Organic acid disorders	• 3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC) • Beta-Ketothiolase Deficiency (BKT) • Glutaric acidemia type I (GA-I) • 3-OH-3-Hydroxy Methyl Glutaric aciduria (HMG) • Isovaleric acidemia (IVA) • Methylmalonic Acidemia(MMA) (B12) • Methylmalonic acidemia (mutase deficiency form) (MUT) • Multiple Carboxylase Deficiency (MCD) • Propionic acidemia (PA)
Other disorders	• Cystic Fibrosis (CF) • Biotinidase deficiency (BIOT) • Congenital adrenal hyperplasia (CAH) • Congenital hypothyroidism (CH) • Galactosemia (GALT) • Sickle Cell Disease (SCD) including HbS/S), Hb S- Beta thalassemia,Hb S/C • Severe Combined ImmunoDeficiency (SCID) • X-linked Adrenoleukodystrophy (X-ALD)

6.2 Genetic Testing

Karyotype or Chromosome Analysis - The karyotype is a method by which the number and appearance of chromosomes in the cell are analyzed microscopically. Chromosome analysis has much lower resolution for detecting genomic deletions or duplications and has largely been replaced by chromosomal microarray analysis (CMA) in the evaluation of children with multiple congenital anomalies and unexplained intellectual disability. However, chromosome analysis remains the first-line genetic test in the evaluation of certain conditions such as balanced translocations, triploidy, mosaicism, and some sex chromosomal abnormalities including Turner syndrome. Karyotype is also recommended for all patients with Down syndrome to determine if the patient has trisomy 21 or a translocation, as the detection of a translocation may affect recurrence risks for the parents. Karyotype study is also recommended for evaluation of other common aneuploidies such as trisomy 18 and 13. Chromosome analysis may take 2-3 weeks to result.

FISH (Fluorescent In Situ Hybridization) - FISH is a method in which a fluorescent DNA probe is hybridized to chromosomes to test whether a specific portion of the chromosome is present or absent. Thus, FISH is used to detect specific duplications or deletions. With the advent of CMA, FISH is less commonly used to test for deletion or duplication syndromes (e.g., del 22q11.2). However, in a situation where a CMA cannot be obtained, FISH for a specific deletion syndrome may be helpful if a patient's presentation is highly suspicious for a particular syndrome. One advantage of FISH is that test results may be obtained in 48-72 hours for aneuploidy if the test is ordered STAT and the sample is received during working hours on the same day as collection. Thus, FISH has become useful for obtaining preliminary results regarding trisomies, particularly trisomy 18 and 13. In addition, STAT FISH for the presence of the X chromosome and SRY may be recommended in the setting of a suspected disorder of sex development.

Chromosomal Microarray Analysis (CMA)

CMA, using microarray-based comparative genomic hybridization (array CGH), is available through the BCM Cytogenetics Laboratory and other commercial laboratories. CMA includes probes for all the known microdeletion/duplication syndromes, pericentromeric regions, and subtelomeric regions. Additionally, CMA includes probes that cover thousands of single genes, and thus can detect exon-specific deletions or duplications within these genes. Typically, when considering array CGH, the "CMA-comprehensive" version is recommended. The advantage of the CMA-comprehensive is that SNP (single nucleotide polymorphism) data are included in the analysis along with the

oligonucleotides, and thus areas of AOH (absence of heterozygosity) and uniparental isodisomy may be identified. CMA provides a major advance to assist the clinician in the identification of patients in which a genetic cause of disability is strongly suspected.

CMA is limited to detection of gain or loss of genomic material. It will not detect balanced translocations, inversions, small balanced insertions, trinucleotide repeat disorders, or point mutations that may be responsible for the clinical phenotype. Furthermore, CMA may detect copy number variants of unknown significance, and counseling regarding the significance of such findings may require parental testing to determine if the variant is inherited from a parent or de novo in origin in the child. Lastly, the CMA tests that incorporate SNP data can also identify consanguinity.

Single Gene Testing

Single gene testing (e.g., sequencing to identify base substitutions or small insertions or deletions) with or without deletion/duplication analysis (e.g., to detect large deletions or duplications) is the genetic testing method of choice when the differential diagnosis has been narrowed to a single disorder that is associated with one or a small group of genes. For example, if biochemical genetics testing is consistent with a diagnosis of ornithine transcarbamylase (OTC) deficiency, sequencing and deletion/ duplication of the OTC gene is the test of choice. If spinal muscular atrophy is strongly suspected in an infant with hypotonia, then single gene testing for this diagnosis should be requested.

Gene Testing Panels - Gene sequencing panels are useful when testing (typically sequencing) for a specific group of genes is desired. Gene testing panels are typically offered for specific diagnoses (e.g. Noonan syndrome panel) or for specific phenotypes (e.g. hypoglycemia panel). Panels can help the clinician interrogate all the known genetic causes of a particular condition simultaneously, and the advancements in DNA sequencing technology (Next Generation Sequencing; NGS) allow for large panels of relevant genes to be developed for use in a timely and cost-effective manner.

WES (Whole Exome Sequencing) - Unlike single gene testing, whole exome sequencing evaluates the coding sequences of thousands of genes simultaneously. The "exome" refers to all of the protein coding regions of all genes (approximately 20,000) and requires a "capture" step to isolate the DNA regions encoding exons. As a result of the wide coverage of the genome, sequence changes in genes that are unrelated to the phenotype in question may be identified. For example, variants in genes associated with adult-onset disorders such as breast cancer genes may be identified in neonates with this test (referred to as "Incidental Findings" and reported as "actionable results", currently constituting 59 genes). Thus, whole exome sequencing is a complex test and requires consent prior to ordering the test. Families should get pre-test counseling and be aware of all possible test results (carrier status, actionable results, etc.) in order to select the information that they would like to receive in the report. Whole exome sequencing is typically performed in patients in whom a specific diagnosis is not obvious even though their phenotype is suspicious for a genetic etiology, for conditions in which a specific genetic test or panel is not available, or for conditions in which the list of associated genes is quite large. In addition, this test may be ordered in patients who are critically ill as the CMA + WES may be the most comprehensive genetic testing available and, in many cases, may provide the best prospects for diagnosis. To facilitate a result in a critically ill patient, WES should be ordered as a "Critical Trio Whole Exome Sequencing" which has ~2 week turnaround time. In such cases, it is important to remember that even if a genetic diagnosis will not alter management of the patient, it may be useful for families in determining recurrence risk and in planning future pregnancies. Currently, the Critical Trio WES provides a specific diagnosis in approximately 40% of infants. WES has limitation in that it does not detect trinucleotide repeat disorders such as congenital myotonic dystrophy. At present, WES is not regularly utilized for assessment of copy number changes in the genome. High resolution CMA is recommended to increase the chance of finding a deletion not detected by DNA sequencing.

WGS (Whole Genome Sequencing) - WGS is being increasingly utilized in select NICUs for rapid genetic diagnosis of critically ill neonates. WGS is able to detect both copy number changes as well as coding variations ascertained by WES. In addition, it can identify trinucleotide and other repeat expansion disorders, and deep intronic and other non-coding changes that may affect RNA splicing or the regulation of gene expression that are not detected by WES. As the cost of WGS decreases, it may become the test of choice for rapid diagnosis of severely ill infants with birth defects. Newer technologies such as RNA sequencing (RNA-Seq) will soon become available clinically and will enhance the diagnostic sensitivity. It is strongly encouraged to consult the genetic team before ordering WGS or RNA sequencing.

Suggested Reading

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Genetic Testing

The most updated and most commonly recommended CMA is the CMA comprehensive (CMA HR+SNP) https://www.bcm.edu/research/medical-genetics labs/test_detail.cfm?testcode=8665&show=1&CFID=21561065&CFTOKEN=29382011 for more details.

Section 7: Hematology

Editors: Caraciolo Fernandes and Joseph Garcia-Prats

7.1 Approach to the Bleeding Neonate

Bleeding problems are commonly encountered in the neonatal intensive care unit. Thrombocytopenia is probably the most common problem, but coagulation abnormalities also are observed, and the two often coexist. Although most bleeding problems in the NICU reflect acquired disorders, inherited conditions occasionally present in the neonatal period. Initiation of therapy for clinically significant bleeding may confound the interpretation of diagnostic studies and delay a definitive diagnosis. Thus, appropriate initial investigation and management of these conditions is crucial.

Neonatal Hemostatic System

Normal hemostasis is a highly complex process that depends on a series of interactions that occur between platelets, endothelial cells, and hemostatic proteins. Historically, the normal platelet count for newborns has been assumed to be similar to adults (150,000 to 450,000/µL). However, healthy preterm and term newborns can have counts significantly outside these ranges: 104,000 to 750,000/µL, representing the 5th and 95th percentiles, respectively. The normal platelet count increases in postnatal life in a sinusoidal fashion with two peaks, at 2-3 weeks and 6-7 weeks. At birth, concentrations of many of the hemostatic proteins are low, as they are solely synthesized by the fetus and do not cross the placenta. Vitamin K dependent factors (II, VII, IX, X) are initially decreased due to reduced hepatic stores, limited placental transfer of vitamin K, limited content of vitamin K in breast milk and sterile gastrointestinal tract. Vitamin K dependent factors and the other contact factors (XI, XII) are about 50% lower than normal adult values in term infants and even lower in preterm infants. Similarly, fibrinolytic capacity is reduced in neonates due to decreased concentrations of antithrombin, protein C, and protein S. Despite the functional immaturity and apparent counterbalances, healthy term and preterm infants rarely display overt bleeding. The hemostatic system matures rapidly during the early weeks and months of life, and the concentrations of most hemostatic proteins reach near-normal adult values by 6 months of age.

Table 7–1. Differential diagnosis of bleeding in the neonate

Clinical Evaluation	Platelet Count	PT	PTT	Likely Diagnosis
'Well'	**N**	**N**	**N**	Bleeding due to local factors (trauma, anatomic abnormalities), qualitative platelet abnormalities, factor XIII deficiency
	N	**N**	**↑**	Hereditary clotting factor deficiencies
	N	**↑**	**↑**	Hemorrhagic disease of the newborn (vitamin K deficiency)
	↓	**N**	**N**	Immune thrombocytopenia, occult infection, thrombosis, bone marrow infiltration/ hypoplasia
'Sick'	**N**	**N**	**N**	Compromised vascular integrity (associated with hypoxia, prematurity, acidosis, hyperosmolarity)
	N	**↑**	**↑**	Liver disease
	↓	**N**	**N**	Platelet consumption (infection, NEC, renal vein thrombosis)
	↓	**↑**	**↑**	DIC

'Well' implies the bleeding problem is an isolated issue. '**Sick'** implies that the bleeding problems is not an isolated issue, but part of another/systemic disorder.

N, **↑**, and **↓** represent normal, increased, and decreased respectively.

Abnormal Bleeding

The diagnostic approach to the bleeding neonate should take into account the infant's history and clinical condition. On the basis of this information, a presumptive diagnosis may be entertained and preliminary investigations and treatment planned **(Table 7–1).**

In the case of bleeding in the early newborn period, important considerations may include:

- maternal history
- details of the labor and delivery
- examination of the placenta
- infant's physical examination
- vitamin K administration
- need for resuscitation

The clinical condition of the infant provides valuable clues to likely diagnoses, as healthy infants are more likely to have immune-mediated or genetic causes of bleeding, while infants with systemic illness are more likely to have bleeding caused by infection, asphyxia, necrotizing enterocolitis, or disseminated intravascular coagulation (DIC). The infant should be examined to determine the bleeding sites, the extent and type of bleeding, and the presence of skin or mucosal lesions, jaundice, hepatosplenomegaly, or dysmorphic features.

Initial laboratory studies should include:

- complete blood count (CBC)
- prothrombin time (PT)
- activated partial thromboplastin time (aPTT)

For infants at risk for DIC, fibrinogen concentration and fibrin split products (d-dimer) should be performed. Infants who appear ill should be evaluated and treated for sepsis.

Inherited Coagulation Disorders

Hemophilia is the most common inherited bleeding disorder to present in the newborn period. Hemophilia A (factor VIII deficiency) presents more frequently than hemophilia B (factor IX deficiency) and both exclusively affect males due to the X-linked recessive inheritance pattern. Bleeding most commonly manifests from iatrogenic causes (prolonged oozing from venipuncture site, circumcision, etc.), but can also present as isolated intracranial or extracranial

hemorrhage (e.g. cephalohematoma or subgaleal hemorrhage). Isolated prolongation of aPTT will be present followed by the confirmation of serum factor levels. Interestingly, it is difficult to diagnose mild hemophilia B in the neonatal period due to previously mentioned relative reduction in factor IX level after birth.

If hemophilia is suspected, acute management consists of the following:

- avoidance of invasive monitoring procedures
- deference of intramuscular vitamin K until hemophilia is excluded
- administration of fresh frozen plasma (15-25 mL/kg) if significant bleeding is present

In the case of inherited coagulation disorders, once the diagnosis has been reached, the infant should be managed in conjunction with the Hematology Service.

Acquired Coagulation Disorders

Vitamin K deficiency bleeding is now rarely seen following the advent of routine vitamin K prophylaxis; however, it may still occur in infants born to mothers on warfarin or anticonvulsants.

Disseminated intravascular coagulation (DIC) is the most common acquired coagulation disorder. DIC is a complex systemic process involving activation and dysregulation of both coagulation and inflammatory processes, and presents clinically with both bleeding and thrombotic problems leading to multiorgan failure.

DIC occurs as a secondary event, and common etiologies include:

- perinatal hypoxia-ischemia
- sepsis
- necrotizing enterocolitis
- respiratory distress syndrome
- meconium aspiration syndrome
- severe hepatic dysfunction
- metabolic disorders (e.g. galactosemia)

Laboratory diagnosis of DIC is usually based on a typical pattern of reduced platelets, prolonged coagulation variables (PT, aPTT with or without thrombin clotting time), reduced fibrinogen, and increased d-dimers or other markers of fibrin or fibrinogen degradation. As DIC is a secondary process, it is important that the underlying cause is promptly recognized and treated. Management of DIC is essentially supportive with the use of fresh frozen plasma, cryoprecipitate, and platelets to try to maintain adequate hemostasis. Fresh frozen plasma (10 to 15 ml/kg) is used to replace multiple hemostatic proteins, and cryoprecipitate (5 to 10 ml/kg) is preferred to treat hypofibrinogenemia.

7.2 Platelet Disorders

Thrombocytopenias

Thrombocytopenia occurs in 1% to 5% of the general newborn population at birth, with severe thrombocytopenia (platelets less than 50,000/μL) occurring in 0.1% to 0.5%. However, thrombocytopenia is more common in sick newborns, and develops in 22% to 35% of babies admitted to the NICU, and in up to 50% of those in the NICU who require intensive care.

The causes of neonatal thrombocytopenia **(Table 7–2)** primarily fall into two broad categories: decreased production and increased destruction, although occasionally both may co-exist. Immune-mediated thrombocytopenia is commonly seen in the early newborn period, especially in otherwise healthy newborns. The most common of these is neonatal alloimmune thrombocytopenia. Thrombocytopenia developing or significantly worsening at greater than 72 hours is almost always caused by late-onset sepsis or NEC.

Treatment consists of controlling and treating the underlying illness in addition to potentially correcting the thrombocytopenia. When thrombocytopenia is severe, affected neonates may require multiple platelet transfusions until sepsis or NEC is controlled, followed by a slow recovery in platelet numbers over the following 4 to 5 days.

There is scant evidence that platelet transfusions improve neonatal outcomes, and most current guidelines are consensus guidelines rather than evidence-based guidelines **(Fig 7–1).** Treatment thresholds for NAIT are given later.

Table 7-2. Causes of neonatal thrombocytopenia

Increased destruction or consumption of platelets

- Immune thrombocytopenia
  - Autoimmune
  - Alloimmune
  - Drug-induced
- Peripheral consumption
  - Hypersplenism
  - Kasabach-Merritt syndrome
  - Disseminated intravascular coagulation
  - Thrombosis
  - Type 2B von Willebrand disease

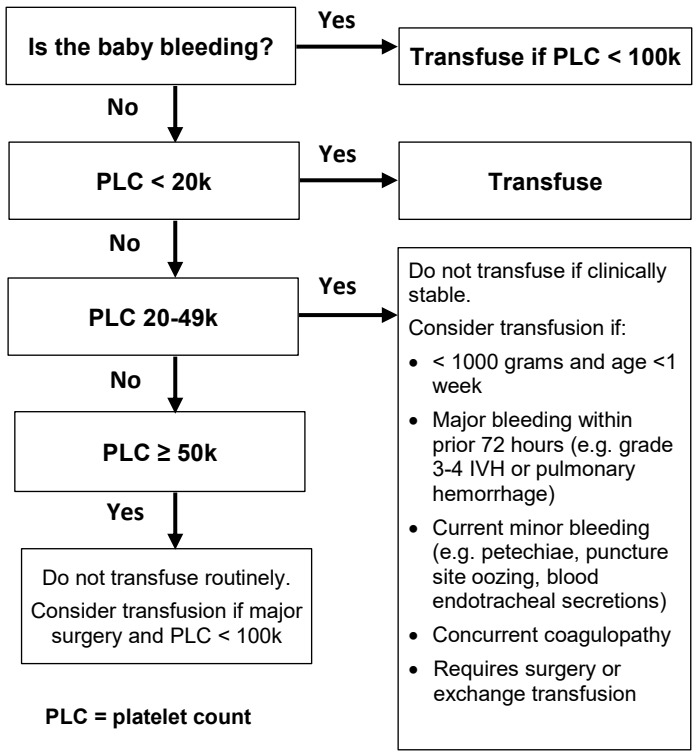
Decreased production of platelets

- Congenital thrombocytopenias
- Infiltrative bone marrow disorders
- Infection-associated marrow suppression: bacterial, viral, or fungal
- Preeclampsia

Miscellaneous

- Infection
- Asphyxia
- Dilution

Figure 7-1. Guidelines for platelet transfusion in the newborn



Neonatal Alloimmune Thrombocytopenia (NAIT)

NAIT is a unique etiology for neonatal thrombocytopenia that can have life-threatening hemorrhagic consequences. It occurs in approximately 1 in 2000 live births and can present in the first pregnancy. It is important to quickly recognize the neonate in whom **NAIT** is a diagnostic consideration. Prompt initiation of the appropriate treatment is crucial in these infants as well as the appropriate serologic testing and follow up.

Background – **NAIT** occurs when fetal platelets express antigens (human platelet antigens, HPA) against which there are circulating maternal antibodies. The HPA-1 (formerly known as PLA1) is responsible for NAIT in approximately 75 to 90 percent of cases in Caucasians; in Asians, HPA-4 (Yuk/Pen) is the most frequent cause of **NAIT**.

NAIT may be distinguished clinically from other etiologies of neonatal thrombocytopenia by the more frequent occurrence of severe thrombocytopenia (usually < 50,000/μL) and bleeding manifestations regardless of platelet counts. Intracranial hemorrhage has been reported to occur in up to 20% of patients with NAIT, making this the most common cause of intracranial hemorrhage in term neonates.

Diagnostic evaluation and treatment for **NAIT** are distinct from other etiologies of neonatal thrombocytopenia, and require prompt collaboration among the treating clinician, pediatric hematologist, and blood bank physician. Delay of management could cause a detrimental outcome for the neonate. Thrombocytopenia may resolve in the first 2 to 3 weeks of life.

Definitions—NAIT should be considered in the differential diagnosis of a neonate (term or preterm) who is < 7 days old and has severe thrombocytopenia (usually <50,000/ μL) for which there is no clear explanation. The other CBC parameters are usually normal. These infant are clinically well appearing, and may have family history of transient neonatal thrombocytopenia.

I. Clinical management of neonates with suspected NAIT

A. Consultation with a pediatric hematologist and a blood bank physician. For some infants, this may necessitate transfer to a tertiary-care facility.

B. If **NAIT** is suspected and a criterion listed below is met, promptly initiate treatment with platelet transfusions. Do NOT wait for definitive test results.

C. Many mild cases of NAIT can be managed with HPA-unselected (random donor) platelets. For patients with severe presentations, or those refractory to standard transfusion, the process for obtaining antigen-negative or maternal platelets will be initiated by the blood bank physician. These products are not immediately available, so transfusion of random donor platelets should be repeated as needed until antigen-negative platelets or washed, irradiated maternal platelets are available.

Platelet transfusion criteria in **NAIT**:

1. Platelet count is less than 30,000/μL in an uncomplicated, term infant
2. Platelet count is less than 50,000/μL in an uncomplicated, preterm infant (i.e. less than 37 weeks gestation)
3. Platelet count is less than 100,000/μL in infants with life-threatening intracranial or gastrointestinal hemorrhage.

Note: Consider transfusion at a higher platelet count (e.g. less than 100,000/μL) in very low birth weight infants (less than 1500 grams), who are at high risk for intraventricular hemorrhage (IVH) and other co-morbid conditions.

D. Check platelet counts 20 minutes to 1 hour after transfusion. Since the recovery and half-life of random donor platelets, presumably antigen-positive, are not optimal, carefully monitor the platelet count. Antigen-negative or maternal platelets are expected to result in higher and longer-lasting platelet counts.

E. Administer IVIG (1 gram/kg). This may be repeated if no increase in platelet counts occurs following the initial dose.

F. If indicated, the blood bank will initiate and conduct testing to identify the platelet antibody. Once the platelet antibody is identified, the blood bank will try to obtain the corresponding antigen-negative platelet units. If maternal platelets are obtained, they must be washed and irradiated prior to transfusion. Once washed, platelets must be transfused within 4 hours (from wash start).

Note: Steroids are not indicated for the treatment of **NAIT**.

II. Clinical follow up for the infant

A. During acute inpatient course:

1. Follow (at a minimum) daily platelet count to assess response to therapy.
2. Obtain radiologic evaluation on all thrombocytopenic infants (head ultrasound vs. CT) even if the infant is asymptomatic.
3. Perform definitive laboratory testing for **NAIT** as directed by hematology**.**

B. After discharge from the hospital:

1. Follow-up with a hematologist should be planned for all infants with **NAIT.** Even if the neonate does not have severe thrombocytopenia, work-up for the parents is needed prior to subsequent pregnancies.
2. Family testing results and counseling about future pregnancies must be discussed and carefully documented.

7.3 Transfusion of Blood Products

Transfusion of Packed Red Blood Cells (PRBC)

Before initial transfusion, written informed consent must be obtained using the Disclosure Panel information outlined by Texas law. For each transfusion, a note outlining the indication for transfusion should be placed in the patient's chart.

The recently published TOP and ETTNO trials have concluded that using lower threshold transfusion cut-offs do not result in significantly higher death or disability at ~ 22-26 months of age. The current guidelines are to be used across all patient populations in the Newborn Center based on these trials.

General indications for blood transfusions in neonates are:

- **Acute, hypovolemic shock** - The goal of therapy is prompt correction of the estimated blood volume deficit with improvement of accompanying circulatory derangements. Whole blood is preferred, but rarely available acutely. Volume expansion may be initiated with normal saline followed by packed RBCs as soon as available.
- **Acute cardiopulmonary disease -** Transfusion may be indicated if hematocrit is less than 32-35% or if symptoms of circulatory insufficiency are present. Symptoms include hypotension, oliguria, lactic acidosis, or impairment of pulmonary perfusion.
- **Diseases associated with low PaO_2 or circulatory insufficiency -** Transfusion may be indicated to improve central oxygen content and thus oxygen delivery even if hematocrit is in normal range.
- **Chronic anemia (e.g., prematurity) -**Transfusion is indicated only if specific symptoms related to anemia occur, such as persistent tachycardia, poor weight gain, or apnea without other discernible cause.
- **Blood group incompatibilities -**Simple transfusion may be indicated if anemia produces specific symptoms or produces evidence of impaired tissue oxygenation.

Decision to transfuse should be based on the symptoms related to anemia and laboratory parameters (Hct/Hb, reticulocyte count). There are no universally accepted guidelines**.** See **Table 7-3** for suggested thresholds.

Transfusion and Risk of Necrotizing Enterocolitis

Evidence relating to the risk of NEC associated with transfusion (TANEC) is limited, primarily retrospective, and conflicting. Moreover, data from recent meta-analyses and randomized trials suggest that transfusions alone may not cause NEC, but rather the severity of anemia that may potentially lead to an increased risk of NEC. **(Ch 13-3. Enteral Nutrition)**

Transfusion Volume

Transfusions should be given as packed red blood cells, 15 mL/kg, over 2 to 4 hours. In infants with hemodynamic instability, a smaller volume (10 mL/kg) may be given more rapidly (over 1 to 2 hours). Exposure to multiple donors should be minimized. In severely anemic infants, an isovolemic blood transfusion should be considered to raise the

Table 7-3. Guidelines for PRBC transfusion

Severity of Illness	Clinical Status	Transfusion Trigger Levels
Severe	• Mechanical ventilation • NIPPV, CPAP or HFNC >2 LPM with FiO2 > 40 % • Hypotension, Acute sepsis or NEC with circulatory failure requiring inotropic or vasopressor support	32-35%
Moderate	NIPPV, CPAP or HFNC >2 LPM with FiO2 ≤ 40%*	28-30%
Mild	No respiratory support or respiratory support ≤ 2LPM but have signs highly likely to be related to anemia such as poor weight gain despite adequate calories, significant apnea and tachycardia for more than 24 hrs.	25%
Asymptomatic		22%
*Presence or absence of signs and symptoms attributed to anemia can also be factored into decision-making		

hematocrit without the risk of causing circulatory overload. The technique of the procedure is similar to that for an exchange transfusion **(Ch 7.5-Management of Neonatal Jaundice),** and the calculation for amount of blood to be exchanged with high Hct-packed cells is similar to that for treatment of polycythemia.

$$\text{Volume exchanged (mL)} = \frac{[\text{Hct}_{\text{desired}} - \text{Hct}_{\text{observed}}] \times \text{Weight (kg)} \times 80\text{mL/kg}}{\text{Hct}_{\text{packed cells of transfusion}}}$$

Erythropoietin

Premature infants have low plasma erythropoietin levels. They typically respond to administration of recombinant human erythropoietin (rh) EPO with an increased reticulocyte count within 96 hours and an increased hematocrit in approximately 5 to 7 days. However, EPO administration has little impact on exposure to transfusions in these patients, even when given within the first 4 days after birth. Additionally, use of EPO in preterm infants has been associated with an increased incidence of hemangiomas. We do **not** recommend routine use of EPO and consider its use only in special circumstances (strong recommendation, moderate quality evidence).

Monitoring for Anemia

Laboratory testing (a hemoglobin/hematocrit with a reticulocyte count, if indicated) to investigate the degree of physiologic anemia of infancy/prematurity should be considered as needed based on an infant's clinical status, need for positive pressure/oxygen support, size, recent phlebotomies, and most recent hematocrit. Frequency of such testing may vary from every 1 to 2 weeks in the sick, tiny premature infant on positive pressure support to once a month or less in a healthy, growing premature infant. Efforts should be made to cluster such routine sampling with other laboratory tests.

Transfusion of Fresh Frozen Plasma (FFP)

FFP is a plasma product made from whole blood and contains all of the coagulation factors and other proteins that were initially in the original unit of blood.

FFP is primarily indicated to replace acquired coagulation factor deficiencies in the following conditions:

- DIC,
- Liver failure
- Vitamin K deficiency- (Factors II, VII, IX, and X)

However, FFP is not a concentrate of any specific factor, and it should not be used as primary therapy to treat specific coagulation factor deficits such as with hemophilia A, hemophilia B, Factor VII deficiency or Factor XIII deficiency (strong recommendation, low quality evidence). Instead, for these situations, specific coagulation factor concentrates exist and should be used instead.

The decision to use FFP is made when a patient's coagulation studies are found to be abnormal (such as in DIC), specifically when PT, PTT, or INR are elevated. FFP should be given in 10-15 mL/kg boluses to replace the hemostatic proteins (10%-30% of most factors) that have likely been consumed in DIC (weak recommendation, low quality evidence). Coagulation studies including PT, PTT, and INR should be rechecked 18-24 hours after FFP.

Transfusion of Cryoprecipitate

Cryoprecipitate is the cold protein fraction obtained from frozen plasma thawed at 4o C a, and thus is called "cryo" (cold) precipitate. It contains concentrated plasma proteins, especially fibrinogen. Cryoprecipitate also includes other proteins such as Factor VIII, Factor XIII, fibronectin and von Willebrand factor. Cryoprecipitate is a reasonable treatment option in cases where a low level of fibrinogen is suspected, such as in cases of surgical bleeding, trauma, or DIC. It is often used in massive transfusion protocols in conjunction with FFP.

In DIC, administration of cryoprecipitate is often recommended if the fibrinogen levels are low, usually below 100 mg/dL. Cryoprecipitate contains less volume than plasma and more concentrated levels of fibrinogen, which makes it the choice for treatment when these low levels of fibrinogen exist. Cryoprecipitate is recommended for FXIII deficiency.

Once the decision has been made to transfuse cryoprecipitate, transfuse 5-10 mL/kg.

If an infant is found to have severe coagulopathy and/or the coagulopathy is resistant to transfusion of FFP and/or cryoprecipitate, consider consulting the Transfusion Medicine service for further evaluation and recommendations on treatment. In addition, if a patient is on ECMO, then the Transfusion Medicine team should be consulted for recommendations for correction of underlying coagulopathies.

Transfusion of Platelets

The standard dose of platelet transfusion is 5-10ml/kg of whole blood derived platelets. Although, this dose is expected to increase platelets by 50-100 x 10^9/L; in neonates, the actual increase is significantly lower as the underlying cause for thrombocytopenia is mostly due to destructive process (DIC, NAIT, Sepsis).

There is scant evidence that platelet transfusions improve neonatal outcomes, and most current guidelines are consensus guidelines rather than evidence-based guidelines. **(Fig 7–1)** As a general rule, platelet transfusions should be administered to thrombocytopenic neonates when there is a significant risk of hemorrhage due to the degree of thrombocytopenia alone or in combination with other complications of the underlying disease. When used, platelet transfusions should always be given in conjunction with aggressive therapy for the underlying disorder that caused the thrombocytopenia**. (Fig 7-1)**

7.4 Neonatal Jaundice

Pathophysiology of Jaundice

Postnatally, bilirubin is formed from breakdown of heme by the reticuloendothelial system, producing unconjugated bilirubin that is fat soluble. Degradation of heme produces equimolar amounts of biliverdin (subsequently metabolized to bilirubin) and carbon monoxide (CO). The end-tidal carbon monoxide concentration (ET-CO) is an index of total bilirubin production. Unconjugated bilirubin can cross cell membranes and is potentially neurotoxic, making infants at risk for bilirubin-induced neurologic dysfunction (BIND). However, such toxicity is avoided by albumin binding bilirubin in circulation for transport to the liver. Under normal circumstances, only a small amount of bilirubin is found in

the unbound state. The functional bilirubin binding capacity of albumin is the major determinant of risk of toxicity when the serum bilirubin level is elevated. Albumin binding capacity is reduced by acidosis, immaturity, and the presence of competitive substances such as salicylates, sulfonamides, and free fatty acids. Free fatty acids are particularly important competitors for bilirubin binding sites in preterm infants. The presence of such competitive substances increases the proportion of free bilirubin present and, thus, increases the risk of BIND.

The liver converts bilirubin using the enzyme uridine diphosphogluconurate glucuronosyltransferase (UGT1A1) to a water-soluble, non-toxic conjugated form. Transport proteins then facilitate passage across the cell membrane into the biliary tree for passage into the intestine with bile flow. Bilirubin ultimately is passed in stool in a variety of forms. A small proportion of conjugated bilirubin is deconjugated in the gut and reabsorbed into the circulation (enterohepatic circulation). Conjugation and intracellular transport may both be impaired in preterm infants.

In a fetus, bilirubin metabolism is more complex. Bilirubin is presented to the placenta for excretion in the fat-soluble (unconjugated) form. To facilitate this, the enterohepatic circulation of bilirubin is quite active. The brush border of the intestines contains enzymes, such as beta-glucuronidase, that deconjugate the water-soluble conjugated bilirubin that is excreted into the lumen of the gut. Then unconjugated bilirubin is reabsorbed into the fetal serum to be recycled to the placenta for ultimate excretion. An understanding of the differing nature of antenatal and postnatal metabolism of bilirubin helps to clarify the effects of superimposed disease processes.

Animal studies using tracer-labeled bilirubin have demonstrated 3 factors contributing to excess bilirubin levels in the newborn period:

- **Increased RBCs with shortened survival time -** Infants typically have a higher hematocrit and shorter RBC life span (90 days compared to about 120 days later in life). Normally this is insignificant, but it becomes the major contributor to net bilirubin load in hemolytic disorders.
- **Reduced intrahepatic conjugation of bilirubin -** This mainly relates to immaturity of the enzymes; UGT activity remains below adult levels until over 3 months of age. Although rarely of importance in term infants, it may become a significant factor in a preterm or critically ill infant.
- **Increased enterohepatic recirculation of bilirubin -** Because this process continues at the accelerated intrauterine rate for several days after birth, it is the most important component of benign neonatal hyperbilirubinemia (physiologic jaundice). It may become a significant factor in any disease process that delays bowel function and stool passage.

More than half of healthy term infants and most preterm infants develop hyperbilirubinemia, and the incidence is highest in breastfed infants. Many will have visible jaundice, but a visual estimate of the bilirubin level may be inaccurate, especially in darkly pigmented infants. In about 8% of infants, the bilirubin level exceeds the 95th percentile for postnatal age during the first week of life. Peak bilirubin levels in term or late preterm infants usually occur on day 3 to 5 of age. A common problem involves hospital re-admission of healthy term infants at 4 to 7 days of age with total serum bilirubin (TSB) levels of 20 mg/dL or higher.

Table 7–4. Risk factors for severe hyperbilirubinemia

Major risk factors
- Predischarge TSB or TcB level in the high-risk zone (**Fig 7–2**)
- Jaundice observed in the first 24 hours
- Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (e.g.G6PD deficiency, elevated ETCOc)
- Gestational age 35–36 weeks
- Previous sibling received phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
- East Asian race*

Minor risk factors
- Predischarge TSB or TcB level in the high intermediate-risk zone
- Gestational age 37–38 weeks
- Jaundice observed before discharge
- Previous sibling with jaundice
- Macrosomic infant of a diabetic mother
- Maternal age 25 years or younger
- Male gender

Decreased risk factors (in order of decreasing importance)
- TSB or TcB level in the low-risk zone (Fig 7–2)
- Gestational age 41 weeks or greater
- Exclusive bottle feeding
- Black race*

*Race as defined by mother's description.

Risk Factors for Severe Hyperbilirubinemia (Table 7-4)

Hyperbilirubinemia Definitions

- **Benign Neonatal Hyperbilirubinemia (Physiologic Jaundice)** – normal and transient increase in total bilirubin (TB) levels, which occurs in most newborns. The upper safe level of bilirubin in these patients is unknown. Although risk of BIND is quite low.
- **Significant Hyperbilirubinemia –** TB levels >95% on the hour-specific Bhutani nomogram in newborns ≥ 35 weeks.
- **Severe Hyperbilirubinemia –** TB > 25 mg/dL. Associated with increased risk for BIND.
- **Extreme Hyperbilirubinemia –** TB > 30 mg/dL. Associated with higher risk for BIND.
- **BIND –** caused by free bilirubin crossing the blood-brain barrier and binding brain tissue. This can result in acute bilirubin encephalopathy (ABE) and/or chronic bilirubin encephalopathy (previously called kernicterus).

Differential Diagnosis of Significant Newborn Hyperbilirubinemia

Risk of hyperbilirubinemia is related to total serum bilirubin level, postnatal age, gestational age, and impact of co-existing illnesses**.** In general, increased serum bilirubin results from increased production, increased enterohepatic circulation, decreased elimination, or a combination of these.

Increased Production

Most common cause of significant unconjugated hyperbilirubinemia:

- **Hemolytic Jaundice*** - Occurs most commonly in infants with blood group isoimmunization and enzyme deficiencies. Cord bilirubin > 4mg/dl or 4-6 hour bilirubin > 6mg/dl with higher retic counts > 7% are associated with increased hemolysis and high risk of rapidly increasing jaundice.
    - **Isoimmune Hemolysis** - Rh, ABO, or minor blood group incompatibilities. Coombs test usually is positive, and a specific transplacentally acquired antibody can be identified in the serum of the infant. Anemia may be severe or absent depending on degree of sensitization. In general, isoimmune hemolytic disorders carry the greatest risk of BIND because intermediary products of heme breakdown compete with bilirubin for albumin binding sites and promote higher levels of free bilirubin than most other forms of hyperbilirubinemia. There is little relationship between bilirubin levels and severity of anemia or between cord bilirubin level and ultimate peak level.
    - **Intrinsic RBC Membrane or Enzymatic Defects** - hereditary spherocytosis, elliptocytosis, infantile pyknocytosis, G6PD deficiency, pyruvate kinase deficiency, congenital erythropoietic porphyria
- **IDM** – related to polycythemia and/or ineffective erythropoiesis
- **Sepsis** – unknown mechanism, though related to oxidative stress damage to RBCs
- **Other** – polycythemia or sequestration (bruising or cephalohematoma)

*Jaundice due to these etiologies often appear early or within 24 hours.

Decreased Clearance

Often related to decreased conjugation due to inherited defects in enzymes, including UGT1A1

- **Crigler-Najjar Syndrome** – Type 1 most severe with nearly absent UGT activity, Type II less severe with low but detectable UGT activity.
- **Gilbert Syndrome** – reduced production of UGT, most common inherited disorder
- **Other** – Maternal diabetes, congenital hypothyroidism, galactosemia, panhypopituitarism

Jaundice due to these etiologies is often persistent past the first week of life.

Increased Enterohepatic Circulation

Often due to impaired intestinal motility related to anatomic or functional intestinal obstruction.

- **Breastfeeding Failure Jaundice** – ineffective or inadequate breastfeeding, associated with hypovolemia and significant weight loss. Typically presents in first week of life.
- **Ileus or Intestinal Obstruction/Malformation** – often associated with delay in passage of meconium and prolonged increase in enterohepatic recirculation. Includes cystic fibrosis.
- **Breast Milk Jaundice** – Usually mild hyperbilirubinemia persisting beyond the first 2-3 weeks in infants receiving exclusively human milk. Underlying mechanism not known, possibly related to high concentrations of beta-glucuronidase which promote increased intestinal absorption.

Cholestatic Jaundice

In these cases, the conjugated and unconjugated bilirubin fractions are elevated, and the condition usually is more chronic. **(Ch 5.3-Cholestasis)**

Causes include:

- TPN cholestasis
- Neonatal hepatitis
- Biliary atresia
- Sepsis
- Chronic, nonspecific cholestasis

Evaluation

Maternal prenatal testing should include ABO and Rh typing. If the mother is blood type O, Rh-negative, antibody screen positive or had no prenatal blood group testing, then a direct Coombs test, blood type, and Rh (D) type are recommended on the infant or cord blood. In infants noted to be jaundiced in the first 24 hours of life, total and direct (or conjugated) serum bilirubin levels should be obtained. Bilirubin levels cannot be adequately assessed by evaluation of skin color. Further workup is warranted if the bilirubin level is elevated or the direct Coombs is positive.

A basic workup for pathologic causes of jaundice might include serum total and direct bilirubin level, hemoglobin and hematocrit, reticulocyte count, direct Coombs test, and determination of maternal and infant blood type. These studies usually will establish a diagnosis of hemolytic disease, if present, and antibody screening of infant serum will detect the specific offending antibody. If the cause of hyperbilirubinemia is not due to isoimmune hemolysis, evaluation and/or testing for other causes should be performed and subspecialty consultation considered. A peripheral blood smear is often useful. The possibility of G6PD deficiency as a contributor to neonatal jaundice must be considered since 11-13% of African Americans are deficient, and the diagnosis is often missed.

Table 7-5. Follow-up recommendations for infants with jaundice

	Gestational Age			
	GA 35-37 6/7 weeks		GA ≥ 38wks	
Bilirubin Risk Zone	With Risk Factors	No Risk Factors	With Risk Factors	No Risk Factors
High	Evaluate for PhotoRx TSB in 4-8h	Evaluate for PhotoRx TSB in 4-24h		Evaluate for PhotoRx TSB in 4-24h
High-Intermediate	Evaluate for PhotoRx TSB in 4-24h	Evaluate for PhotoRx TSB in 24 h		F/U in 2 d Consider TSB/TcB
Low-Intermediate	If D/C < 72 h F/U within 2 d Consider TSB/TcB	If D/C < 72 h F/U within 2 d		If D/C < 72 h, F/U in 2-3 d
Low	If D/C < 72 h F/U within 2 d	If D/C < 72 h, F/U in 2-3 d		F/U per non-jaundice indications

Note: Predischarge bilirubin recommended for all newborns.
Use Figure 7-2 to assign Bilirubin Risk Zone and Figure 7-3 to classify as With or No Risk Factors.

7.5 Management of Neonatal Jaundice

Follow-up of Healthy Term and Late-term Infants at Risk for Hyperbilirubinemia

In an attempt to address the increasing number of reports of kernicterus in healthy infants 35 or more weeks' gestation, the American Academy of Pediatrics (AAP) published recommendations for risk reduction strategies in July 2004.

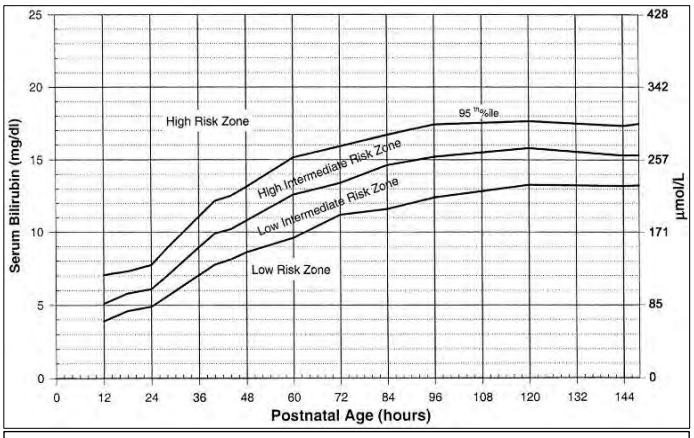


Figure 7-2. Nomogram for designation of risk in 2840 well newborns at ≥36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone) as shown in Appendix 1, Table 4 (of source publication). Used with permission from Bhutani et al. See Appendix 1 for additional information about this nomogram, which should not be used to represent the natural history of neonatal hyperbilirubinemia.

All infants 35 weeks' or greater gestation who are discharged from the hospital before or at 72 hours of life should have a total serum bilirubin (TSB) measured on capillary blood before discharge (at the time of the metabolic screen), and the resultant bilirubin value should be plotted on the hour-specific nomogram predicting sub-sequent risk of severe hyperbilirubinemia **(Fig 7–2).** Additionally, all infants should have a follow-up evaluation at 3 to 5 days of age, when the bilirubin level usually is highest. Timing of this evaluation is determined by the length of nursery stay and the presence or absence of risk factors for hyperbilirubinemia. **(Table 7-5)**

Management

General measures of management include early feeding to establish good caloric intake. The AAP discourages interruption of breastfeeding in healthy term newborns. In these infants, supplementing nursing with water or dextrose water does not lower bilirubin levels. A main goal of feeding is the stimulation of bowel motility and increased stooling to decrease enterohepatic circulation of bilirubin; however, other options, beyond simple observation, are recognized, including supplementing breastfeeding with formula or breast milk obtained by pump or temporary interruption of breastfeeding with formula substitution, any of which can be accompanied by phototherapy.

Phototherapy

Efficacy of phototherapy is determined by:

- light source (blue-green spectrum is best),
- irradiance or energy output in the blue spectrum, and
- surface area exposed
- distance of infant from light source.

Light in the 450-nanometer (blue-green) range converts unconjugated bilirubin to soluble, nontoxic photoisomers. It also stimulates bile flow and excretion of bilirubin in bile, as

well as enhancing gut motility. Degradation of bilirubin increases with increasing blue light irradiance.

Standard phototherapy is used for infants who meet the AAP guidelines for phototherapy but with TSB not at or near exchange transfusion levels**.** (strong recommendation, moderate quality evidence) Use a high-intensity phototherapy device per institution availability placed at a distance of 12 inches (30.5 cm) from the patient. This will deliver an irradiance of > 12 microWatts/cm^2/nm. Checking the light intensity before each use is recommended where feasible to confirm correct positioning and irradiance of the light over the infant.

Intensive phototherapy is used for infants with TSB levels at or near exchange transfusion levels. Intensive phototherapy combines an over-head high-intensity phototherapy device with a fiber-optic phototherapy pad placed beneath the infant. The overhead device should be positioned to deliver an irradiance dose of at least 30 microWatts/cm2/nm as measured with a radiometer. The fiber optic pad should be covered only with a disposable cover furnished by the manufacturer. This technique both increases delivered irradiance and recruits additional surface area for light exposure.

In healthy term infants, discontinue phototherapy when TSB levels fall below 13 to 14 mg/dL. In infants without hemolytic disease, average bilirubin rebound is less than 1 mg/dL. In most cases, no further bilirubin measurements are necessary and hospital discharge need not be delayed. Management recommendations are summarized in **Table 7-5.**

Phototherapy is not a benign medical treatment. Pototherapy is associated with rash, hyperthermia, reduction in parental bonding, interruption of breastfeeding, loose stools, increase in insensible water loss (albeit not seen with current LED phototherapy), oxidative injury to the cell and a small increased incidence of infantile seizures (low quality evidence).

Management of Hyperbilirubinemia in Low Birth Weight Infants

Currently, there are no AAP recommendations for treatment of hyperbilirubinemia in LBW, VLBW, or ELBW infants. Baylor affiliated nurseries have adapted consensus-based guidelines derived from controlled trials and expert opinions in the literature. These guidelines are summarized in **Table 7-6.** Birthweight, as opposed to the infants current daily weight, should be used when interpreting **Table 7-6.**

Intravenous Immune Globulin

Since 2004, the AAP has recommended the administration of Intravenous Immune globulin (IVIG) to infants with isoimmune hemolytic disease to decrease the need for exchange transfusion. A Cochrane systematic review published in 2018 on the use of IVIG concluded that IVIG decreases the need for exchange transfusion and the number of exchange transfusions (9 trials, 958 infants, VERY LOW certainty evidence). In a sensitivity analysis, if only the trials with a placebo group are included, there was no significant difference in exchange transfusion (2 RCTs, 172 infants, MODERATE certainty evidence).

We recommend that in our NICUs for an infant with isoimmune hemolytic disease whose TSB level rises despite intensive phototherapy or is within 2 – 3mg/dl of exchange transfusion IVIG may be administered at a dose of 0.5 to 1g/kg over 2 hours and may be repeated after 12 hours if necessary. (Very low certainty of evidence, weak recommendation).

Infants whose bilirubin levels do not respond to IVIG with intensive phototherapy should be transferred in a timely manner to a higher of level of care where an exchange transfusions could be performed to prevent bilirubin-induced neurological damage.

Table 7-6. Guidelines for management of hyperbilirubinemia in low-birth-weight infants

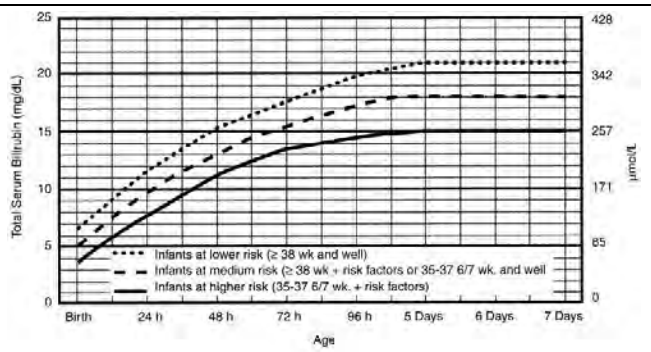
Total Serum Bilirubin levels (mg/dL) to initiate therapy						
	Phototherapy					Exchange Transfusion
Birth weight	≤ 24 hours	24 to 48 hours	48 to 72 hours	72 to 168 hours	2nd week	
< 750 g	≥ 5					> 13
750-999 g	≥ 5				≥ 7	> 15
1000-1499 g	5 - 7	7 - 9			10 - 12	15 - 16
1500-1999 g	5 - 8	8 - 10	10 - 12		13 - 15	16 - 18
2000-2500 g	5 - 8	8 - 11	11 - 13	13 - 15	14 - 15	18 - 19

- Lower concentrations should be used for infants who are sick (presence of acidosis, sepsis, hemolytic disease, hypoalbuminemia, etc).
- For SGA and LGA infants, consider using the "50th percentile weight for GA" to decide TSB level for treatment
- In VLBW infants, TSB measured per guidelines in "Care for the VLBW infants" at 24 hours and daily for the first few days.

Indications for Exchange Transfusion

The classic indication for exchange transfusion in Rh erythroblastosis is a serum bilirubin level of 20 mg/dL. This disease carries a greater risk of kernicterus than other forms of hemolytic or non-hemolytic jaundice because of the brisk hemolysis, which produces high levels of intermediary products of heme breakdown that compete for albumin binding sites. Exchange transfusion also has been used to manage other types of isoimmune blood group incompatibilities (such as ABO and minor group incompatibility), using the same threshold bilirubin level of 20 mg/dL.

Figure 7–3. Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35-37$^{6}/_{7}$ wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37$^{6}/_{7}$ wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2–3 mg/dL (35–50 mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Note: These guidelines are based on limited evidence and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy which should be used when the TSB exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, and the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin.

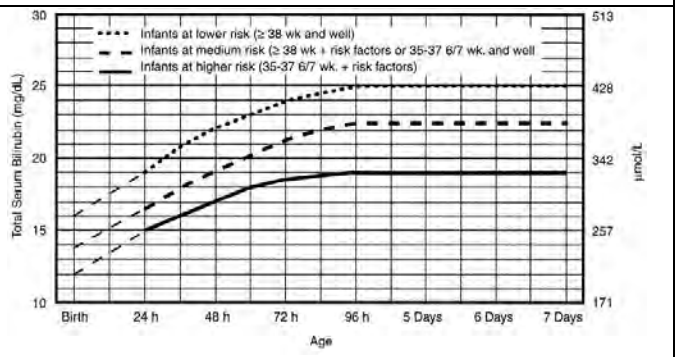
"Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 μW/cm^2 per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system.

See Appendix 2 [of source publication] for additional information on measuring the dose of phototherapy, a description of intensive phototherapy, and of light sources used. If total serum bilirubin levels approach or exceed the exchange transfusion line [Figure 7-4], the sides of the bassinet, incubator, or warmer should be lined with aluminum foil or white material. This will increase the surface area of the infant exposed and increase the efficacy of phototherapy.

If the total serum bilirubin does not decrease or continues to rise in an infant who is receiving intensive phototherapy, this strongly suggests the presence of hemolysis.

Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice) may develop the bronze-baby syndrome. See Appendix 2 [of source publication] for the use of phototherapy in these infants.

Figure 7-4. Guidelines for exchange transfusion in infants 35 or more weeks' gestation.



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is ≥5 mg/dL (85 μmol/L) above these lines.
- Risk factors: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35–37$^{6}/_{7}$ wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. See ref. 3 [of source publication] for risks and complications of exchange transfusion. During birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours.

The following B/A ratios can be used together with but not in lieu of the TSB level as an additional factor in determining the need for exchange transfusion.

Risk Category	B/A Ratio at which exchange transfusion should be considered	
	TSB mg/dL/Alb, g/dL	TSB μmol/L/Alb, μmol/L
Infants ≥ 38 0/7 wk	8.0	0.94
Infants 35 0/7-36 $^{6}/_{7}$ wk and well or ≥38 $^{0}/_{7}$ wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	7.2	0.84
Infants 35 0/7-37 $^{6}/_{7}$ wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.8

If the TSB is at or approaching the exchange level, send blood for immediate type and crossmatch. Blood for exchange transfusion is modified whole blood (red cells and plasma) cross-matched against the mother and compatible with the infant.

Risk of kernicterus in healthy term newborns with non-hemolytic jaundice is low and the role of exchange transfusion remains uncertain. The AAP has reviewed these issues in a published practice guideline. Management recommendations are summarized in **Fig 7-4.**

In addition to the TSB level, the ratio of bilirubin to albumin (B/A) can be used as an additional factor to determine the need for exchange transfusion. Using the 3 risk categories in **Fig 7-4**, the B/A ratios at which should be considered are 8.0, 7.2, and 6.8 TSB mg/dL to albumin g/dL for infants at low, medium, and higher risk

Exchange Transfusion

Exchange transfusion is used primarily to manage infants with isoimmune hemolytic disease with hyperbilirubinemia. Occasionally, it is used to treat extremely high bilirubin levels of other pathologic origin.

Planning

Place the infant in an environment that provides:

- a radiant warmer,
- electronic heart rate monitoring,
- a method to determine blood pressure, and
- a nurse available to provide continuous assistance and frequent documentation of monitored parameters during the procedure.

Preparation

- Have immediately available: oxygen, suction, and emergency equipment for resuscitation.
- Obtain a sterile, disposable exchange transfusion set to provide all equipment needed for the procedure.
- Order blood as the equivalent of whole blood.
- Ask the blood bank to mix packed RBCs and plasma to a resulting hematocrit of 40%. Optimal efficiency occurs with a double-volume exchange. Thus, the amount of blood required is 2 times the blood volume (90 mL/kg × body weight × 2) plus an additional 30 to 50 mL to prime the tubing system before the procedure.

Equipment

- Perform the exchange using the #8 French catheter supplied in the exchange set.
- Fill the catheter with heparinized saline and pass it into the umbilical vein.
- Optimally, position for catheter tip is the level of the right diaphragm. If the position cannot be achieved, advance catheter only far enough to obtain free flow of blood when gentle suction is applied. Confirm catheter position with a radiograph.
- Secure the catheter at the umbilicus during the procedure.
- Routine priming with albumin before exchange transfusion is not currently indicated.

Instructions to assemble the tubing system are in the exchange set and should be followed to the letter. The result will be a completely closed system that allows each step of the procedure to be performed by simply turning the main stopcock one stage clockwise.

Occasionally, circumstances arise that prevent the use of standard exchange transfusion methodology. These usually are technical, and the attending physician decides what form of alternative methodology is most appropriate for the circumstances.

Before the Exchange

Completely prime the system with donor blood and exhaust all air before beginning the exchange.

Important Points to Remember

- Turn the stopcock clockwise only.
- Exchange increments of 5 to 20 mL of blood, depending on patient size and condition.
- On the form provided in the exchange set, document the amount of blood in and out for each pass.
- Take and record vital signs every 15 to 30 minutes.
- Routine infusion of calcium salts during an exchange is not recommended.

Exchange Procedure

Most double-volume exchanges should be completed in 1 to 1.5 hours.

- Using the master stopcock, initially remove 5 to 20 mL of blood from the infant for any required studies.
- Turn the stopcock clockwise one step to the waste bag port, and flush.
- Turn the stopcock clockwise one step to the donor blood port, and draw replacement donor blood.
- Turn the stopcock clockwise one step.
- Infuse the donor blood into the patient.
- After a short dwell time, draw 5 to 20 mL of blood from the catheter.
- Turn the stopcock clockwise one step to the waste bag port, and flush.
- Turn the stopcock clockwise one step, and draw a similar amount of blood from the donor bag.
- Turn the stopcock clockwise one step.
- Infuse the donor blood into the infant.
- Repeat this procedure as necessary to complete a double volume of exchange.

After the Exchange

- Closely monitor vital signs for 2 hours after the procedure.
- Send a blood sample for CBC, TSB, calcium, electrolytes.

Send a new blood sample for typing to be available if another exchange is required.

Delayed Cord Clamping

Placental transfusion by delayed clamping of the cord (> 30 sec) in preterm infants has been associated with improved neonatal outcomes, including decreased mortality at 36 weeks corrected gestational age, increased hematocrit, decreased need

for transfusion, and hemodynamic stability requiring decreased use of vasopressors in the first 24 hours. AAP and ACOG recommend delayed cord clamping in preterm infants when feasible. It is currently part of routine neonatal care in the delivery room in many institutions. Umbilical cord milking is currently not recommended as randomized controlled trial evidence suggests increased incidence of IVH when milking is compared to delayed cord clamping. In healthy term infants, growing evidence suggests that delayed cord clamping increases early hemoglobin concentrations and iron stores in infants, and likely to be beneficial as long as access to treatment for jaundice requiring phototherapy is available.

7.6 Polycythemia

Neonatal polycythemia is defined as a venous hematocrit or hemoglobin concentration that is greater than two standard deviations above the normal value for gestational and postnatal age. This condition affects approximately 1 to 5 percent of newborns. Most affected infants are asymptomatic. Clinical features may include cyanosis, tachypnea, tachycardia, vomiting, poor feeding, hypoglycemia, and hyperbilirubinemia and are thought to result from hyperviscosity and/or the metabolic effects of an increased red blood cell mass.

Diagnosis - A term infant is considered to be polycythemic if the hematocrit from a peripheral venous sample is greater than 65%. The diagnosis is based upon peripheral venous samples because of the variability in measurements obtained from capillary samples (heel sticks).

Hematocrits of blood from venous samples (venous sample or from UVC) are usually 5%-15% lower than those obtained from capillary samples.

Management

- There is no consensus in the management of infants with polycythemia due to lack of evidence behind various treatment strategies. The following guidelines are offered in an effort to minimize variation in our practice. Management of **asymptomatic** infants is usually guided by the hematocrit with emphasis on ensuring adequate hydration, glucose intake and monitoring for neurologic and cardiovascular symptoms and common complications, such as hypoglycemia and hyperbilirubinemia. **(Fig 7-5)** (strong recommendation, moderate quality evidence).
- Optimal management of **symptomatic** infants has not been determined. Some practitioners may choose to lower the hematocrit by use of a partial volume exchange transfusion (PET). While PET may improve cerebral blood flow and hemodynamic parameters, it has not been shown to alter long-term outcomes, and in one study has shown to be associated with an increased risk of adverse GI symptoms and NEC. See **Fig 7-5** for recommended management strategies (strong recommendation, moderate quality evidence).
- If a partial exchange transfusion is done for polycythemia, replace the removed blood with an equal volume of normal saline.

Table 7-7. Causes of neonatal polycythemia

Erythrocyte transfusion (passive)
• Delayed clamping of the umbilical cord (e.g. >2 minutes after birth) • Uncontrolled or precipitous delivery • Intrapartum hypoxia • Twin-to-twin transfusion (10 to 15 percent of monochorionic twins) • Maternal-fetal transfusion (rare)
Increased intrauterine erythropoiesis (active)
Placental insufficiency • Preeclampsia • Other hypertensive disorders • Other vascular disorders
Maternal hypoxemia due to cardiac or pulmonary disorders • Cardiac or pulmonary disorders • Drugs (e.g. propranolol) • Smoking • High altitude • Post term delivery
Infant risk factors • Large for gestational age • Maternal diabetes mellitus • Beckwith-Wiedemann syndrome • Endocrine abnormalities (congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism) • Chromosomal anomalies (trisomy 21, 18, and 13)

- If a decision is made to perform PET, it should be done as soon as possible as the neonatal hematocrit and blood viscosity peaks between two and four hours after birth.
- Calculate the exchange volume using the formula below.

$$\text{Vol (replaced)} = \frac{[\text{Hct}_{\text{initial}} - \text{Hct}_{\text{desired}}] \times \text{Weight (kg)} \times 80 \text{ mL/kg}}{\text{Hct}_{\text{initial}}}$$

7.7 Neonatal Thrombosis

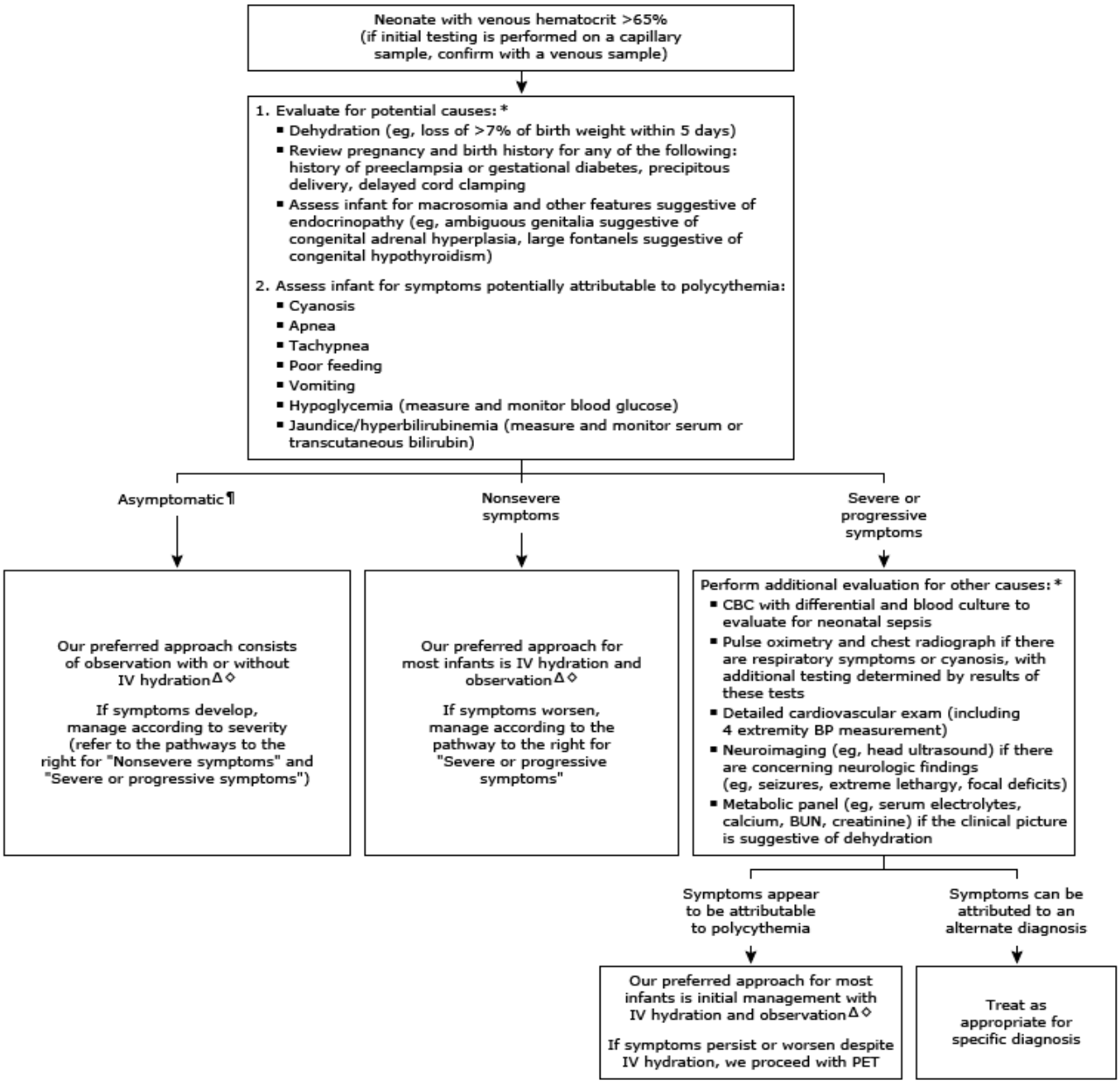
Introduction

Neonates are at the greatest risk for development of thrombosis. Although several prothrombotic disorders are implicated in neonatal thrombosis, their specific role in this pathology is not well established. More than 80% of thromboembolic events are related to the use of central venous and or arterial catheters (CVAC). Neonatal thrombosis is rapidly increasing; recent reports cite ~6.8 per 1000 NICU admissions when compared to 2.4 per 1000 NICU admissions in 1995.

Risk factors

Prenatal risk factors include maternal infections, preeclampsia, diabetes, PROM, placental diseases, emergency cesarean delivery, inherited thrombophilia. Neonatal risk factors include sepsis, IUGR, asphyxia, hypotension, polycythemia (HCT>65%), cardiac disease, major surgery, CVAC, mechanical ventilation.

Figure 7-5. Algorithm for managment of neonatal polycythemia



There are limited data on the efficacy and safety of PET in neonates. IV: intravenous; CBC: complete blood count; BP: blood pressure; BUN: blood urea nitrogen; PET: partial exchange transfusion.

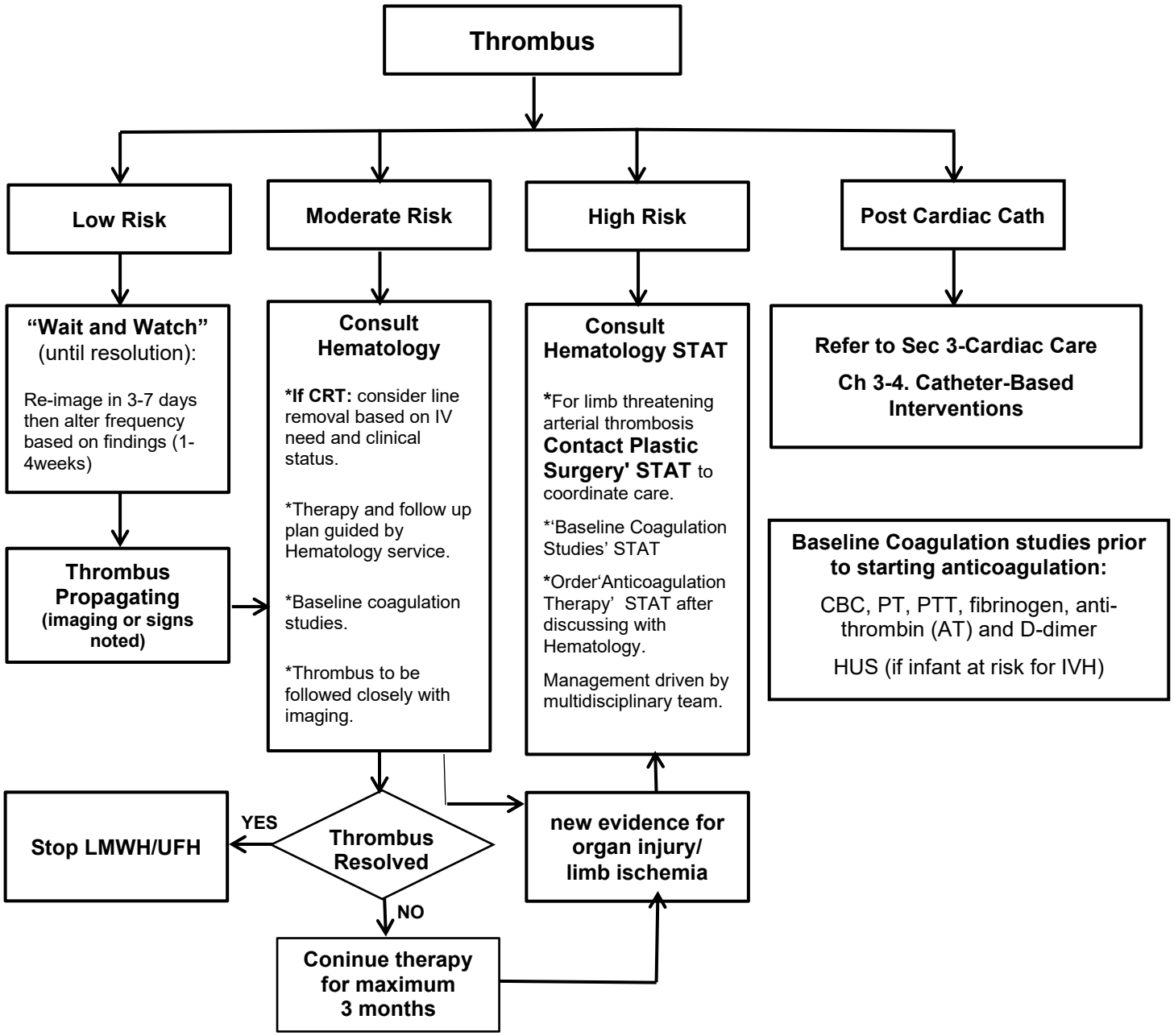
* For a complete list of causes, **See Table 7-7 Causes of neonatal polycythemia**.

Asymptomatic infants are included in this algorithm to provide guidance for situations when polycythemia is an incidental finding on laboratory testing performed for other reasons (e.g. sepsis evaluation). We do not routinely measure the hematocrit to screen for polycythemia in term infants who appear well.

Δ Observation includes ongoing assessment of symptoms; monitoring intake, urine output, and daily weight; serial blood glucose and bilirubin testing (frequency depends on initial results); and repeat hematocrit every 12 to 24 hours until polycythemia has resolved.

◊ The main rationale for administering IV hydration is to prevent hypoglycemia. Hypoglycemia is a common complication of polycythemia, particularly if the hematocrit is >70%. Dextrose-containing IV fluids are provided for the first 24 to 48 hours of age at a rate of at least 100 mL/kg per day (glucose infusion rate of 6 to 8 mg/kg per min), while the infant is closely monitored.

Figure 7-6. Clinical algorithm for neonatal thrombus



Catheter related thrombosis (CRT)

Presence of central venous catheter (CVC) is one of the most important risk factor for thrombosis. In a recent meta-analysis, the incidence of CRT was 9.2% (1.1%-66.7%). UVC's are typically associated with asymptomatic transient thrombosis. A fibrin layer has shown to form within 2 days of inserting a catheter setting the stage for thrombus development. CRT can present with catheter dysfunction, limb swelling distal to insertion site, recurrent CLABSI's (especially with same organism). Spontaneous regression of neonatal thrombi can occur. Also, CRT can increase in size causing complications. **(Ch 2.2-Circulatory Insufficiency)**

Clinical presentation

In many instances, identification of thrombus is an incidental finding. A thrombus identified in the first few days of life has a high chance of being associated with inherited thrombophilia, especially in the presence of positive family history. Clinical features are highly variable and depend on the site and size of thrombus.

Venous Thrombosis

Extremities: swelling, pain, cyanosis, hyperemia.

Portal vein - Portal vein thrombosis (PVT) is usually asymptomatic and spontaneous regression can occur especially in cases with partial thrombi (>70%). It is specifically related to intrahepatic placement of UVC placement. PVT can uncommonly lead to the development of portal hypertension (splenomegaly, GI bleeding, gastroesophageal varices, and abdominal pain) and liver atrophy.

Renal Vein - Renal vein thrombosis (RVT) typically presents in male infants and has a left side presentation in majority cases. Classic clinical triad of RVT: hematuria, proteinuria and abdominal mass. Hypertension can be a late finding.

Vena Cava - swelling of face and head with superior vena cava syndrome, unexplained pleural effusion or ascites as a result of inferior vena cava syndrome, both kidneys palpable, hematuria, lower leg edema.

Cerebral sinus venous - Cerebral sinus venous thrombosis (CSVT) may present in the first week of life, often with seizures, lethargy, apnea, irritability, and poor feeding.

Arterial thrombosis - Typically preceded by the use of catheters.

Extremities - pain, discoloration (pallor, mottling, or purple to black), swelling, prolonged capillary refill time, loss of pulses, decreased temperature.

Renal Artery - Hypertension, which, in severe cases, leads to renal failure.

Investigations

Imaging

Imaging studies should document the presence and extent of thrombus. Doppler US is the initial imaging study of choice for thrombus in the upper venous system, lower limbs, superior vena cava (SVC), inferior vena cava (IVC) and aorta. ECHO is useful for thrombus located in the SVC. Alternate imaging modalities that could be used, depending on the site of thrombus, are MRA, MRV and CTA.

Baseline Coagulation Studies

CBC, PT, PTT, antithrombin, fibrinogen, D-dimer as needed, and platelet count. It is highly recommended to consult with the Hematology Service prior to performing advanced thrombosis workup. Routine testing for genetic thrombophilia in neonates with thrombosis is controversial. In most cases, the results of thrombophilia testing will not influence immediate management of the patient (exceptions include rare severe deficiencies such as, protein C, protein S, antithrombin, which should be considered in cases of large thrombus burden and/or purpura fulminans). If advanced evaluation is considered, the studies are ordered as a DVT panel **(Table 7-8).** Step 1 tests are the most helpful in this age group and should be obtained first. Steps 2 and 3 may be obtained in any order based on clinical discretion.

Management

The principles of management of neonatal thrombosis are largely based on case series, cohort studies and expert opinion. The treatment options include: a) observation, b) anticoagulant or thrombolytic therapy c) surgery. A risk stratified treatment recommendation **(Table 7-9)** and clinical algorithms **(Fig 7-6)** are suggested below (weak recommendations, low quality evidence).

Treatment (Tables 7-10, 11, 12)

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are the agents of choice for the management of neonatal thrombosis. LMWH has several advantages over UFH: less frequent laboratory monitoring, subcutaneous administration (and therefore no need for an intravenous line), and ability to discharge on home therapy. Patients with renal dysfunction should not be managed with enoxaparin (LMWH) as it is renally eliminated. Patients with renal dysfunction and acute thrombosis can be managed with UFH.

In general, venous thrombi are typically treated with either UFH or LMWH for 6 weeks to 3 months of total therapy. Repeat ultrasound should be obtained to assess the resolution of the thrombus prior to discontinuation of anticoagulation. If the thrombus was associated with a central line, prophylactic anticoagulation may be considered until central line removal. Before starting UFH, obtain baseline CBC, PT, PTT, fibrinogen, antithrombin (AT) and D-dimer (can consider checking baseline antiphospholipid antibody panel, and lupus anticoagulant). Obtain heparin level and PTT 4 hours after loading dose and 4 hours after every infusion rate change. Once stable, heparin level and PTT should be checked every 12 hours, and platelet counts every 3 days.

Table 7-8. Three step DVT panel

Step 1	Step 2	Step 3
Protein C, Protein S, Antithrombin, Factor 8, Lupus anticoagulant	Anticardiolipin antibody Anti-β2-GP1 Lipoprotein (a) Homocysteine	FV Leiden Prothrombin gene mutation
1 blue top, 2.7 mL	1 red top, 3.0 mL	1 purple top, 1.0 mL

Table 7-9. Risk stratification*

Low Risk	Non-occlusive and asymptomatic venous thrombus (CRT, PVT, unilateral RVT), chronic organized venous thrombus.
Moderate Risk	Any symptomatic or acute occlusive venous thrombus without ischemia or organ failure (CRT,RVT,PVT), Bilateral RVT , propagating venous thrombus on serial imaging, thrombus extending in to central vein (SVC, IVC).
High Risk	Any arterial thrombus, Any thrombus causing limb ischemia or organ injury (renal impairment, cardiac failure), occlusive central artery or vein (Aorta, SVC, IVC), symptomatic pulmonary embolism.

* Cerebral sinus venous thrombosis and thrombosis related to congenital heart disease are excluded.

Table 7-10. Heparin for line patency

To prevent clot formation in central lines, heparin 1 unit/mL containing fluids should be continuously administered using the following rates:

	Weight < 1250 grams	Weight >1250 grams
UAC	0.3 mL/hr	0.5 mL/hr
UVC	0.3 mL/hr	0.5 mL/hr
PICC	0.5 mL/hr	0.5 mL/hr
PAL	0.5 mL/hr	0.5 mL/hr

Table 7-11. Enoxaparin dosage and titration		
Enoxaparin		
Initial dose	PMA < 32 weeks	2 mg/kg/DOSE every 12H
	PMA 32-40 weeks	1.7 mg/kg/DOSE every 12H
	PMA > 40 weeks	1.5 mg/kg/DOSE every 12H
Prophylaxis	> 2 months age	0.5 mg/kg/DOSE q12h
	< 2 months age	0.75 mg/kg/DOSE q12h
Rounding	Weight < 2.5 kg	Round to the nearest whole mg
	Weight ≥ 2.5 kg	Round UP to the nearest whole mg

Anti-Xa levels (a.k.a. Lovenox Level) should be obtained 4 hours after administration of enoxaparin to accurately assess laboratory value. A minimum of 2 doses of enoxaparin should be administered prior to obtaining the first anti-Xa level to allow for a steady state concentration.

Lovenox® Level (units/mL)

Treatment Goal level = 0.5-1	Prophylaxis Goal level = 0.2-0.4	Dose Titration	Time to Repeat Lovenox® Level
<0.35	<0.15	Increase dose by 25%	4 h after next dose
0.35-0.49	0.15-0.19	Increase dose by 10%	4 h after next dose
0.5-1	0.2-0.4	Keep same dosage	Check level weekly (4 h after dose)
1.1-1.5	0.41-1	Decrease dose by 20%	4 h after next dose
1.6-2	1.1-2	Decrease dose by 30% and hold dose for 3 hours from next due time	4 h after next dose
>2	>2	Repeat Lovenox® level; hold all doses until Lovenox® level is 0.5 units/mL, then decrease dose by 40%	Check level every 12 h until Lovenox® level <0.5 units/mL

Key points in treatment:

- In 'High Risk' cases, especially in life/limb threatening scenarios, anticoagulation therapy should be started ASAP by the attending neonatologist with guidance of the hematology service.
- Total duration of treatment for venous thromboembolism is between 6 weeks to 3 months.
- For acute femoral artery thrombosis, at least 5-7 days of therapeutic anticoagulation should be completed.

Heparin should be stopped 2-4 hours prior to:

- surgery/invasive procedure. Lovenox should be stopped at least 24 hours prior to surgery/invasive procedure.
- Removal of CVAC catheters should be considered in CRT, depending on continued need for venous access and the patient's clinical status. The Chest guidelines recommend 3-5days of anticoagulant therapy prior to line removal, but clinical judgement should prevail.

Atrial/Ventricular thrombi and cerebral sinus venous thrombi (CSVT) have high risk for complications. Cardiology service for Atrial/Ventricular thrombi and Neurology service for CSVT should be consulted immediately.

Table 7-12. Heparin dosage and titration	
Initial dosing for unfractionated heparin in patients <1 year of age not currently on ECMO:	75 units/kg administered over 10 minutes followed by a continuous infusion initiated at 28 units/kg/hr

- Adjust dose according to heparin and PTT levels.
- Typically Heparin assay can be influenced by other variables such as high plasma free HgB, Sr. Bilirubin and low antithrombin levels. When there is discordance between Heparin assay and PTT levels, ensure the other variables are within range before using Heparin assay.
- Do not administer bolus in patients with stroke, active bleed, or high risk of bleed.

Heparin Level Goal level = 0.3-0.7 units/mL	PTT Goal level = 70-101 (seconds)	Dosage Adjustment	Time to Repeat Heparin level & PTT
<0.2	<60	Give 50 units/kg bolus and increase infusion rate by 10%	4 h after rate change
0.2-0.29	60-69	Increase infusion rate by 10%	4 h after rate change
0.3-0.7	70-101	Keep rate the same	Every 12 h
0.71-0.8	102-112	Decrease infusion rate by 10%	4 h after rate change
0.81-0.99	113-130	Hold infusion for 30 minutes and decrease infusion rate by 10%	4 h after rate change
≥1	>130	Repeat heparin level; hold infusion for 60 minutes and decrease infusion rate by 15%	4 h after rate change

Suggested Reading

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Section 8: Infectious Diseases

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8.1 Infection Control and Prevention

Infection Control and Prevention is a key component in protecting NICU patients and minimizing in-hospital infections.

Hand Hygiene

Good, effective hand hygiene is one of the most simple and vital ways providers and families can prevent the spread of pathogens that are harmful to infants. In order to comply with proper hand hygiene, the NICU has adopted a "Bare Below the Elbow" policy in which all care providers should remain bare from hands to elbows by removing jewelry (except wedding bands without stones), watches, and white coats until contact with patients is finished. Sleeves of clothing should remain above elbows during hand hygiene and while handling patients.

In addition, all care providers, staff, and visitors must perform an initial sanitizing scrub from elbows to fingertips in the following situations:

- Upon first NICU entry for the day or work shift
- Upon re-entry to the NICU after exiting the building

A hospital-provided alcohol-based sanitizer should be used for the initial sanitizing scrub. Use one pump of sanitizer and rub onto arm from wrist to elbow for 30 seconds or until completely dry. Repeat this process for the other arm, followed by a third pump of sanitizer for both hands. This initial sanitizing scrub should take between 60-90 seconds.

All care providers should also perform hand hygiene in accordance with the World Health Care Organization's "5 Moments for Hand Hygiene".

The 5 moments for hand hygiene are:

1. Before touching a patient or their surroundings or donning gloves
2. Before a clean/aseptic procedure
3. After contact with body fluids
4. After touching a patient or removing gloves
5. After touching patient surroundings

Use of an alcohol-based hand sanitizer is the preferred method for hand hygiene in most situations (see next paragraph for soap and water indications). Alcohol-based sanitizers require an adequate amount of product to fully cover hands/wrists. Rub the product in until it dries – no fanning/waving, or drying hands with paper towels or clothes.

Use soap and water for hand hygiene any time hands are visibly soiled, after care of a patient on Special Contact Precautions (i.e., *C. difficile* and norovirus infections), and after using the restroom. Vigorously scrub all areas of the hands/wrists for at least 20 seconds, rinse, and use paper towels to turn off the faucet.

Isolation Precautions and Personal Protective Equipment (PPE)

Patients with isolation precautions require all healthcare workers to use specific PPE to minimize the spread of pathogens within the NICU. Types of common isolation precautions along with room and PPE requirements can be found in **Table 8-8 in Ch 8.19-Screening for Viral Illness in the NICU**.

In the isolation area, infection control practices are to be strictly enforced. Designated PPE must be worn and hand hygiene upon exiting these areas is mandatory, even if there has been no patient contact. PPE must be removed and discarded appropriately when leaving the area.

For patients not on isolation, use of gloves for every patient contact is not required and is determined by individual hospital infection control practices. If wearing gloves, hand hygiene should always be performed before gloving and after glove removal.

Cloth gowns are not required when entering the NICU. However, gowns are to be worn by anyone who will be holding an infant against their clothing (this excludes skin-to-skin holding) or by anyone who requests a gown while in the NICU.

Liquid impermeable gowns should be worn when entering isolation areas only. These gowns are not to be worn outside of isolation areas.

Masks, head covers, beard bags, and sterile gowns should be worn when placing umbilical catheters and percutaneous lines. Individuals assisting with the procedure, or who must remain in the room, should also wear masks and head covers.

Patient Space

In a NICU environment with private rooms, the patient space is the entirety of the room from the doorway. For a NICU environment with open pods, the patient space includes the bed or isolette, and the surrounding area encompassing all patient equipment, counters, cabinets, chart, and visitor chairs. If barrier screens are being utilized in an open pod, the patient space includes the entirety of the area encompassed by the barrier screen.

Each patient should a have a dedicated stethoscope. Stethoscopes should be cleaned with alcohol before and after each use.

Consider patient charts "dirty." Hands must be washed or sanitized after touching a chart and before handling a patient.

For multiples in the same room, each infant should be handled separately when it comes to hygiene practices and isolation. Hand hygiene (in accordance with the "5 Moments") before and after contact with each infant or their unique environment is expected. Multiples should not share equipment.

Visitors

All visitors will be screened at unit entry for common symptoms of illness. Any visitor who screens positive for symptoms should be discouraged from entering the NICU until all symptoms have resolved for at least 24-48 hours.

All visitors and families are also required to perform hand hygiene prior to contact with infants and their surroundings. We discourage families and visitors from placing personal items, such as cellphones or toys, within a patient's bedspace due to the risk of transferring pathogens into the bedspace.

Visitation policy is subject to change at any time in order to provide a safe environment in the NICU.

MRSA Decolonization

MRSA decolonization has been shown to significantly decrease invasive MRSA infections in patients who are colonized with MRSA or have a history of MRSA infection.

Table 8-1. MRSA decolonization

Patient Age	Mupirocin	Bath
≥ 36 weeks PMA **OR** ≥ 4 weeks chronologic age	Apply to nares BID x 5 days	CHG wipe bath daily x 5 days (concurrent with mupirocin application) *See **Table 8-2** for detailed instructions on how to perform*
< 36 weeks PMA **AND** < 4 weeks chronologic age	Apply to nares BID x 5 days	Regular bath per protocol, no CHG wipes

MRSA positive patients may qualify for decolonization treatment using the criteria and regimen outlined in **Table 8-1**.

If a patient is found to be MRSA positive, weekly MRSA surveillance swab testing should be discontinued.

At this time, patients who are MRSA positive will remain on contact isolation for the duration of their NICU hospitalization, regardless if they have completed decolonization.

Chlorhexidine Gluconate (CHG) Use

CHG is a broad spectrum biocide with activity against gram positive and gram negative bacteria, and fungi, with some effectiveness against bacterial spores, protozoa, viruses and biofilm formation. It significantly reduces the level of bacteria on skin when used for antisepsis and has been shown to decrease central line associated bloodstream infections (CLABSI) in neonates bathed with CHG wipes. In topical solutions, CHG binds to skin, resulting in a longer duration of antimicrobial activity for at least 24 hours after application. Limited data shows that trace amounts of CHG can be absorbed through the skin, however no clinical sequelae have been reported in neonates. We suggest using CHG with the following criteria (**Table 8-2**) while avoiding use in more premature neonates with immature skin and in neonates with certain skin conditions.

Table 8-2. Chlorhexidine Gluconate (CHG) use

	Antisepsis for Skin Puncture or Central Line Dressing Change ^^	CHG Bathing Due to Presence of a Central Line ^^	CHG Bathing for MRSA Decolonization ^^
CRITERIA ^^ ***(see exclusions below)***	**ALL of the following**: ≥ 7 DOL ≥ 1000 grams ≥ 28 weeks PMA **OR** ≥36 weeks gestational age	≥ 36 weeks PMA **OR** > 50 days old	≥ 36 weeks PMA **OR** ≥ 4 weeks chronologic age
SCHEDULE	As needed for skin puncture or central line dressing change	Daily while central line is present Use CHG wipes 1 hour after bathing with soap and water	Daily for 5 days Use CHG wipes 1 hour after bathing with soap and water *See **Table 8-1** for full MRSA decolonization regimen*
HOW TO PERFORM	Use CHG prep or swab stick to local skin area 30 sec scrub and minimum 30 sec dry time	• CHG cloths should **not** be applied to the face or head. • Use only below the jaw line, as follows, for infants < 10kg: o CHG Cloth 1 = Neck, Chest, Both Arms, Back o CHG Cloth 2 = Both legs, Buttocks, Perineum • Use each cloth to thoroughly wipe each area in a circular or back and forth motion, making sure all skin is cleansed. • Dispose of all cloths in a trash receptacle. • Certain lotions or creams will deactivate the antiseptic; use non-compatible solutions only as needed for skin protection.	

^^ CHG EXCLUSIONS: Do NOT use CHG in any of the following conditions:
- On any open wounds, burns, or skin breakdown.
- On any part of the face or head.
- On infants receiving phototherapy.
- On patients with known allergies to CHG or any other ingredients in the product.
- On patients with severe skin disease (e.g. epidermolysis bullosa, GVHD).

8.2 Bacterial Sepsis

Background

If bacterial sepsis is suspected, cultures should be obtained and antibiotic therapy initiated promptly. In neonates with bacterial meningitis, blood cultures can be sterile in as many as 15% to 50% of cases.

Current semi-automated, computer assisted blood culture systems can identify bacterial pathogens in blood rapidly(within 24–36 hours) and with a sensitivity close to 100% when cultures are performed correctly with a minimum of 1mL of blood. *Candida* species also grow in this system, but occasionally can take longer.

If an infant is ELBW (less than 1000 grams), has renal dysfunction, or is to be treated for more than 72 hours with gentamicin or amikacin, serum levels should be monitored. **(Sec 18-Medications)**

"Outbreaks" in any NICU may dictate temporary changes in the suggested empirical drug regimens.

A serum ammonia level should be drawn if lethargy, hypotonia, or both are present in term infants more than 72 hours of age with suspected sepsis.

Early-Onset Sepsis (Age 0 to 72 Hours, Maternally Acquired Sepsis)

EOS in relation to GBS is discussed separately in **Ch 8.4 Group B Streptococcus**.

Indications for Evaluation

Infants ≥35 0/7 weeks' gestation

- Infant exhibits signs suggesting sepsis: cultures and antibiotics are indicated.
- Born to a mother who has fever (greater than 100.4°F, 38°C) before delivery or within 24 hours afterwards: Review the maternal history and obtain information from the obstetrician. If the obstetrician considers maternal chorioamnionitis, endometritis or other systemic bacterial infection to be present in the mother, use the Web-based Neonatal Early Onset Sepsis Risk Calculator (https://neonatalsepsiscalculator.kaiserpermanente.org) to determine further action. Empirical antibiotics are not given to the infant unless recommended by the calculator. Monitoring vital signs every 4 hours is recommended, even if well appearing.
- Delivered after prolonged rupture of membranes (greater than 18 hours), but has no signs suggesting infection, and mother had no fever or other signs suggesting infection: Observe in hospital for 48 hours. If the infant's clinical condition changes to suggest the presence of infection, obtain cultures and initiate antibiotics.

Infants ≤34 6/7 weeks' gestation)

- Prolonged rupture of membranes (greater than 18 hours), maternal fever (greater than 100.4°F, 38°C) before or within 24 hours after delivery, chorioamnionitis, unexplained premature labor, maternal antibiotic therapy for a suspected bacterial infection, or signs of sepsis in the infant: Obtain cultures and initiate antibiotics.
- If none of these risk factors is present and the infant is delivered by cesarean section without labor or ruptured membranes, evaluation is not necessary unless sepsis is suspected clinically.

Evaluation

Infants >35 0/7 weeks' gestation

- **Infants with signs of sepsis** (e.g., respiratory distress, hypotension, lethargy, apnea, temperature instability, seizures, tachycardia, vomiting, diarrhea, abdominal distention, poor feeding, jaundice, etc.): Evaluate with a CBC, obtain cultures of blood and CSF, and initiate antibiotics. If a blood culture grows a pathogen, a repeat culture of blood should be obtained 24-48 hours after initiation of appropriate therapy and until sterility is documented. If CSF culture grows a pathogen, repeat a CSF culture 24-48 hours after appropriate therapy to document sterility. In patients with skin lesions with purulent drainage, pustules, or vesicles either related to a surgical incision site or not, clinicians should strongly consider sending the fluid from the skin lesion for culture.
- **Healthy-appearing infants:** These infants should receive close follow-up by their pediatricians after discharge. These infants should receive an appointment to either a clinic or their primary care provider 2-5 days after discharge. If the infant develops signs of sepsis after the initiation of antibiotics, reevaluate the infant with a CBC, a lumbar puncture (LP), and obtain another blood culture. Antibiotics should be increased to meningeal levels.

Infants <34 6/7 weeks' gestation

- **Infants with signs of sepsis** (e.g., respiratory distress, hypotension, lethargy, apnea, temperature instability, seizures, tachycardia, vomiting, diarrhea, abdominal distention, poor feeding, jaundice, etc.): Obtain a CBC, cultures of blood and CSF, and initiate antibiotics. If the blood culture grows a pathogen, a repeat culture of the blood should be obtained 24-48 hours after initiation of appropriate therapy and until sterility is documented. If CSF culture grows a pathogen, a repeat a CSF culture 24-48 hours after appropriate therapy is recommended to document sterility.
- **Healthy-appearing infants at risk for early-onset sepsis:** Evaluate by obtaining a CBC and blood culture (a LP is at the discretion of the Neonatology attending physician) and initiate meningeal doses of antibiotics. If the infant develops signs of sepsis [see above], or has a positive blood culture, perform another CBC, LP, and repeat blood culture(s).
- Very low birth weight infants who have a clinical course and an evaluation that make sepsis extremely unlikely may not require a lumbar puncture. If the infant's clinical course is not compatible with infection and the blood culture is negative, performing a LP is at the discretion of the Neonatology attending physician.

When evaluating infants for early-onset sepsis, ancillary inflammatory markers such as CRP and procalcitonin have little to no value in confirming or ruling out infection and therefore are not recommended.

Initial Empirical Therapy

For empiric antibiotic regimens for EOS, **refer to Ch 8.3-Guidelines for Antibiotic Therapy in NICU Patients**.

For specific medication doses, **refer to Sec 18-Medications.**

If CSF is abnormal or cannot be obtained when a lumbar puncture is performed or if gram-negative organisms are suspected, meningeal doses should be used.

If CSF is normal, non-meningeal doses are appropriate.

Duration of Therapy

Infants with signs of sepsis – Depending upon the isolated pathogen and clinical course, a minimum 7 to 10 days of therapy is given if sepsis is strongly suspected or proven; minimum 14 to 21 days is given if meningitis is strongly suspected or proven.

Healthy-appearing infants or those whose course does not suggest sepsis - Therapy in term infants can be discontinued when the blood culture is documented to be sterile after 24 to 48 hours of incubation.

If cultures are negative and the clinical course is not felt to be compatible with sepsis, discontinue antibiotics no later than 48 hours after therapy is initiated. Treatment of culture negative sepsis for more than 36 - 48 hours is discouraged.

Late-Onset Sepsis (Age > 72 hours)

Age older than 3 days and continuous Level 1-4 care. Refer to **Fig 8-1** for LOS evaluation and treatment algorithm.

Indications for Evaluation

Signs of sepsis or focal infections such as pneumonia, urinary tract infection, soft tissue infection, bone or joint infection, NEC, or meningitis. Consider maternal, viral, and hospital-associated sources for infection.

Evaluation

Obtain a CBC and cultures of blood, CSF, and urine. In certain circumstances, consider pleural fluid, abscess material, bone, joint or peritoneal fluid cultures when infection is localized to those sites. A tracheal aspirate culture that grows a pathogen, including CONS, may not define pneumonia and can reflect colonization of the endotracheal tube. In infants less than 1500 grams, there can be difficulty in obtaining an uncontaminated urine specimen by catheterization and bladder tap may need to be performed. Urine culture, in this birth weight group, is always indicated for infants who are being evaluated for:

- suspected fungal infection,
- known renal anomalies, or
- more than one episode of gram-negative bacteremia without a source identified

In other VLBW infants, the likelihood of a primary UTI is between 7% and 10%; omitting a urine culture is at the discretion of the attending physician.

Ancillary Inflammatory Markers

Ancillary inflammatory markers may offer limited value in ruling out infection in the neonatal population. CRP has been the best studied in the evaluation of LOS with most recent data showing that a CRP at 24 hours after initiation of a sepsis work-up may be helpful. A CRP value $\leq$1 mg/dL is unlikely to be present in bacterial infection and could minimize the use of antibiotics. Routine measurements of CRP in well-appearing infants are not otherwise recommended to screen for infection.

Procalcitonin is another inflammatory marker that has been used in the evaluation of sepsis. However, it is not recommended for routine use in the general assessment of a neonate with features of late onset sepsis.

Initial Empirical Therapy

For empiric antibiotic regimens for LOS, **refer to Ch 8.3-Guidelines for Antibiotic Therapy in NICU Patients**.

For specific doses, **refer to Sec 18-Medications.**

Suspected disseminated staphylococcal infection - Administer both vancomycin and nafcillin with amikacin until culture results and antibiotic susceptibilities are known. Nafcillin is more effective than vancomycin in the treatment of MSSA.

Meningitis - If suspected or proven, an Infectious Disease consultation and at least 24-hour observation in the Level III/IV NICU are recommended to assist with management.

Infection of bone, joint, or both - Administer vancomycin, nafcillin and amikacin; an Infectious Diseases consultation early in the course is advised to determine whether surgical intervention is needed.

Intravascular catheter-related infection (Central Line Associated Blood Stream Infection [CLABSI]). Administer nafcillin and amikacin. If caused by yeast, enterococcus, or gram-negative rods, S. aureus or multiple organisms, the catheter should be removed to eliminate the potential source of infection and prevent further dissemination. In patients who remain "septic" despite antibiotics or in whom secondary foci of infection appear on therapy, the catheter must be removed immediately.

8.3 Guidelines for Antibiotic Therapy in NICU Patients

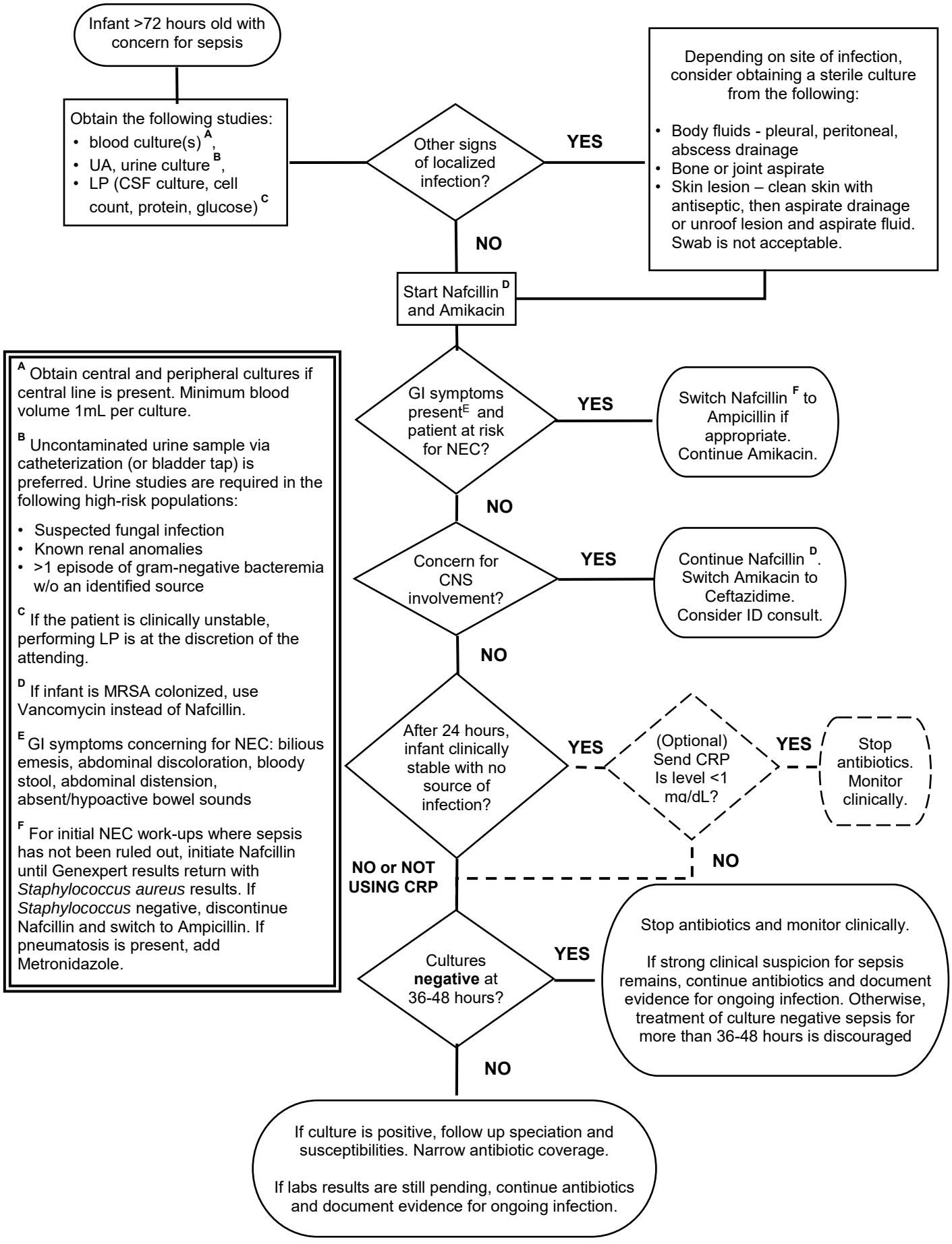
Empiric Antibiotic Regimens

The following suggested treatment regimens **(Table 8-3)** are based off the local TCH antibiogram and should be used for empiric treatment of bacterial infections.

Antibiotic Stewardship

Although not clearly defined, antibiotic administration in the neonate has been associated with alterations in the gut microbiome and increased risk for childhood diseases, including wheezing, obesity, food allergy, and inflammatory bowel disease. The risks and benefits must be evaluated when initiating empiric antibiotics and when continuing empiric therapy in the absence of proven infection. Therefore, in clinical scenarios where no positive culture has been identified, we strongly recommend discontinuing antibiotics after 48 hours of empiric treatment and negative cultures.

Figure 8-1. Late-onset sepsis algorithm



A Obtain central and peripheral cultures if central line is present. Minimum blood volume 1mL per culture.

B Uncontaminated urine sample via catheterization (or bladder tap) is preferred. Urine studies are required in the following high-risk populations:

- Suspected fungal infection
- Known renal anomalies
- >1 episode of gram-negative bacteremia w/o an identified source

C If the patient is clinically unstable, performing LP is at the discretion of the attending.

D If infant is MRSA colonized, use Vancomycin instead of Nafcillin.

E GI symptoms concerning for NEC: bilious emesis, abdominal discoloration, bloody stool, abdominal distension, absent/hypoactive bowel sounds

F For initial NEC work-ups where sepsis has not been ruled out, initiate Nafcillin until Genexpert results return with *Staphylococcus aureus* results. If *Staphylococcus* negative, discontinue Nafcillin and switch to Ampicillin. If pneumatosis is present, add Metronidazole.

Table 8-3. Empiric antibiotic regimens

	Diagnosis	Suggested Regimen	Alternate Regimen [a]	Maximum Duration of Therapy
SEPSIS	EOS (first 72 hours of life)	Ampicillin, Amikacin	N/A	48 hour rule out, 7-10 days organism-specific therapy if culture positive
	EOS with suspected CNS involvement	Ampicillin, Ceftazidime	N/A	48 hour rule out, organism-specific duration for meningitis
	LOS	Nafcillin, Amikacin	N/A	48 hour rule out, 7-10 days organism-specific therapy if culture positive
	LOS with suspected CNS involvement	Nafcillin, Ceftazidime	N/A	48 hour rule out, organism-specific duration for meningitis
NEC [b]	Medical NEC without evidence of pneumatosis	Ampicillin, Amikacin	Piperacillin/ tazobactam	7 days
	Medical NEC with evidence of pneumatosis	Ampicillin, Amikacin, Metronidazole	Piperacillin/ tazobactam	7 days
	Surgical NEC or SIP or post-abdominal drain placement or post-laparotomy	Ampicillin, Amikacin, Metronidazole	Piperacillin/ tazobactam	10 days
OTHER	Small bowel atresia repair or gastroschisis abdominal closure	Cefazolin for perioperative coverage or Cefoxitin for patients requiring anaerobic coverage	N/A	Until skin closure only

[a] Alternate regimen should only be used in select cases when routine antibiotic coverage is deemed to be inadequate based on antibiotic susceptibility patterns or failure to improve on the standard regimen.

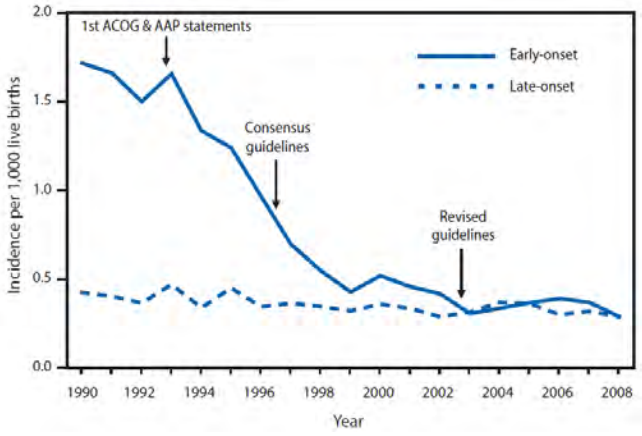
[b] For initial NEC work-ups where sepsis has not been ruled out, initiate Nafcillin and Amikacin(+/- Metronidazole) until Genexpert results return with *Staphylococcus aureus* results. If *Staphylococcus* negative, discontinue Nafcillin and initiate Ampicillin.

8.4 Group B Streptococcus (GBS)

The CDC previously published and updated GBS recommendations in collaboration with multiple professional organizations. This task is now the responsibility of 3 main organizations: (1) American College of Obstetricians and Gynecologists (ACOG) for guidance on screening and prophylaxis in mothers, (2) American Academy of Pediatrics (AAP) for guidance on risk assessment and treatment in newborns, and (3) American Society for Microbiology (ASM) for detection and identification of GBS through standardized laboratory practices. While these publications are separate, they are aligned in p GBS is found in the maternal gastrointestinal and genitourinary tracts (15–35%), and infection results from vertical transmission during labor or delivery. Since the introduction of routine maternal GBS culture screening and intrapartum antibiotic prophylaxis (IAP), the incidence of early-onset (0-6 days) GBS disease has decreased from 1 to 4 cases per 1000 live births to approximately 0.25 cases per 1000 live births, while having no effect on late-onset (7-89 days) GBS disease **(Fig 8-2)**.

The risk of early-onset disease is increased in preterm infants, rupture of membranes longer than 18 hours, maternal fever >100.4°F, intra-amniotic infection (formerly chorioamnionitis), GBS bacteruria during the current pregnancy, or a previous infant with GBS disease. Signs of early onset disease occur within the first 24–48 hours of life in more than 95% of babies. It is usually characterized by septicemia (80-85%), pneumonia (5-10%), or meningitis (5–10%). Recurrence of GBS in appropriately treated infants is 1-3%. Gram stains typically show GPC in pairs or short chains. Growth in culture is diagnostic.

Figure 8-2. Incidence of early- and late-onset GBS disease



Abbreviations: ACOG=American College of Obstetricians and Gynecologists and AAP=American Academy of Pediatrics

*Incidence rates for 2009 are preliminary because the live birth denominator has not been finalized.

Adapted from Jordan HT, Farley MM, Craig A, et al. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease. Pediatr Infect Dis J 2008;27:1057-64.

Source: Prevention of Perinatal Group B Streptococcal Disease. Revised Guidelines from CDC, *MMWR* 2010;59(RR-10):

Table 8-4. Indications for IAP to prevent neonatal early onset GBS disease

Intrapartum GBS prophylaxis indicated	Intrapartum GBS prophylaxis NOT indicated
Previous neonate with invasive GBS disease GBS bacteriuria during any trimester of current pregnancy * Positive GBS vaginal-rectal screening culture obtained at **36 0/7 weeks gestation or later** * Unknown GBS status at the onset of labor (culture not done or results unknown) and any of the following risk factors: 1. Delivery at < 37 weeks gestation 2. Amniotic membrane rupture ≥ 18 hours 3. Intrapartum temperature ≥ 100.4^0 F (38.0^0 C) # 4. Intrapartum NAAT result positive for GBS 5. Intrapartum NAAT result negative but intrapartum risk factors develop (*risks factors # 1-3 above*) 6. Known GBS positive status in a prior pregnancy	GBS colonization in a prior pregnancy (unless an IAP indication is present in current pregnancy or unknown status at onset of labor at term) GBS bacteriuria in a prior pregnancy (unless an IAP indication is present in current pregnancy) Negative GBS vaginal-rectal screening culture obtained at **36 0/7 weeks gestation or later**, regardless of intrapartum risk factors (*risks factors # 1-3 to the left*) Unknown GBS status at onset of labor, negative NAAT result, and no intrapartum risk factors (*risks factors # 1-3 to the left*) Cesarean delivery is performed before onset of labor with intact amniotic membranes, regardless of GBS colonization status or gestational age

* IAP is not indicated in this circumstance if a cesarean delivery is performed before onset of labor with intact amniotic membranes

If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

Abbreviations: GBS, Group B streptococcus; NAAT, nucleic acid amplification test

Modified from Verani JR, McGee I, Schrag SJ. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC, 2010. Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep 2010, 59(RR-10):1-36. (This Committee Opinion, including Table 1, Box 2, and Figure 1-3, updates and replaces the obstetric components of the CDC 2010 guidelines, "Prevention of Perinatal Group B Streptococcal Disease: Revised Guidelines from CDC, 2010.")

ACOG now recommends universal GBS screening between 36 0/7 and 37 6/7 weeks of gestation. All women with GBS positive vaginal-rectal cultures should receive IAP unless a cesarean delivery is performed without labor with intact membranes. Adequate IAP is defined as receiving antibiotics (penicillin, ampicillin, or cefazolin) at least 4 hours prior to delivery. Indications for IAP are described in **(Table 8–4)**:

- **Preferred:** Penicillin (5 million U initially, then 2.5 to 3.0 million U, every 4 hours, until delivery)
- **Alternative:** Ampicillin (2 g initially, then 1 g every 4 hours until delivery)
- **Penicillin-allergic women:**
  - **Low Risk Allergy** (nonspecific symptoms, morbilliform rash without systemic symptoms, pruritis without rash, family history of allergy but no personal history, history but no recollection of symptoms or treatment): Cefazolin (2 g initially, then 1 g every 8 hours until delivery)
  - **High Risk Allergy** (IgE mediated event with pruritic rash, urticaria, immediate flushing, hypotension, angioedema, respiratory symptoms, anaphylaxis, recurrent reactions, reactions to beta lactams, positive penicillin allergy test, severe delayed onset reaction): request Clindamycin susceptibility
    - » Clindamycin-susceptible: Clindamycin (900 mg every 8 hours until delivery)
    - » Clindamycin-resistant: Vancomycin (20mg/kg every 8 hours).
  - The efficacy of clindamycin or vancomycin in preventing early-onset GBS is not established, and therefore **not** considered adequate IAP.

Evaluation

Risk assessment and recommendations for evaluation of newborns exposed to GBS are outlined in the algorithms **(Fig 8–3 to Fig 8-4)** from the 2019 AAP guidelines. Infants who receive the limited evaluation are triaged to Level 1 Newborn Nursery and are not candidates for early discharge (<48 hours).

Treatment

Consultation with Infectious Diseases Service should be considered in neonates with confirmed GBS disease, especially in those with meningitis or site-specific infection. Initial recommendations for treatment of early-onset and late-onset GBS disease are provided from the 2019 AAP guidelines adapted from *Red Book* (**Table 8-5**).

8.5 Coronavirus (SARS-CoV-2 or COVID-19)

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and is the cause of the COVID-19 (novel coronavirus disease-2019) global pandemic. The outbreak is continuously evolving and guidelines to minimize in-hospital exposure and transmission of SARS-CoV-2 are frequently being changed to address the need. Providers are advised to check their local institutional policies and guidelines for the most up to date information.

SARS-CoV-2 is a single-stranded RNA virus belonging to the *Coronaviridae* family that is encapsulated with characteristic spike glycoproteins on its envelope. Transmission is predominantly via respiratory droplets, although airborne transmission can occur under special circumstances (including

Table 8-5. Recommendations for treatment of early-onset and late-onset GBS disease

	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	125 000 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 o Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:915-919. GA, gestational age; PNA, postnatal age.

Reproduced with permission from Pediatrics, Puopolo KM, Lynfield R, Cummings JJ. American Academy of Pediatrics, Committee on Infectious Diseases.Management of Infants at Risk for Group B Streptococcal Disease. Pediatrics. 2019 Aug;144(2):e20191881. 2013;131(2):e635.© 2019 by the AAP.

aerosol-generating populations and procedures in the hospital). Infectivity is thought to occur by the spike proteins binding ACE-2 receptors found on human epithelial cells in the respiratory tract. Prevention of spread focuses on 3 main tasks: (1) wearing an appropriately fitted mask covering both mouth and nose; (2) physical distancing to maintain at least 6 feet of distance from others while also avoiding large crowds and gatherings; (3) frequently handwashing or use of an alcohol-based sanitizer.

In the neonatal population, special consideration must be given to pregnant women and newborns exposed to SARS-CoV-2 or with COVID-19. Pregnant women with COVID-19 are at increased risk of having severe illness, defined as needing hospitalization, intensive care, or invasive ventilation, in addition to higher rates of ECMO and mortality compared to non-pregnant women. This in turn may affect rates of
c-section deliveries and preterm births. Vertical transmission of SARS-CoV-2 from mother to neonate is infrequent and uncommon but can occur via: (1) intrauterine transmission with infected amniotic fluid or transplacental spread; (2) intrapartum transmission with exposure to infected secretions or blood during the birthing process. The predominant method of maternal-neonatal spread is via horizontal transmission of respiratory droplets from an infected mother (or another individual) to a newborn during or soon after birth.

Long term impacts of neonatal COVID-19 or exposure to COVID-19 in utero are yet to be determined.

Presentation

Early-onset disease refers to newborns presenting with COVID-19 up to 5-7 days of life. These infants are typically asymptomatic or have minor symptoms. Late-onset disease refers to neonates presenting after 5-7 days of life. Majority of symptomatic neonatal COVID-19 is seen in late-onset disease, and is most commonly the result of horizontal transmission.

Symptoms of neonatal COVID-19 are generally nonspecific and similar to other respiratory viral illnesses, including: rhinorrhea, cough, fever, respiratory distress, poor feeding, hypotonia, vomiting/diarrhea. An overwhelming majority of exposed and/or infected newborns are asymptomatic and are cared for in the mother-baby unit. Severe illness, multi-organ failure, and coagulopathy are uncommon but have been reported. Neonatal multisystem inflammatory syndrome (similar to MIS-C in children) has rarely been reported, and data is limited in the neonatal population.

Evaluation

RT-PCR using a nasopharyngeal swab is the test of choice for detecting SARS-CoV-2 viral RNA at TCH.

Any newborn born to mother with suspected or confirmed COVID-19 at the time of delivery should have an RT-PCR test at both 24 and 48 hours of life (if still hospitalized). Any neonate in the NICU with symptoms concerning for COVID-19 should be tested immediately with RT-PCR in addition to testing for other common respiratory viral illnesses. If a NICU patient has been exposed to confirmed COVID-19 while hospitalized, testing should be obtained 5 days after the first exposure.

Other laboratory evidence is not required but may reveal nonspecific findings, such as elevated or decreased WBC, thrombocytopenia, elevated lactate, or DIC. Chest radiographs may show nonspecific opacities.

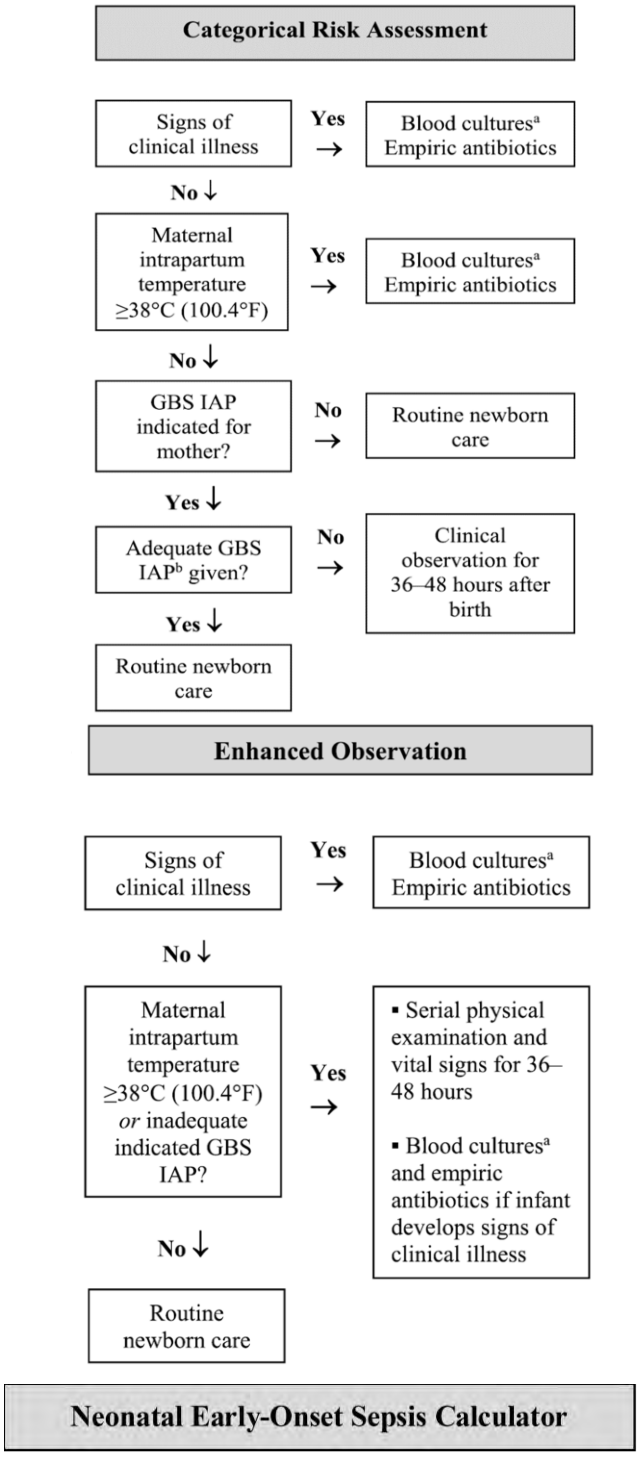
Isolation

Enhanced respiratory precautions are required when caring for any patient with suspected or confirmed COVID-19; this includes attending deliveries and for neonatal resuscitation. Required personal protective equipment (PPE) includes gown, gloves, N95 respirator (or CAPR/PAPR), and eye protection at minimum. Specific details regarding isolation and PPE are provided in the NBC COVID-19 Guidelines. Infection Control must also be notified immediately if a NICU patient is positive for COVID-19.

Management

- Delayed cord clamping for newborns born to COVID-19 positive mothers should be continued per current TCH practice as benefits outweigh the risks.
- Use of breast milk from mothers with COVID-19 or in those who have received COVID-19 vaccination(s) is encouraged as breast milk benefits outweigh the risks. IgG antibodies have been found in breast milk of these mothers and may be protective against infection in the neonate. Guidelines for direct breastfeeding and EBM use are provided in the NBC COVID-19 Guidelines.
- Separation of mother-baby dyad in the mother-baby unit is not required, however certain circumstances may exist in which it can be encouraged (mother who is critically ill, mother who is symptomatic). Guidelines for rooming-in with isolation are provided in the NBC COVID-19 Guidelines.

Figure 8-3. Options for EOS risk assessment among infants born ≥35 weeks' gestation



https://neonatalsepsiscalculator.kaiserpermanente

a Consider LP and CSF culture before initiation of empiric antibiotics for infants at highest risk of infection and those with critical illness, if clinical condition permits. Antibiotics should be administered promptly and not deferred because of procedure delays.

b Adequate GBS IAP is penicillin G, ampicillin, or cefazolin ≥ hours before delivery.

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Management of neonatal COVID-19 is largely supportive for those infants who are symptomatic. Asymptomatic infants can be cared for in the mother-baby unit and discharged when medically ready; they do not require a prolonged hospital stay or automatic NICU admission due to COVID-19. Neonates with a more severe presentation may require the use of respiratory support, fluid resuscitation, IV nutrition, antipyretics, monitoring for multi-organ failure. ID consultation should be obtained for any COVID-19 positive neonate in the NICU. There are no approved or emergency use authorized medications for the treatment of neonatal COVID-19. Data is limited regarding the use of convalescent plasma, remdesivir, and dexamethasone in the treatment of neonatal COVID-19 and a multidisciplinary approach should be used for such evaluations.

8.6 Cytomegalovirus (CMV)

Background

CMV is the most common congenital viral infection in the US. Most neonates with congenital CMV infection are usually asymptomatic at birth with a proportion of these infants developing hearing loss (15%) or developmental delay later in life. However, approximately 10% of infants exhibit clinical findings at birth (symptomatic congenital CMV disease), including: intrauterine growth restriction, jaundice (conjugated and unconjugated), purpura, hepatosplenomegaly, hearing loss, microcephaly, periventricular calcifications, retinitis, and death (3-10%).

Congenital CMV is the leading cause of sensorineural hearing loss (SNHL) in children in the US, accounting for 20% of all hearing loss at birth and 25% of all hearing loss at 4 years of age. SNHL may be unilateral or bilateral and is often the only clinical finding. A large proportion of patients who develop congenital CMV-associated SNHL will not have hearing loss detectable within the first month of life. Such children should be evaluated at regular intervals for early detection of hearing loss or progression of disease.

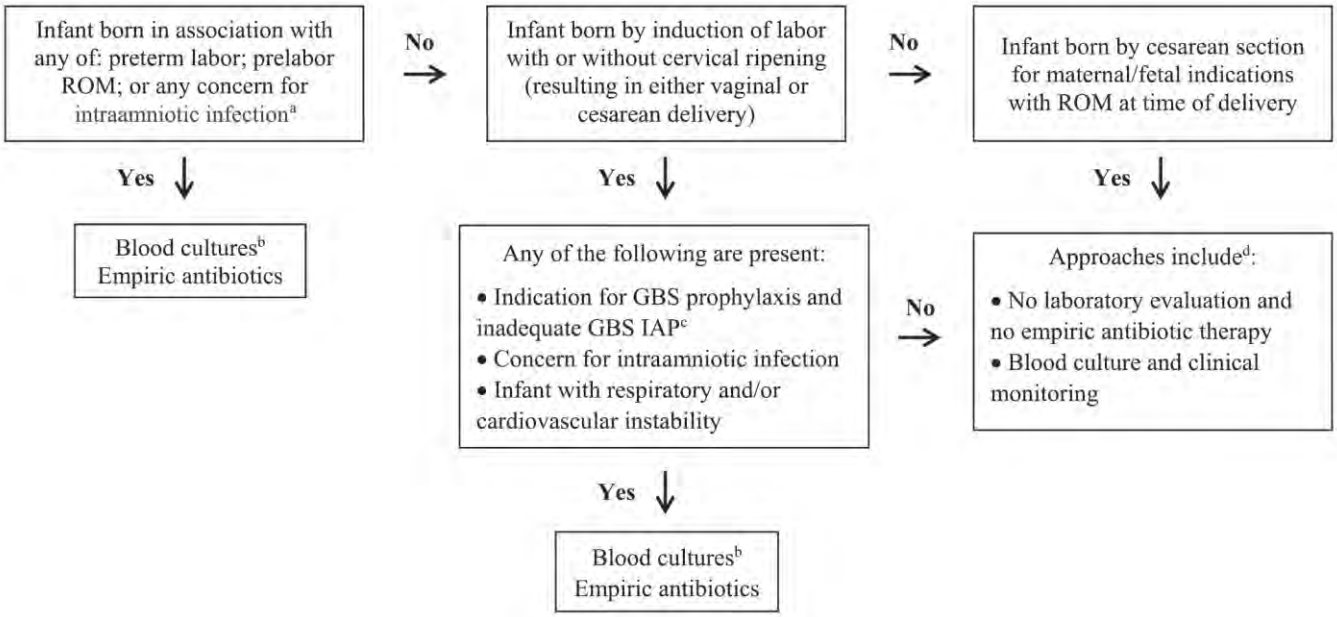
Acquired CMV infection can occur at birth or shortly thereafter via breast milk or transfusion but is usually not associated with clinical illness, except in preterm infants where acute infection has been associated with hepatitis, interstitial pneumonia, hematologic abnormalities (thrombocytopenia, leukopenia), and a viral sepsis syndrome.

Evaluation

Virus can be isolated from several bodily fluids, including but not limited to urine, nasal pharyngeal secretions, and peripheral blood leukocytes. Typically, testing must be completed within 2 to 4 weeks of birth to diagnose a congenital infection. Differentiation between congenital and acquired infection is difficult at later than 2 to 4 weeks of age unless clinical manifestations of the former, such as chorioretinitis or intracranial calcifications, are present.

Detection of CMV by polymerase chain reaction (PCR) is often the most preferred testing. For initial evaluation, a bag urine specimen for urine CMV PCR is sufficient. If positive, plasma CMV PCR (quantitative) should be obtained as it correlates with active infection and can be used to monitor disease progression.

Figure 8-4. Options for EOS risk assessment among infants born ≤34 weeks' gestation



a Intraamniotic infection should be considered when a pregnant woman presents with unexplained decreased fetal movement and/or there is sudden and unexplained poor fetal testing.

b Consider LP and CSF culture before initiation of empiric antibiotics for infants at highest risk of infection if clinical condition permits. Antibiotics should be administered promptly and not deferred because of procedural delays.

c Adequate GBS IAP is penicillin G, ampicillin, or cefazolin ≥ 4 hours before delivery.

d For infants who do not improve after initial stabilization and/or those who have severe systemic instability, the administration of empiric antibiotics may be reasonable but is not mandatory.

Serologic testing with CMV IgM at birth may also be diagnostic, but these tests commonly have reduced specificity and may yield false-positive results. Traditional "TORCH titers" have little value and are not recommended.

Treatment

An Infectious Disease consult should be obtained for all infants with CMV infection. Treatment typically includes IV ganciclovir or PO valganciclovir for 6 months. Antiviral therapy should be limited to patients with moderate to severe symptomatic congenital CMV disease who are able to start treatment within the first month of life. Neonates with asymptomatic, mild symptomatic disease, or with isolated SNHL and no other disease manifestations should not routinely receive antiviral treatment. Absolute neutrophil counts and serum alanine transaminase should be followed while on antiviral treatment.

8.7 Fungal Infection (Candida)

Background

The most common fungal infections are due to *Candida* species, typically *Candida albicans* and *Candida parapsilosis*. However, in some NICUs, the incidence of fungemia and disseminated disease can be attributed to other *Candida* species (*C. tropicalis, C. lusitiani, C. krusei,* and *C. glabrata*). Disseminated candidiasis typically occurs in very low birth weight newborns (especially those less than 1000 grams or less than 27 weeks gestational age) and can involve almost any organ. Candidemia can occur with or without organ dissemination in patients with indwelling central lines. Systemic corticosteroids as well as prolonged broad-spectrum antibiotics (especially third generation cephalosporins and meropenem) increase the risk of invasive candidiasis. Other reported risk factors include total parenteral nutrition, intralipids, abdominal surgery, and H_2 blockers.

Evaluation

A presumptive diagnosis of disseminated candidiasis can be made by isolation of *Candida* from blood, CSF, infected tissue, or urine (obtained by suprapubic aspiration or catheterization with $\geq 10^4$ CFU/mL). Invasive fungal dermatitis, which can be caused by *Candida* or other fungi (e.g., Aspergillosis), is a diagnosis made by clinical suspicion and confirmed by histopathology of a skin biopsy.

Ophthalmologic examination, lumbar puncture, abdominal ultrasonography, and echocardiogram are indicated for all cases of disseminated candidiasis. MRI of the brain with contrast is appropriate for evaluation of *Candida* infection in the CNS. Diagnostic imaging studies should be performed in the late 2nd or 3rd week of therapy since initial evaluation can be misleading early in the course of therapy.

Chemoprophylaxis

Several studies, including 3 multicenter randomized studies, have compared the effect of prophylactic intravenous fluconazole versus placebo for six weeks in very low or extremely low birth weight infants. Both colonization with *Candida* and invasive candidiasis have been significantly reduced with prophylaxis. The prophylaxis regimen is safe,

and in NICUs using this approach for 6 and 10 years, respectively, no resistant *Candida* spp. have emerged. The 2018 Red Book recommends routine fluconazole prophylaxis for infants weighting less than 1000 g at birth in NICUs where the incidence of invasive candidiasis is high (>10%). This recommendation is based on moderate quality of evidence.

Treatment

Disseminated candidiasis requires treatment with amphotericin B deoxycholate (1 mg/kg IV daily). Renal indices (serum BUN and creatinine) and serum potassium levels initially must be monitored frequently. Flucytosine (150 mg/kg per day orally in 4 divided doses) can be considered in combination with amphotericin B if CNS infection by *C. albicans* is present. For step-down treatment after the patient has responded to initial treatment, fluconazole 12 mg/kg daily may be used for isolates that are susceptible.

Length of therapy will vary with site(s) of infection and with clinical response. Disseminated fungal disease due to unusual fungi and yeast (*Aspergillus, Curvularia, Fusarium, Trichosporon*, and rare species of *Candida*) has been reported in very low birth weight infants and requires specific antifungal therapy. Indwelling vascular catheters must be removed as soon as it is feasible. Consultation with the Infectious Disease Service is suggested for any patient with disseminated candidiasis or other invasive fungal infection.

8.8 Gonococcal Disease

Background

N. gonorrhoeae infection is the second most common sexually transmitted infection (STI) in the US. Infections in the newborn usually involve the eyes. Other sites of infection include septicemia, arthritis, meningitis, or scalp abscess. Transmission is through contact with exudate and secretions from infected mucosal surfaces with an incubation period of 2 to 7 days. Both the mother and her sexual partner(s) should be evaluated and treated appropriately. All cases of gonorrhea must be reported to local public health officials.

Managing Asymptomatic Infants

All infants should receive routine eye prophylaxis immediately after birth (may be delayed up to 1 hour to promote mother-infant bonding). If the mother has untreated gonorrhea at the time of delivery, the infant should receive a single dose of ceftriaxone (25 to 50 mg/kg (maximum dose, 125 mg), intravenously or intramuscularly). When systemic ceftriaxone therapy is administered prophylactically, topical antimicrobial therapy is not necessary.

Managing Symptomatic Infants

In cases of symptomatic neonatal disease, cultures of blood, CSF, eye discharge, or other sites of infection (e.g., synovial fluid) should be obtained to confirm the diagnosis and determine the antibiotic susceptibility of the organism. Testing for other STIs is recommended.

Ophthalmia Neonatorum- Recommended antimicrobial therapy is a single one-time dose of ceftriaxone (25 to 50 mg/kg, intravenously or intramuscularly, not to exceed 125 mg). These infants should be hospitalized and evaluated for disseminated infection, including arthritis or septicemia. Infants should also receive eye irrigations with saline solution at frequent intervals until discharge is eliminated.

Disseminated Neonatal Infections or Abscesses: Recommended therapy for arthritis, septicemia, or abscess is ceftriaxone (25 to 50 mg/kg/day, intravenously or intramuscularly, in a single daily dose for 7 days) or cefotaxime in cases with hyperbilirubinemia (25 mg/kg, every 12 hours for 7 days), and in documented meningitis for 10 to 14 days.

8.9 Hepatitis B

Background

Without postexposure prophylaxis, the risk of an infant acquiring HBV vertically from an infected mother who is HBsAg and HBeAg positive as a result of perinatal exposure is 70% to 90%. The risk is 5% to 20% for infants born to HBsAg-positive but HBeAg-negative mothers.

Newborn infants with acute HBV infection rarely show clinical or biochemical signs of disease at birth (<1%). Affected newborns remain asymptomatic, and develop chronic antigenemia with mild liver enzyme elevations beginning at 2 to 6 months of age **(Fig 8–5)**. A small number of patients will develop acute hepatitis by 2 months of age with jaundice or fulminant hepatitis. Up to 90% of infants infected perinatally or in the first year of life will develop chronic infection.

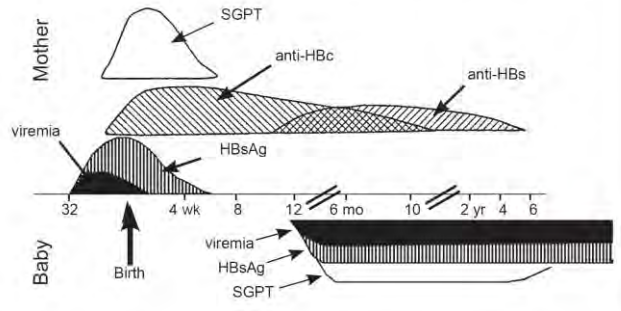
- All mothers have an HBsAg determination performed before or at the time of delivery.
- All outborn newborn admissions should have maternal blood sent to the laboratory for HBsAg testing if results of maternal hepatitis screening are not otherwise available.
- The results of the maternal HbsAg test should be ascertained before the infant is discharged.

Maternal Screen Status

HBsAg Positive

- For all infants, give Hepatitis B Immune Globulin (HBIG) 0.5 mL IM and Hepatitis B vaccine (10 mcg/mL) 5 mcg IM within 12 hours of birth. Give concurrently with separate syringes at separate sites according to current dosage guidelines.

Figure 8-5. Time course of acute hepatitis B at term and chronic neonatal infection



Adapted from: Kohler PF. Hepatitis B virus infection—in pregnancy, neonates. *Perinatal Care* March 1978;1(3):7–12. Used with permission.

- For infants who weigh less than 2 kg at birth, do not count the initial dose of vaccine in the required 3-dose schedule, and give the subsequent 3 doses in accordance with the schedule. Thus, a total of 4 doses are recommended in this circumstance.
- Schedule follow-up with the primary care provider at 1 (preferable) to 2 months chronological age (regardless of BW or GA) and at 6 months of age to receive doses 2 and 3 of the vaccine. Follow-up is very important.
- With appropriate immunoprophylaxis, including HBIG, breastfeeding of babies born to HBsAg-positive mothers poses no additional risk of HBV transmission.
- Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg (anti-HBs) at 9 to 12 months of age, after completion of at least 3 doses of a licensed Hepatitis B vaccine series.

Unknown

If the report of the maternal screen is not available at delivery, maternal HBsAg status should be determined as soon as possible through maternal testing.

- All infants should receive hepatitis B vaccine (10 mcg/mL) 5 mcg within 12 hours of age, regardless of gestational age and weight.
- Infants who weigh less than 2 kg at birth should also be given HBIG (0.5 mL) with the vaccine within 12 hours of birth because of the poor immunogenicity of the vaccine in these patients. This initial vaccine dose should not be counted in the required 3 doses to complete the immunization series.
- Infants with a birth weight 2 kg or higher should await maternal testing results. If the mother is determined to be positive, these infants should receive HBIG (0.5 mL) as soon as possible, but within 7 days of birth.
- If mother is HBsAg-negative, the infant should complete the vaccination schedule recommended below for routine immunization of term and preterm infants, respectively.

Routine Vaccination

Recommended Doses of Hepatitis B Virus Vaccine:

- Recombivax HB vaccine, pediatric formulation, 5 mcg (0.5 mL) IM
- Energix-B, 10 mcg (0.5 mL) IM

Term infants' vaccination schedule:

Dose 1: Birth (before discharge).

Dose 2: 1 through 2 months after initial dose.

Dose 3: 6 through 18 months of age.

Premature infants' birthweight (< 2000 grams) vaccination schedule:

Dose 1: These infants **should** receive the first dose of hepatitis B single antigen vaccine starting at 1 month of chronological age or at hospital discharge if before 1 month of chronologic age.

If single antigen vaccines are used:

Dose 2: 1 to 2 months after initial dose.

Dose 3: 6 through 18 months of age.

If combination vaccines are used:

Dose 2: 2 months chronologic age

Dose 3: 4 months chronologic age

Dose 4: 6 mo (Pediarix) or 12 through 15 mo (Comvax)

In general, the various brands of age-appropriate hepatitis B vaccines are interchangeable within an immunization series. The immune response using 1 or 2 doses of a vaccine produced by one manufacturer followed by 1 or more subsequent doses from a different manufacturer is comparable to a full course of immunization with a single product. However, one should attempt to use the same product throughout the series, if possible.

Serologic testing is not necessary after routine vaccination.

Follow-up

The attending physician is responsible for follow-up and to order additional doses of vaccine. If the patient remains hospitalized, the provider will order hepatitis B vaccine doses 2 and 3 according to the schedule appropriate for that patient.

8.10 Hepatitis C

Hepatitis C virus (HCV) is transmitted vertically to 5% to 6% of infants by perinatal exposure of blood from HCV RNA-positive mothers at the time of delivery. Serologic testing at 18 months of age is recommended for infants born to women previously identified to be HCV infected. Factors that increase perinatal transmission include internal fetal monitoring, vaginal lacerations, rupture of membranes >6 hours, and maternal coinfection with HIV.

Testing for anti-HCV should not be performed until after 18 months of age due to the presence of passive maternal antibody. Testing for HCV RNA by NAAT can determine HCV viremia at an early age. The test is not recommended for use in the first month of life. If HCV RNA testing at 1 to 2 months of age determines that an infant is HCV infected, the Infectious Disease Service should be consulted for further follow-up and recommendations. Transmission by breastfeeding has not been documented; consideration should be given to stopping breastfeeding for a period of time if the nipples are cracked or bleeding.

8.11 Herpes Simplex Virus (HSV)

Background

The incidence of neonatal HSV infection is approximately 1 in 3000 live births in the US. Infection may be caused by either HSV type 1 or type 2 but most caused by HSV 1. With maternal primary infection at the time of delivery, there is a 25% to 60% risk of disease transmission; with recurrent infection, the risk decreases to < 2%. Exposure of the newborn typically occurs during delivery through the birth canal (intrapartum transmission). Documented in utero and post-partum transmission is rare. Of those infants who become infected, more than 75% are born to mothers without a history or clinical finding of herpes infection during pregnancy.

Mortality and morbidity are high for neonatal HSV, even with treatment.

Presentation

Neonatal HSV can present as:

- Disseminated disease (25% of cases) involving multiple organs, most prominently liver and lungs, and in 60% to 75% of cases also involving the central nervous system (CNS)
- localized CNS disease (30% of cases) with or without skin, eye, or mouth involvement
- SEM disease (45% of cases) involving the skin, eyes, and/or mouth

Initial signs of HSV infection can occur anytime between birth and 6 weeks of age, although almost all infected infants develop clinical disease within the first month of life. Infants with disseminated disease and SEM disease have an earlier age of onset, typically presenting between the first and second weeks of life; infants with CNS disease usually present with illness between the second and third weeks of life. Virtually all HSV infections in neonates are symptomatic. However, early signs of HSV frequently are non-specific and subtle. The possibility of HSV should be considered in any neonate with vesicular lesions or with unexplained illness (including respiratory distress, seizures, sepsis, liver dysfunction, coagulopathy, fever). Other viruses (e.g., enterovirus [enterovirus, echovirus and coxsackie A & B virus], adenovirus) also may cause systemic disease that mimics overwhelming bacterial sepsis.

A Careful History

A careful exploration of both the paternal and maternal history is critical in determining the risk of HSV infection in the neonate. If the mother or father has a history of HSV infection, the following details should be obtained: when and how the diagnosis was made, the time of the last symptoms, and if any treatment was given.

A negative maternal history does not exclude the possibility of infection in a neonate with symptoms suggestive of HSV infection because many women with primary or recurrent HSV infection are asymptomatic.

At-Risk Infants

Consider infants at-risk if born by any delivery method to a mother with **either** HSV genital lesions at delivery or during the post- partum hospitalization, **or** a positive maternal HSV culture at delivery, regardless of the nature of the maternal infection status (e.g., primary or secondary [i.e., recurrent]).

Factors that might increase disease transmission to at-risk infants include:

Maternal factors

- primary genital infection
- cervical or vaginal rather than vulvar lesions
- status (primary or recurrent) is unknown
- rupture of membranes more than 4 hours

Neonatal Factors

- prematurity (37 or fewer weeks' gestation)
- fetal scalp monitor
- skin trauma or laceration at delivery

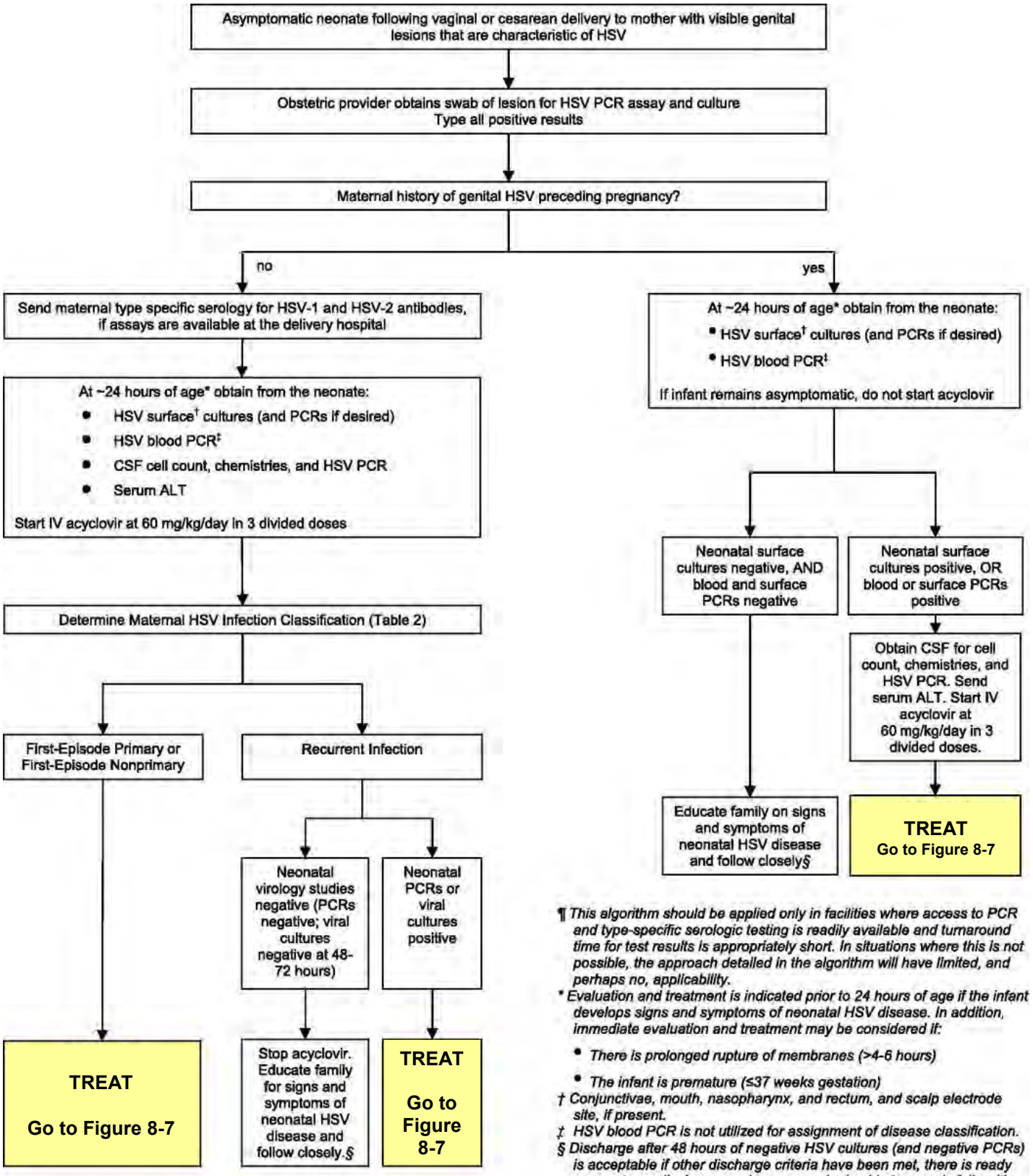
Management

- Consultation with the Infectious Disease Service may be considered for all at-risk infants to ensure that HSV cultures and PCR are properly collected and transported to the Virology Laboratory and to determine the need for antiviral treatment.
- Infants with HSV infection should be placed in an isolation room (when available) with contact isolation precautions. At BTGH, these babies are placed in an incubator with contact isolation in ICN if the mother is unable to room-in. The mother should be instructed that before touching her infant, she should carefully wash her hands and wear a clean hospital gown.
- Breastfeeding is permitted unless breast or hand HSV lesions are present. The mother or any family member with oral lesions should not kiss or nuzzle the infant; they should wear a surgical mask until lesions have crusted and dried. Mothers with oral or breast lesions should be instructed in proper hygiene and have no infant contact with the lesions until they are healed.

Asymptomatic Infants

- **Fig 8-6** to **Fig 8-7** details the AAP algorithms for evaluation and management of asymptomatic neonates following vaginal or cesarean delivery to women with active genital HSV lesions.
- At ~24 hours of age, cultures for isolating HSV should be obtained from swabs of the nasopharynx, conjunctivae, mouth, rectum, and scalp electrode site, if present. All sites are sampled and duplicate swabs are placed into viral transport media, agitated, and discarded. Positive cultures obtained from any of the surface sites more than 12 to 24 hours after birth indicate viral replication and are, therefore, suggestive of infant infection rather than contamination after intrapartum exposure.
- In mothers with active genital herpes from a primary infection or the status is unknown, the following tests should be obtained in the infant: viral cultures as stated above, blood HSV DNA polymerase chain reaction (PCR), CSF studies (cell count, glucose, protein, culture, and HSV PCR), and liver function tests (ALT). Acyclovir should be empirically started.
- In mothers with known recurrent genital herpes, the following tests should be obtained in the infant: viral cultures as stated above, and blood HSV DNA PCR. Acyclovir should not be empirically started.
- Consider also sending a CBC with differential and platelet count, electrolytes, and renal function tests. PCR for enterovirus RNA in CSF can be performed to help distinguish between the 2 etiologies as well.

Figure 8-6. Evaluation algorithm for asymptomatic neonates following vaginal or cesarean delivery to women with active genital herpes lesions.



¶ This algorithm should be applied only in facilities where access to PCR and type-specific serologic testing is readily available and turnaround time for test results is appropriately short. In situations where this is not possible, the approach detailed in the algorithm will have limited, and perhaps no, applicability.

** Evaluation and treatment is indicated prior to 24 hours of age if the infant develops signs and symptoms of neonatal HSV disease. In addition, immediate evaluation and treatment may be considered if:*

- *There is prolonged rupture of membranes (>4-6 hours)*
- *The infant is premature (≤37 weeks gestation)*

† Conjunctivae, mouth, nasopharynx, and rectum, and scalp electrode site, if present.

‡ HSV blood PCR is not utilized for assignment of disease classification.

§ Discharge after 48 hours of negative HSV cultures (and negative PCRs) is acceptable if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital until HSV cultures are finalized as negative or are negative for 96 hours after being set up in cell culture, whichever is shorter.

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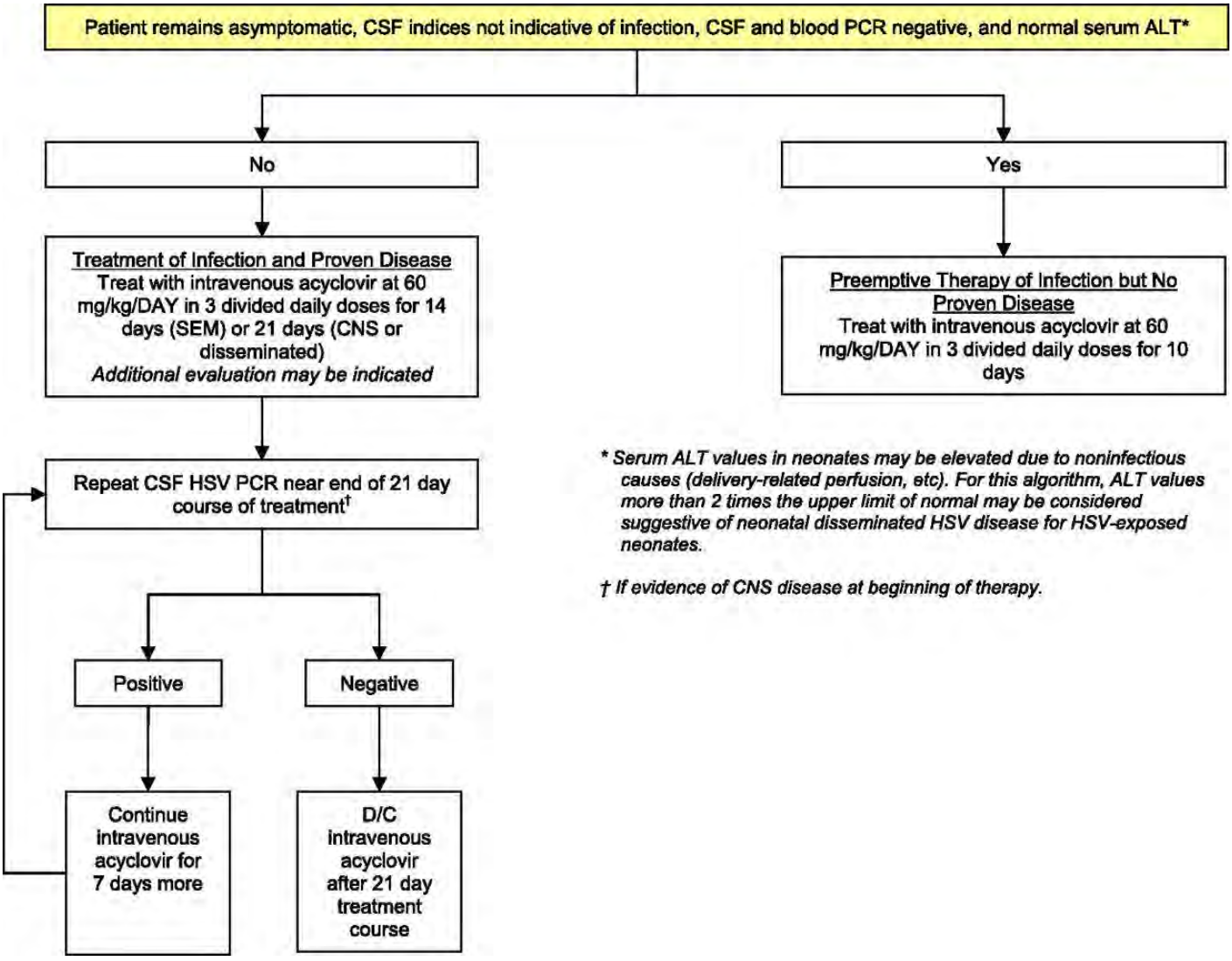
Figure 8-7. Treatment algorithm for asymptomatic neonates following vaginal or cesarean delivery to women with active genital herpes lesions.



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- If HSV cultures and PCRs are negative at 48 hours, the infant is a candidate for discharge if all the events below can be arranged:
  - » Parent education about early symptoms of neonatal HSV infection (skin lesions, poor feeding, fever, lethargy, etc.).
  - » Ensure access to medical care with close follow up with the pediatrician.
  - » Do not promise families discharge unless both events have been arranged. If the above cannot be accomplished, the infants must be observed in the hospital until the cultures are finalized as negative or negative for 96 hours, whichever is shorter

Treatment

- **Fig 8-6 to Fig 8-7** details the AAP algorithms for evaluation and management of asymptomatic neonates following vaginal or cesarean delivery to women with active genital HSV lesions.
- In most asymptomatic patients born to mothers with recurrent herpes, no treatment is necessary.
- Empiric parenteral antiviral therapy may be warranted before the onset of overt disease due to the infant's risk of infection in the following situations:
  - » Infants of mothers with active lesions at birth and
  - » primary infection or unknown maternal status
  - » Asymptomatic infants with any positive HSV test results
  - » Symptomatic infants
- Treatment of choice is acyclovir 60 mg/kg/day in 3 divided doses given intravenously:
  - » SEM disease: 14 days
  - » Viremia (blood HSV PCR positive), disseminated, or CNS disease: 21 days minimum

  - » A repeat CSF HSV PCR near the end of a 21-day course of treatment is recommended. If the PCR is still positive, continue intravenous acyclovir for 7 more days and repeat the CSF PCR at the end of that time.
  - » Infants born to mothers with primary HSV infection, with normal CSF indices, negative HSV PCRs, normal ALT: 10 days
  - » If ocular involvement, use 1% trifluridine or 0.15% ganciclovir) in addition to parenteral therapy.
  - » All infants with neonatal HSV disease, regardless of disease classification, should have an ophthalmologic examination and neuroimaging to establish baseline brain anatomy; magnetic resonance imaging is the most sensitive imaging modality but may require sedation, so computed tomography or ultrasonography of the head are acceptable alternatives.
- Consult with the Infectious Diseases and Ophthalmology Services to assist in the evaluation and management.

Suppressive therapy

- Oral acyclovir (300 mg/m2/dose, administered 3 times daily, for 6 months) should be given to all infants surviving neonatal HSV disease of any classification.
- Suppressive therapy has been shown to improve neurodevelopmental outcomes in infants with CNS disease and to prevent skin recurrences with any HSV disease.
- Monitoring of absolute neutrophil counts should be performed at 2 and 4 weeks after initiating suppressive therapy and then monthly thereafter during the treatment period.

8.12 Human Immunodeficiency Virus (HIV)

In the absence of breastfeeding, the risk of HIV infection for an infant born to an untreated HIV-infected mother in the United States is approximately 25%, with most transmission occurring around the intrapartum period. Mothers who receive antiretroviral prophylaxis (ARV) during pregnancy and labor who have undetectable viral loads at delivery have a <1% HIV transmission rate to their newborn. Risk of perinatal transmission has largely decreased due to ARV, cesarean delivery before rupture of membranes and onset of labor, and complete avoidance of breastfeeding.

Classification of infants at risk of perinatal HIV transmission is as follows:

- **Low risk**: Infants with mothers that have received antiretroviral therapy during pregnancy with sustained viral suppression (defined as HIV RNA <50 copies/ml) near delivery and no concerns related to adherence
- **Higher risk:** Infants with mothers that have (1) received neither antepartum nor intrapartum ARV drugs; (2) received only intrapartum ARV drugs; (3) received antepartum and intrapartum ARV drugs but who do not demonstrate viral suppression near delivery, particularly if delivery was vaginal; (4) acute or primary HIV infection during pregnancy or are breastfeeding (in which case, the mother should discontinue breastfeeding); (5) Mothers with unconfirmed HIV status and at least one positive HIV test at delivery/postpartum or newborns with positive HIV Ab test.

Management of HIV-exposed infants

- Consultation with the Retrovirology or the Allergy & Immunology Service to assist with the diagnostic evaluation and management is recommended. If this service is not available where you are, you can call the National Perinatal HIV Hotline: 888-448-8765.
- Breastfeeding should be avoided since HIV can be transmitted via breastmilk. Mothers with suspected HIV infection due to a positive initial screening test should stop breastfeeding or "pump and dump" vs freeze breastmilk as desired until HIV infection has been confirmed or ruled out on subsequent testing.
- Infants should be bathed and cleansed of maternal secretions (particularly bloody secretions) as soon as possible after birth.
- A newborn infant whose mother's HIV infection status is unknown should have rapid HIV antibody testing performed on the mother or the infant and the test results should be reported immediately to the physician to allow effective prophylaxis to be administered to the infant ideally within 6-12 hours.
- Zidovudine (ZDV or AZT) should be given as soon as possible after birth (preferably within 6-12 hours of delivery) to any HIV-exposed infant, whether or not the mother received treatment or ARV. Treatment is generally continued for the first 4-6 weeks of life and adjusted based on the infant's risk classification for perinatal HIV transmission.
- HIV–exposed infants can resume breastfeeding and stop all antiretroviral medications once subsequent testing proves the mother does not have HIV.

Treatment

Low risk infants

- **ZDV ≥ 35 weeks gestation:** 4 mg/kg/dose given orally twice daily, through 4 weeks of age.
- **ZDV ≥ 30 to < 35 weeks gestation:** 2 mg/kg/dose given orally twice daily, for 14 days. At 15 days postnatal age, increase the dose to 3 mg/kg/dose orally twice daily, through 4-6 weeks of age.
- **ZDV < 30 weeks gestation:** 2 mg/kg/dose given orally twice daily, through 4-6 weeks of age.
- For newborns unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.

Higher risk infants

- 2-drug prophylaxis with ZDV x 6 weeks AND 3 doses of NVP in the first week of life (1st dose within 48 hours of birth, 2nd dose 48 hours after 1st dose, 3rd dose 96 hours after 2nd dose).

» **NVP for birth weight 1.5-2 kg:** 8 mg/dose PO

» **NVP for birth weight > 2 kg:** 12 mg/dose PO

OR

- Empiric 3 drug anti-retroviral therapy with ZDV, Lamivudine (3TC), and either NVP or Raltegravir (RAL) in treatment doses. Dolutegravir and lopinavir/ritonavir are other ARV medication options in certain circumstances.

Infants with confirmed HIV infection

- 3 drug anti-retroviral therapy with ZDV, 3TC, and either NVP or RAL in treatment doses.

Immunizations

All recommended childhood vaccines should be given to HIV-exposed infants. Infants with confirmed HIV infection should follow immunization recommendations for HIV-infected individuals.

8.13 Respiratory Syncytial Virus (RSV)

Background

RSV lower respiratory tract infection is the leading cause of hospitalization during the first year of life. Hospitalization typically occurs during the first 6 months of life (highest between 30 and 60 days of age), with more severe illness occurring in extremely premature infants and infants with hemodynamically significant congenital heart disease, chronic lung disease, and certain immunodeficiency states. Close or direct contact with either secretions or fomites is necessary for transmission. RSV can persist on surfaces (fomites) for several hours and for one-half hour or more on hands.

Palivizumab prophylaxis has been associated with an approximately 55% reduction in hospitalization secondary to RSV disease in certain high-risk patients including premature infants and infants with hemodynamically significant congenital heart disease. Palivizumab does not prevent or treat infection from RSV, rather it reduces the risk of lower respiratory tract disease among infants with increased risk for severe disease.

Management of RSV Infection

Patients with suspected or proven RSV (or other respiratory viral infection) are <u>not</u> admitted to the Newborn Center under usual circumstances.

Indications for Use of Palivizumab Prophylaxis

When Palivizumab prophylaxis is given, it should be started within 2-3 days prior to NICU discharge or promptly after discharge. Palivizumab is continued throughout the season with injections given monthly for a maximum of 5 doses. For qualifying infants born during the RSV season, fewer than 5 doses will be needed to provide protection until the RSV season ends. It does not interfere with the response to other vaccines.

Palivizumab prophylaxis should be considered for infants:

- born <29 weeks 0 days gestation and ≤12 months at start of RSV season
- born <32 weeks, 0 days gestation with chronic lung disease (defined as needing >21% oxygen for first 28 days of life)
  - » Should receive Palivizumab in 1st year of life
  - » Should receive Palivizumab in 2nd year of life if receiving continued medical support in the form of chronic corticosteroid or diuretic therapy, or supplemental oxygen (bronchodilator use alone is not an indication) during the 6-month period before the start of the second RSV season
- with hemodynamically significant congenital heart disease at ≤12 months of age
- in the immediate post-operative period after cardiac bypass or ECMO during RSV season and ≤24 months if would otherwise qualify due to primary diagnosis (due to mean decrease of serum Palivizumab concentration of up to 58%)
- who are profoundly immunocompromised (e.g., s/p solid organ/hematopoietic stem cell transplantation) or s/p cardiac transplantation during RSV season and ≤24 months of age
- with neuromuscular disease, or a congenital airway anomaly which interferes with ability to clear airway secretions and ≤12 months of age
- with Cystic Fibrosis with evidence of chronic lung disease /nutritional compromise and ≤12 months of age.
  - » Can continue into the 2nd year of age, if severe lung disease (hospitalized during first year of life with a pulmonary exacerbation or persistent abnormalities in CXR/Chest CT when stable.
- Special consideration can be given to certain populations (Alaskan Native, American Indian) in the first year of life due to much higher hospitalization rates vs other US children.

Palivizumab prophylaxis should be discontinued (for the current RSV season) in any patient who experiences a breakthrough RSV hospitalization. This is recommended since the chance of a second hospitalization during the same season is remote (<0.5%).

Palivizumab is not recommended to prevent nosocomial RSV infection.

Dosage

Administer 15 mg/kg IM once every 30 days according to package instructions.

8.14 Rotavirus

Rotavirus infection is highly contagious and is transmitted by the fecal-oral route. In Houston, infections typically occur in late winter and spring. It most commonly causes diarrhea, emesis, and fever, and may rarely cause abdominal distention and NEC in premature neonates. Thus, in an infant with the above clinical findings, it is recommended that a stool sample be sent for examination for viral particles by election microscopy. Other diagnostic tools include EIAs, which have high sensitivity and specificity, electrophoresis and silver staining, reverse transcriptase-polymerase chain reaction (RT-PCR) assay for detection of viral genomic RNA, and culture.

Currently there are 2 licensed live attenuated vaccines: RotaTeq®, RV5 and Rotarix®, RV1. RotaTeq® is given as a 3-dose regimen; Rotarix® as a 2-dose regimen; both are oral vaccines. Rotavirus immunization is recommended for all infants at the time of discharge from the hospital if they meet age criteria. The first dose should be administered between 6 weeks and 14 weeks of age. Subsequent doses are administered at intervals of 4 weeks with the maximum age for the last dose being 8 months 0 days. Latex rubber is contained in the applicator of RV1; therefore, that vaccine should not be given to any infant with risk of latex allergy (e.g., neural tube defect).

8.15 Syphilis, Congenital

Background

Congenital syphilis is contracted from an infected mother *via* transplacental transmission of *Treponema pallidum* at any time during pregnancy, or at birth from contact with maternal lesions. Infection can be transmitted to the fetus at any stage of maternal disease. The rate of transmission is 60% to 100% during primary and secondary syphilis and slowly decreases with later stages of maternal infection.

Among women with untreated early syphilis, up to 40% of pregnancies result in spontaneous abortion, stillbirth, or perinatal death. Intrauterine infection with *T pallidum* can also result in hydrops fetalis, preterm birth, or may be asymptomatic. Infected infants can have hepatosplenomegaly; snuffles (copious nasal secretions); lymphadenopathy; mucocutaneous lesions; pneumonia; osteochondritis, periostitis, and pseudoparalysis; edema; maculopapular rash (most severe on the hands and feet); hemolytic anemia; or thrombocytopenia. Skin lesions and moist nasal secretions are highly infectious. However, organisms rarely are found in lesions more than 24 hours after treatment has begun.

Evaluation

Evaluation and therapy of any infant thought to have congenital syphilis is primarily based on maternal history. By law all mothers are serologically screened for syphilis during the 3rd trimester with either an RPR or a treponemal antibody test (Syphilis IgG). If the RPR is positive, a TP-PA is done. If the mother's 3rd trimester syphilis status is unknown when she presents for delivery, a treponemal antibody test is done upon admission to L&D. If the treponemal antibody test is positive, then an RPR is performed. If the RPR is positive, a confirmatory syphilis test is done with either a TP-PA or FTA-ABS. No infant should be discharged before the maternal serologic status is known. If the maternal RPR is positive, her documented treatment history (including diagnosis, date(s) of treatment, drug, drug dosage, and follow-up serologies) and clinical status must be determined to decide what evaluation or therapy her infant requires.

The HIV-STD Surveillance Section of the City of Houston Health Department keeps records of RPR-positive patients. This office may provide useful information on maternal therapy and prior serologies. To retrieve data, they require mother's name(s), alias, and date of birth. Maternal history of treatment should be confirmed, through City Health or the medical facility rendering treatment, and documented in the chart. The HIV-STD Surveillance Section, City of Houston Health Department, can be reached at 832-393-5080 or fax 832-393-5230 or 5232, from 8am to 5pm, Monday through Friday.

Next, determine if the mother's therapy was documented and adequate to prevent congenital infection.

Adequate maternal treatment:

- Treatment with 2.4 million units once with benzathine penicillin for primary, secondary, or early latent syphilis.
- Treatment with 2.4 million units of benzathine penicillin weekly for 3 consecutive weeks for late latent syphilis.
- During pregnancy, penicillin is the only appropriate drug. (See CDC STD guidelines for adequate non-penicillin treatment before pregnancy.)
- Treatment completed least 4 weeks before delivery.
- RPR monitored during pregnancy.
- Documented, expected serologic response (sustained four-fold or greater drop in titer; e.g., an RPR decrease from 1:16 to 1:4).

History that does not meet the preceding criteria is considered inadequate treatment and should be evaluated and treated as outlined below.

Assessment: Figures 8-8 to 8-9

Symptomatic Infants or Infants Born to Symptomatic Mothers

Full evaluation including CBC with diff/platelets, CSF cell count, protein concentration, and CSF VDRL, x-ray of long bones; 10 to 14 days of aqueous PCN G 50,000 units/kg/dose every 8 to 12 hours IV **(preferred)** or procaine PCN 50,000 units/kg daily for 10 days should be given; report the case. Follow-up should be by private pediatrician or by arrangement with ID service.

Asymptomatic Infants

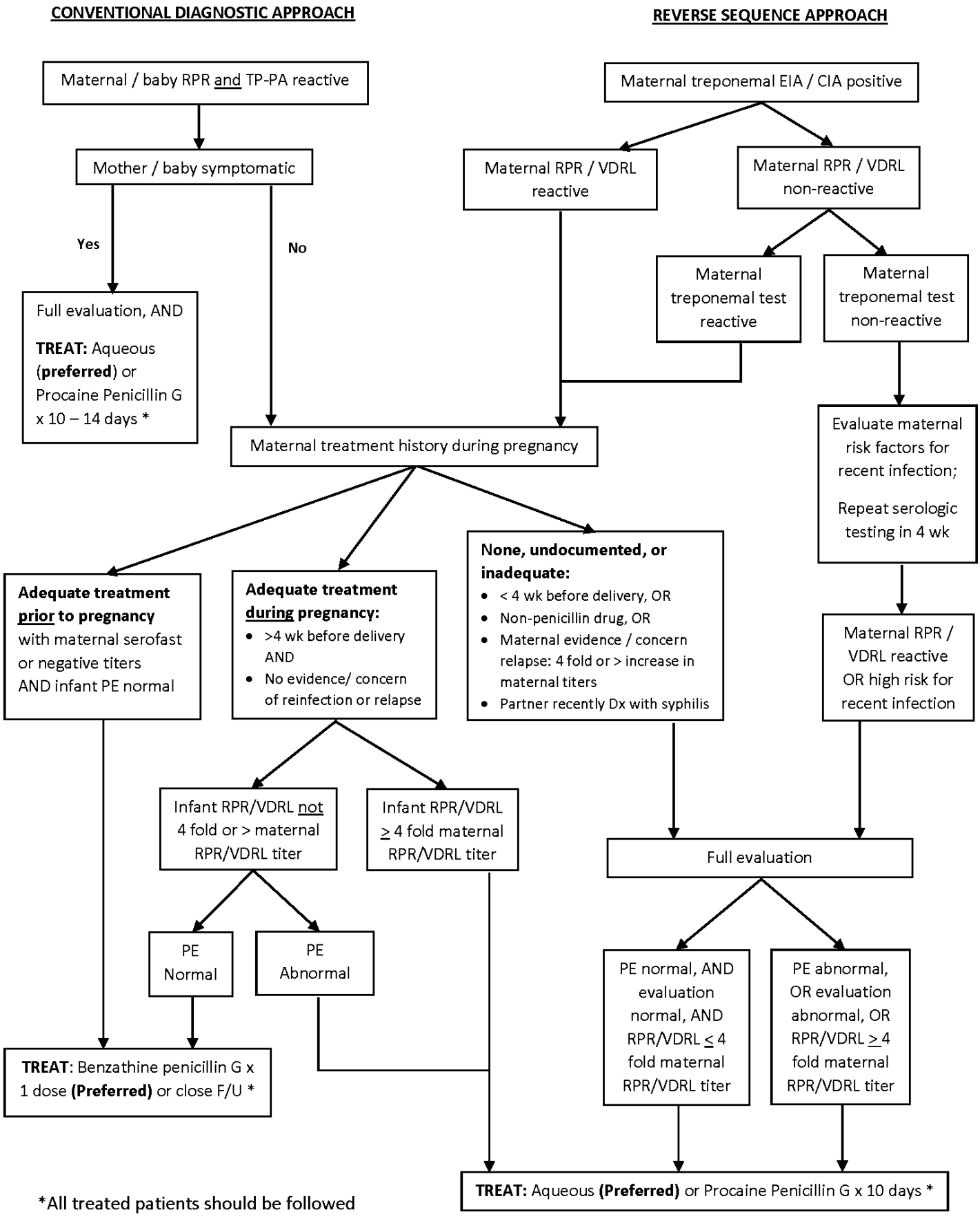
Mother adequately treated more than 4 weeks prior to delivery: Infant requires RPR and TP-PA. If RPR is the same or < fourfold of the maternal titer at delivery, give a 10 day course of aqueous PCN G 50,000 units/kg/dose every 8 to 12 hours IV for 10 days (preferred) or a single daily dose of Procaine PCN, 50,000 units/kg daily for 10 days. If mother was adequately treated before pregnancy and is serofast or with negative titers & infant PE normal, give a single dose of IM benzathine PCN. If the RPR is > fourfold of the maternal titer, give 10 days of IV therapy (preferred) or a single daily dose of Procaine PCN, 50,000 units/kg daily for 10 days. Follow-up should be by private pediatrician or by arrangement with ID service.

Figure 8-8. Treponemal and non-treponemal serologic tests in infant and mother

Treponemal (TP-PA)			Non-treponemal (VDRL, RPR)	
Infant	Mother		Infant	Mother
+	+	*	+ or +/-	+
		#		
-	-		+	
+	+	^	-	-

* Mother with recent or previous syphilis or latent infection and possible syphilis or the infant.
# No syphilis infection in mother or infant; false-positive non-treponemal tests.
^ Mother treated successfully in early pregnancy or before, or false-positive serologic test due to yaws, pinta, Lyme disease.

Figure 8-9. Evaluation algorithm for infants born to mothers with positive syphillis screening



Mothers who were never treated, were inadequately treated, whose treatment was undocumented, were treated less than 4 weeks before delivery, were treated during pregnancy with a non-penicillin regimen, have no documentation of declining RPRs after therapy, or no documentation of RPRs, or have maternal evidence or reinfection or relapse: The infant should have a full evaluation and receive 10 days of IV PCN therapy (preferred) or a single daily dose of Procaine PCN, 50,000 units/kg daily for 10 days. Follow-up by private pediatrician or by arrangement with ID service.

Biologic False-positive RPR

This diagnosis is unusual and requires documented, serial, antenatal, repeatedly low-titer RPR with a nonreactive TP-PA. If antenatal documentation is not available, the baby should be evaluated and receive at least a single dose of benzathine PCN (since in early primary syphilis the, RPR may convert to positive before the TP-PA).

If a biologic false-positive is confirmed, the infant should have a baseline RPR and TP-PA (RPR should be low or nonreactive, TP-PA should be nonreactive) and follow-up by a private pediatrician or by arrangement with ID service.

Since IgG is transferred across the placenta, at birth the TP-PA of the baby is not diagnostic of congenital syphilis and usually reflects only the mother's status.

Evaluation for At-Risk Infants

- Careful physical examination
- CBC with differential/platelets
- Baseline RPR and baseline TP-PA (infant sample not cord blood)
- LP for CSF VDRL, cell count, and protein
- X-rays of long bones
- Other clinically indicated tests, (e.g., ABER, CXR, UA, LFTs)

Therapy

Administer either aqueous penicillin G or procaine penicillin G as detailed below. Ampicillin is not an appropriate therapy because CSF levels cannot be sustained with ampicillin. Infants with HIV-positive status will require at least 21 days of therapy.

Dosing

Aqueous penicillin G potassium 100,000 to 150,000 units/kg per day, IV, given as 50,000 units/kg per dose for 10 days. Every 12 hours if < 7 days of life; every 8 hours if older than 1 week. Some would treat neurosyphilis with 14 days of penicillin.

Procaine penicillin G 50,000 units/kg per day, IM, as a single daily dose for 10 days.

If 24 or more hours of therapy is missed, the entire course must be restarted.

ID Consultation

Neurosyphilis or severe symptomatic syphilis warrants an ID consult. Mothers who are HIV positive or have AIDS may have variable response to syphilis therapy; therefore, their infants may be at higher risk for syphilis. ID consultation regarding therapy may be indicated.

Follow-up

Follow-up should occur at 2, 4, 6, and 12 months of age. At 2, 4, 6 and 12 months of age; repeat serum RPR testing should be done. Titers should have decreased by 3 months of age and become non-reactive by 6 months of age. Infants with increasing titers should be re-evaluated.

8.16 Tuberculosis

Newborns of Tuberculin Skin Test (TST)-Positive Mothers

These guidelines pertain only to term, healthy newborns. They are housed in the Level 1 setting.

- Mothers who have been screened (by history, prenatal records, and chest x-ray) by the OB service and deemed non-infectious are allowed contact with their infants.
- The AAP recommends continued direct breastfeeding except if mother has pulmonary TB and is contagious, untreated or treated < 3 weeks, has multidrug resistant tuberculosis, or is non-adherent to treatment. In these cases, the infant is isolated and the mother is encouraged to provide expressed breast milk as an alternative. Breastfed infants do not require Pyridoxine supplementation unless they are receiving Isoniazid.
- Mothers with documentation of adequate management for TB disease or infection (prenatal records or TB Control records) and found to be non-infectious do not need to be separated from their infants.
- If the mother has TB disease and is contagious or without adequate treatment, the infant should be evaluated for congenital tuberculosis (see below).
- All household contacts and family members who visit the nursery should be screened adequately (history of cough, night sweats, or weight loss) for historical evidence of past or present tuberculosis. Those visitors who are found to be symptomatic (possibly contagious) must wear isolation attire.
- Household contacts and family members with symptoms suggestive of TB infection or disease should be referred to TB Control for placement of TST, chest x-ray, chemoprophylaxis, follow-up, etc.
- If the mother is found to be non-infectious and the newborn is ready for discharge, discharge should not be delayed pending screening of household contacts and family members.
- Treatment and follow-up of the infant should be guided by the Infectious Disease team.

Congenital TB Infection

- While congenital tuberculosis is rare, in utero infection can occur via the maternal blood stream or by aspiration/swallowing of infected amniotic fluid.
- The mother and the infant should be separated until the mother and infant are receiving appropriate

antituberculosis therapy, the mother wears a mask, and the mother understands and is willing to adhere to infection-control measures.

- In a baby with suspected infection, the following should be performed: consultation with the Infectious Disease Team, both TST and Interferon-gamma release assay (IGRA) test (QuantiFERON®-TB Gold or T-SPOT®), chest x-ray, lumbar puncture, and appropriate cultures of blood, urine and CSF.
- TST is the preferred testing method for children younger than 2 years. IGRAs are immunologic based tests that measures ex vivo interferon-gamma production from T-lymphocytes in response to stimulation. IGRAs are not recommended to replace the TST, even though most TSTs in newborns with congenital or perinatally acquired TB are negative.
- The placenta should always be cultured and examined for granulomata and AFB.
- Treatment and follow-up of the infant should be guided by the Infectious Disease team.

8.17 Varicella-Zoster Virus (VZV)

Background

Varicella (VZV) infection during pregnancy is rare, occurring in 1 to 5 cases per 10,000 pregnancies. Most neonatal transmission of VZV is vertical; however, intrauterine infection may occur albeit rarely. The incubation period of VZV (exposure to onset of rash) usually is 14 to 16 days (range 10 to 21).

Perinatal Exposure

Classically, a mother's exposure to varicella occurs in the last 2 to 3 weeks of pregnancy. Varicella can develop between 2 and 16 days after birth in infants born to mothers with active varicella around the time of delivery; the usual interval from onset of rash in a mother to onset in her neonate is 9 to 15 days. Neonatal disease generally occurs during the first 10 days of life. Timing of maternal disease is critical to neonatal disease presentation:

- **Maternal disease onset 6 days or more before delivery** with neonatal clinical infection in the first 4 days of life. This infection is mild due to passage of maternal antibodies.
- **Maternal disease onset within 5 days before delivery up to 48 hours after delivery** allows insufficient time for the development of maternal IgG and passive transfer of antibody protection to the fetus, and is associated with neonatal clinical infection between 5 and 10 days of age. This infection can be fulminant with mortality rates of 5% to 30%. In these neonates, VZV infection may be characterized by severe pneumonia, hepatitis, or meningoencephalitis.

Clinical Syndromes and Varicella Embryopathy

Varicella embryopathy results from maternal varicella during the 1st or early 2nd trimester. (Fewer than 2 percent of women who have acquired varicella infection during the first 20 weeks of gestation have subsequently given birth to an infant with this embryopathy). Clinical signs include cutaneous scarring of the trunk (100%), limb hypoplasia, encephalitis with cortical atrophy (60%), low birth weight (60%), rudimentary digits, chorioretinitis or optic atrophy, cataracts or microphthalmia, and clubfoot (30% to 40%). Infants who are prenatally exposed to VZV, even if asymptomatic, may have measurable varicella-specific IgM antibody during the newborn period, have persistent varicella-specific IgG immunity after 1 year of age without a history of postnatal varicella, or demonstrate positive lymphocyte transformation in response to VZV antigen.

Note: Infants with intrauterine infection do not require varicella-zoster immune globulin (VariZIG®).

Management and Treatment

An Infectious Disease Service consult is recommended.

Varicella-Zoster Immune Globulin (VariZIG®)

VariZIG® is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies. VariZIG® does not prevent varicella, though it helps to modify the clinical disease. If VariZIG® is not available, IVIG may be used.

Indications:

- Newborn infant of a mother who had onset of chickenpox within 5 days or less before delivery or within 48 hours after delivery
- Exposed premature infants within 10 days (28 or more weeks' gestation) whose mother has no history of chickenpox or do not have signs of immunity
- Exposed premature infants within 10 days (less than 28 weeks' gestation or ≤1000 grams) regardless of maternal history
- Exposure is defined as contact in the same 2-to 4-bed room, adjacent in a ward, or face-to-face contact with an infectious staff member or patient with varicella.
- VariZIG® is not indicated for normal, term infants exposed to varicella including those whose mothers develop varicella more than 2 days after delivery.

Dosing:

- To be most effective, VariZIG® should be administered within 96 hours of exposure, ideally within 48 hours. CDC recommends administration of VariZIG® as soon as possible after exposure to varicella-zoster virus and within 10 days.
- The dose for term or preterm newborns is 125 units/10 kg body weight, up to a maximum of 625 units IM.
- Do not give VariZIG® intravenously. VariZIG® is lyophilized and must be reconstituted for intramuscular administration.

Vaccination should be delayed until 5 months after VariZIG® administration. Varicella vaccine is not indicated if the patient develops clinical varicella after the administration of the IVIG for post exposure prophylaxis.

Intravenous Immune Globulin (IVIG)

If VariZIG® is not available within 96 hours of exposure, IVIG can be used.

Indications:

- The indications for IVIG are the same as those for VariZIG®.

Dosing:

- The recommended dose for post exposure prophylaxis is 400 mg/kg administered once. This is a consensus recommendation; no clinical data exist demonstrating effectiveness of IVIG for post exposure prophylaxis of varicella.

Any patient receiving IVIG should subsequently receive varicella vaccine, provided that the vaccine is not contraindicated. Vaccination should be delayed until 5 months after IVIG administration. Varicella vaccine is not indicated if the patient develops clinical varicella after the administration of the IVIG for post exposure prophylaxis.

Any patient who receives passive immunoprophylaxis should be observed closely for signs or symptoms of varicella for 28 days after exposure because IVIG might prolong the incubation period by one or more weeks. Antiviral therapy (intravenous or oral acyclovir, oral valacyclovir) may be instituted if signs or symptoms of varicella disease occur in this high- risk population. The route and duration of antiviral therapy should be determined by specific host factors, extent of infections and initial response to therapy.

Isolation

Airborne and contact isolation are recommended for infants born to mothers with varicella and if still hospitalized, until 21 days of age or 28 days of age if they received VariZIG.

Discharge

Infants who receive VariZIG may go home with their mothers and should be followed closely. Document a working home telephone number and involve Social Services as needed.

Infants who have not received VariZIG should be discharged home after maternal lesions have crusted over. If varicella infection is present in the household, the newborn should remain hospitalized until these lesions in household contacts are crusted over. Again, close follow-up and parental education before discharge are imperative.

Note: No surface cultures are necessary. No eye ointment is necessary.

8.18 Zika Virus (ZIKV)

Background

Zika virus (ZIKV) is a single-stranded RNA arbovirus in the *Flaviviridae* family primarily transmitted via the bite of an infected mosquito of the *Aedes* genus. Initially from Africa, it has since spread throughout Asia, Oceania, and South and Central America with a few endemic cases reported in the Texas-Mexico border. Most commonly, the infection is asymptomatic. However, older children and humans can have flu-like symptoms and even Guillan-Barre Syndrome associated with ZIKV infection. If a pregnant woman is infected, Congenital Zika Syndrome can occur. In rare instances perinatal transmission has occurred in and around the time of delivery.

Congenital Zika Syndrome (CZS)

Pregnant women infected with ZIKV during pregnancy can have normal fetuses. However, in some infected women, several key findings have been found which are collectively called CZS. A neonate need not have all the symptoms to be considered CZS.

The symptoms include the following:

- Microcephaly (FOC < 3rd percentile)
- Intracranial calcifications
- Ophthalmic anomalies
- Brain anomalies

The diagnosis of CZS microcephaly is made when the FOC is disproportionately small when compared to the length and weight of the neonate and not explained by other etiologies. Neonates with CZS may develop microcephaly in utero or during the first year of life. Ophthalmic anomalies include macular atrophy, hyperopia, chorioretinitis, pigment mottling of the macula, lack of foveal reflex, colobomas, and optic nerve hypoplasia.

Evaluation

If a neonate is born to a mother with laboratory evidence of ZIKV infection **OR** a neonate has clinical findings suggestive of CZS (see above) with a maternal link (travel to an area that is known to have endemic ZIKV cases, OR sexual activity with an individual who has traveled to an area known to have endemic ZIKV cases) suggestive of possible transmission, then that neonate should undergo ZIKV screening which should include the following:

- Comprehensive physical examination
- Head ultrasound
- Standard hearing assessment (ABR)
- Laboratory testing within 2 days of birth (cord blood not recommended)
  - » Zika RT-PCR of infant serum and urine
  - » Infant blood for Zika virus IgM ELISA
- Consider RT-PCR and IgM testing of the CSF

A lumbar puncture is not recommended for the sole purpose of evaluating for ZIKV infection. If a lumbar puncture is obtained for other reasons, then the CSF should be sent for PCR and IgM testing for ZIKV. If the infant has negative testing of the blood and urine, then CSF testing should strongly be considered to investigate for ZIKV infection. There are documented cases of infants with only CSF positive for ZIKV when blood and urine were both negative. Depending upon the results of these tests, the neonate should receive further evaluation and follow up per the Zika screening guidelines.

Consider storing the placenta, which may be required for potential histopathological evaluation for ZIKV pending the infant's testing.

Breastfeeding Recommendations
Of note, although ZIKV has been detected in breast milk, there have been no proven cases describing transmission of ZIKV through breastfeeding. Therefore, the CDC recommends that women who have been diagnosed with ZIKV infection can still breastfeed their infants as the benefits outweigh the risks.

Treatment
Although many different therapies are under investigation, there are currently no FDA recommended therapies for the treatment of CZS in affected neonates.

Isolation
Routine universal precautions should be followed for patients with confirmed or suspected CZS. It is not necessary at this time to use contact precautions if the only concern is for CZS.

Discharge and Follow-Up
An Infectious Disease consult is recommended.

8.19 Screening for Viral Illness in the NICU

Background
Viral illnesses have a significant impact on term and preterm neonates and have been associated with increased length of hospital stay, increased antimicrobial use, and more severe disease presentation. The most common respiratory pathogens in the neonatal period are Respiratory Syncytial Virus (RSV) and Influenza virus (Flu), however patients with these lower respiratory tract infections are not typically managed in the NICU. Other frequently seen respiratory pathogens include Adenovirus, Human Metapneumovirus (hMPV), Rhinovirus, and Parainfluenza. COVID-19 is discussed separately in **Ch 8.5 Coronavirus (SARS-CoV-2)**. The most common gastrointestinal pathogens include Adenovirus, Norovirus, and Rotavirus.

Common presenting symptoms for viral illness are nonspecific and include the following:

- **Respiratory Pathogens:** apnea, bradycardia, desaturations, tachypnea, increased secretions, increased work of breathing, need for increasing respiratory support, temperature instability
- **Gastrointestinal Pathogens:** diarrhea, foul-smelling stool, bloody stool, electrolyte abnormalities, poor weight gain, temperature instability, apnea, bradycardia

Pathogens
Table 8-6 details the life-cycle of viral pathogens and the testing options for screening symptomatic patients for viral illness.

Laboratory Testing Reference
Table 8-7 provides in depth details for the various testing options for viral illness screening.

When generalized viral screening is desired, the preferred testing is a multi-pathogen panel to test for multiple viruses at once:

- **Respiratory illness**: send "Winter Resp Viral Detection" (during Flu and RSV season) or "Summer Resp Viral Detection" (outside of Flu and RSV season)
- **Gastrointestinal illness**: send "GI Pathogen Panel"

If testing for a single specific pathogen is desired, other lab orders are available **(Tables 8-6 to 8-7)** and may be more appropriate. This may arise in instances where patients have a known exposure to a specific virus. For any patient who is positive for a viral illness, please notify Nursing and Medical leadership. In select cases, Infection Control must also be notified.

Isolation Precautions
When screening patients for viral illness, appropriate Isolation Precautions **(Table 8-8)** should be **initiated immediately at symptom onset, exposure, or when testing is collected, *whichever is earliest*:**

- **Respiratory illness**: Contact and Droplet (or Enhanced Respiratory specifically for COVID-19)
- **Gastrointestinal illness**: Contact

Isolation Precautions can be adjusted accordingly based on test results and identification of a pathogen. Duration of Isolation Precautions should be followed as outlined in **Table 8-8** for all symptomatic patients, regardless if test results are positive or negative. Symptomatic patients with negative test results may be infected with a pathogen that is not routinely tested for, stressing the importance of remaining on Isolation Precautions for the appropriate duration of time.

Additional guidance on Isolation Precautions can be found by contacting Infection Control.

Clearance of Viral Infections
Patients are generally considered recovered or "clear" of their viral illness after the following conditions are met:

- **Respiratory illness**: at least 24 hours after all the following conditions are met
  - » Resolution of fever without the use of antipyretic medications
  - » Resolution of nasal symptoms (i.e., congestion, runny nose, need for suctioning) and cough
  - » Resolution of any other symptoms attributed to the infection
- **Gastrointestinal illness**: once free of diarrhea and vomiting for at least 48 hours

If the above conditions are met, isolation precautions can be discontinued as outlined in **Table 8-8**. **In select cases, Infection Control clearance may be required prior to discontinuing isolation precautions.** Repeat testing for non-COVID-19 viruses is typically **not** warranted or required due to the variable viral shedding period of each pathogen **(Table 8-6)**. If repeat testing for non-COVID-19 viruses is sent during the viral shedding period, it will likely remain positive, even in the absence of clinical illness or symptoms. After initial infection, patients that have repeat positive test results **in the absence of symptoms** would not be considered as still "infectious."

Routine Immunization of Hospitalized Infants

For current recommended immunization schedules and current updates see http://www.cdc.gov/vaccines/schedules.

Table 8-6. Life-cycle of viral pathogens and testing options for viral illness screening

VIRUS	ISOLATION PRECAUTIONS [a]	INCUBATION PERIOD	VIRAL SHEDDING	LAB TESTING OPTIONS [b]
Adenovirus	**Resp**: Contact and Droplet **GI**: Contact	**Resp**: 2-14 days **GI**: 3-10 days	Several weeks	**Resp**: • "Winter Resp Viral Detection" • "Summer Resp Viral Detection" **GI**: • "GI Pathogen Panel" • "Adenovirus qnPCR Fecal"
Coronavirus (COVID-19) *Data for COVID-19 is rapidly evolving and these estimates are subject to change.*	Enhanced Respiratory[c]	4-5 days (up to 14 days)	2 days prior to symptoms to 10 days, (up to 20-90 days)	• "SARS-COV-2 (2019 novel Coronavirus) Detection by real-time RT-PCR" • "SARS-CoV-2 Rapid RT-PCR"
Enterovirus	Contact **Resp**: Contact and Droplet	3-6 days	1-3 weeks (up to several weeks)	• "Enterovirus PCR, Blood" • "Enterovirus PCR (CSF)" **Resp**: • "Respiratory Pathogen Panel PCR (Viral + Atypical Bacteria)"
Human metapneumovirus (hMPV)	Contact	3-5 days	1-2 weeks	• "Winter Resp Viral Detection" • "Summer Resp Viral Detection" • "Respiratory Pathogen Panel PCR (Viral + Atypical Bacteria)"
Influenza	Droplet [c]	1-4 days	7-10 days	• "Flu, RSV, SARS Admission Panel" • "Winter Resp Viral Detection" • "Respiratory Pathogen Panel PCR (Viral + Atypical Bacteria)"
Norovirus	Special Contact	12 hours – 2 days	4 weeks	• "GI Pathogen Panel" • "Norovirus PCR Stool"
Parainfluenza	Contact	2-6 days	1-3 weeks	• "Winter Resp Viral Detection" • "Summer Resp Viral Detection" • "Respiratory Pathogen Panel PCR (Viral + Atypical Bacteria)"
Rhinovirus	Contact and Droplet	2-3 days	7-10 days (up to 7 weeks)	• "Winter Resp Viral Detection" • "Summer Resp Viral Detection" • "Respiratory Pathogen Panel PCR (Viral + Atypical Bacteria)"
Rotavirus	Contact	Less than 2 days	10 days (up to 30 days)	• "Rotavirus"
RSV	Contact	2-8 days	3-8 days (up to 4 weeks)	• "Flu, RSV, SARS Admission Panel" • "Winter Resp Viral Detection" • "Respiratory Pathogen Panel PCR (Viral + Atypical Bacteria)"

[a,c] see **Table 8-8.** Isolation precautions for more detail

[b] see **Table 8-7.** Laboratory testing reference for more detail

Table 8-7. Laboratory testing reference

LAB NAME	EPIC ORDER CODE	TEST TYPE	TURNAROUND TIME	COMMENTS
Adenovirus qnPCR Fecal	LABADENST	PCR	Multiple days	• *Send-out lab*
Enterovirus PCR, Blood	LABEVPCR1	PCR	1-2 days	
Enterovirus PCR (CSF)	LABEVCSF	PCR	4 hours	
Flu, RSV, SARS Admission Panel	LAB1230243	PCR	4 hours	• Panel includes: Flu, RSV, SARS-CoV-2 • If panel is negative: Parainfluenza 1/2/3/4, Adenovirus, hMPV, Rhinovirus are tested next
GI Pathogen Panel	O82188	PCR and EIA	1-2 days	**1st choice for gastrointestinal viral screening** Comprehensive panel includes: • Adenovirus F 40/41 • Astrovirus • Norovirus GI/GII • Rotavirus A • Sapovirus • Several other bacterial pathogens
Norovirus PCR Stool	LABNORO	PCR	Same day after lab receives specimen	• *Send-out lab*
Respiratory Pathogen Panel PCR (Viral + Atypical Bacteria)	LAB1230222	PCR	1 day	**Comprehensive panel includes:** • 3 Influenza A subtypes (H1/H3/H1 2009) • Influenza B • RSV • hMPV • Parainfluenza 1-4 • Rhinovirus • Enterovirus • 4 non-SARS Coronaviruses, SARS-CoV-2 • 4 bacteria: *B. pertussis, B. parapertussis, M. pneumoniae, C. pneumoniae*
Rotavirus	LABRTV	EIA	15 minutes after lab receives specimen	
SARS-COV-2 (2019 novel Coronavirus) Detection by real-time RT-PCR	LAB123099	RT-PCR	6-8 hours	**1st choice for COVID-19 testing** • Testing performed 7 days/week from 7am to 11:30pm
SARS-CoV-2 Rapid RT-PCR	LAB1230225	RT-PCR	4 hours	• Limited resource, use for emergent indications only
Summer Resp Viral Detection	LABSUMRES	PCR	1-3 days	**1st choice for respiratory viral screening** • Use outside of Flu and RSV season • Panel includes: Parainfluenza 1/2/3/4, Adenovirus, hMPV, Rhinovirus
Winter Resp Viral Detection	LABPROFLU	PCR	1-3 days	**1st choice for respiratory viral screening** • Use during Flu and RSV season • Flu and RSV are tested first • If Flu/RSV are negative: Parainfluenza 1/2/3/4, Adenovirus, hMPV, Rhinovirus are tested next

Table 8-8. Isolation precautions

PRECAUTION TYPE	PERSONAL PROTECTIVE EQUIPMENT (PPE)	ROOM REQUIREMENT	DURATION OF PRECAUTIONS[#]	COMMENTS
Contact	• Gown • Gloves	Private room preferred	**Resp**: Until resolution of all symptoms (including fever off of antipyretics) for at least 24 hours **GI**: Until free of diarrhea and vomiting for at least 48 hours	
Droplet	• Surgical mask	Private room preferred	Until resolution of all symptoms (including fever off of antipyretics) for at least 24 hours **Influenza (+) specific:** Until afebrile (<100.4°) for 24 hours off of antipyretics **OR** for 7 days from symptom onset, whichever is longer	
Enhanced Respiratory	• Gown • Gloves • N95 respirator (or CAPR/PAPR) • Eye protection	Private room preferred • **COVID-19 (+) specific**: private room **required**, negative-pressure or anteroom configuration preferred	**COVID-19 (+) specific**: Until cleared by Infection Control	
Special Contact	• Gown • Gloves	Private room **required**	Until free of diarrhea and vomiting for at least 48 hours	• Perform hand washing with soap and water. • Use EPA approved disinfectant (bleach wipes) for cleaning and disinfection.

[#] In select cases, Infection Control clearance may be required prior to discontinuing isolation precautions.

Suggested Reading

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12. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

13. Updated guidance for Palivizumab Prophylaxis Among Infants and Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. Committee on Infectious Disease and Bronchiolitis Guidelines Committee. *Pediatrics*. 2014: 134(2): 415-420.

Section 9: Metabolic Management

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9.1 Fluid and Electrolyte Therapy

Water Balance

The chief routes of water loss in infants are evaporation (through the skin and from the lungs) and urinary losses. About 65% of evaporative (insensible) water loss occurs via the skin and is related to surface area, skin maturity, humidity, and air temperature. About 33% of evaporative loss occurs via the lungs and is related to respiratory rate and environmental humidity. Decreasing humidity increases evaporative water loss. A wide range of insensible water loss exists in infants due to wide variations in size and conditions of the environment. **(Table 9-1)**

Table 9-1. Fluid (H_2O) loss (mL/kg/day) in standard incubators

Weight (g)	Evaporative		Urine	Total	
<1000	65	(100)[1]	45	110	(145)[1]
1001-1250	55	(80)[1]	45	100	(125)[1]
1251-1500	38	(60)[1]	45	83	(105)[1]
<1500	17	(25)[1]	45	62	(90)[1]

[1]Increases due to radiant warmer, phototherapy or extreme prematurity

A radiant warmer or phototherapy increases evaporative losses 50-190%. A humidified environment can greatly reduce insensible losses and allow for better fluid/electrolyte management. Infants < 32 weeks' gestation and/or < than 1250 grams birth weight should be placed into humidified incubators, if available. Normal urine water loss is around 45 mL/kg/day. This volume allows for excretion of the usual solute load and maintenance of adequately dilute urine.

Daily maintenance fluids are given to replace evaporative and urine water losses as well as any unusual loss that might be present.

Neonatal replacement fluid requirements vary widely depending upon environmental conditions, body weight, and gestation. **Table 9-2** shows suggested total fluid requirements (ml/kg/day) by birth weight based on anticipated fluid needs to replace losses. The anticipated fluid needs include parenteral nutrition volume, TKOs (keep open fluids) for catheters such as UAC, UVC, or central line, medications, and flushes. If fluid losses are increased due to loss from high urine output, orogastric tube, Replogle tube, or chest tubes, infants will require more total fluids. Monitoring of serum sodium is recommended to help guide total fluid adjustment for infants <1000 g birth weight.

Electrolyte Balance

Electrolyte composition of fluid evaporated from skin and lungs, as well as that lost as urine, normally is hypotonic (20-40 mEq of Na and K per liter). Usual maintenance electrolyte recommendations after first 24-48 hours of life are: Sodium (2-4 mEq/kg/day) and Potassium (2-3mEq/kg/day) Fluid losses from gastric or small bowel drainage should be replaced with normal saline as outlined in GI chapter.

Fluid Composition

Calculate water need independently of electrolyte needs; then combine the two to determine IV fluid composition.

Example: Maintenance fluids for 3-day-old, 2-kg infant

(a) Water needs= 100 mL/kg/day × 2 kg = 200 mL per day

(b) Na, K needs= 2 mEq/kg/day × 2 kg = 4 mEq per day

(c) 4 mEq per day= 2 mEq/100 mL of IV fluids

(d) 200 mL per day 24 hours

(e) Fluid prescription = $D_{10}W$ + 2 mEq NaCl + 2 mEq KCl/100 mL to run at 8.3 mL/hour

9.2 Hyperkalemia and Hypokalemia

Hyperkalemia is a medical emergency that requires close observation of the patient, continuous cardiac monitoring, and measurement of serial potassium levels.

Table 9-2a. Fluid requirements in stable term and late preterm infants who can be exclusively enterally fed

EXCLUSIVELY ENTERALLY FED Term and Late preterm infants (BW> 2000 gm)
MINIMUM Suggested total fluid requirements (ml/kg/d)*

	Day 0-1	Day 2-3	> Day 4
	30-40	30-40	> 50

*Neonatal fluid requirements vary widely depending upon environmental conditions, body weight and gestation

*Neonatal fluid requirements vary widely depending upon environmental conditions, body weight and gestation
Refer to **Table 13-8h for further guidance in **Ch 13.3-Enteral Nutrition**

Table 9-2b. Fluid requirements in critically ill infants who require intravenous support +/- enteral nutrition

Suggested total fluid requirements (ml/kg/d)*

Birth Weight (g)	Day 0-1	Day 2	>Day4
<750	130	140	150
751-1000	110	130	150
1001-1250	80-110	120	150
1251-1500	80	100-120	150
1501-2000	65-80	100	150
>2000**	65-80	100	150

*Neonatal fluid requirements vary widely depending upon environmental conditions, body weight and gestation
** Refer to **Tables 13-8b to 13-8h** for further guidance in **Ch 13-Enteral Nutrition**

Normal serum potassium levels in neonates range between 4 and 6.5 mEq/L. Levels above this range warrant investigation, though some may be a result of hemolysis or sampling artifacts. The etiology for hyperkalemia in neonates includes:

- decreased removal of potassium (acute renal failure, positive potassium balance in the premature infant during the first days of life, adrenal failure as in congenital adrenal hyperplasia, and medications such as Captopril)
- increased load of potassium (hemolysis, IVH, hematoma, excess potassium administration)
- redistribution of potassium from cells (common with metabolic acidosis, also seen with sepsis, necrotizing enterocolitis, and medications such as dig
- factitious causes (hemolyzed blood such as in heel-stick specimen, thrombocytosis).

Evaluation and Treatment

Specific laboratory studies helpful in determining the etiology and management of hyperkalemia include electrolytes, BUN, creatinine, platelet count, blood gas, serum ionized calcium, total calcium and magnesium levels. An infant should be assessed for cardiac changes associated with progressive increases in serum potassium levels (i.e., peaked T waves, prolonged PR interval, loss of P wave, widening QRS, sine wave QRST, first-degree AV block, ventricular dysrhythmia, and, finally, asystole).

Suspected Hyperkalemia

Immediately change to an IV solution without potassium. If the infant is on gentamicin, hold doses pending evaluation of renal status and gentamicin trough levels. Keep in mind that the effects of hyperkalemia can be worsened by hypocalcemia and hypomagnesemia.

Hyperkalemia with Cardiac Changes

Acutely perform the following interventions.

- With continuous cardiac monitoring, give 100 mg/kg per dose (1 mL/kg per dose) IV of 10% calcium gluconate or 20 mg/kg per dose (0.2 mL/kg per dose) of 10% calcium chloride rapidly over 1 minute. This will decrease myocardial excitability and, therefore, prevent cardiac arrhythmia. May repeat calcium dose in 10 minutes if abnormal cardiac changes persist. **Administration of calcium does not lower serum potassium levels.**
- Give sodium bicarbonate 1 to 2 mEq/kg IV bolus over 5-10 minutes; 1 mEq/kg of sodium bicarbonate will lower potassium by 1 mEq by driving potassium ions into the cells. If the infant has respiratory acidosis, correct this first, before administering sodium bicarbonate.
- To enhance transfer of potassium ions into the intracellular compartment, give 4 ml/kg D10W (400 mg/kg) followed by 0.1 unit/kg regular insulin (glucose alone is ineffective). The desired ratio is 1 unit of insulin for every 4 grams of glucose. However, some critically ill infants may have concurrent hyperglycemia and may require reduction in glucose dose to 2 ml/kg D10W (200 mg/kg). The bolus dose may be repeated if necessary or a continuous insulin infusion started at 0.05 unit/kg/hr in conjunction with an increase in GIR.

Hypokalemia

Renal K^+ wasting is most commonly caused by the administration of diuretics, particularly loop and thiazide diuretics. Loop diuretics inhibit the coupled reabsorption of $Na^+/K^+/2Cl^-$ at the luminal border of the thick ascending loop (TAL). There is both flow dependent K^+ secretion and enhanced K^+ secretion caused by the resultant increase in aldosterone and diuretic induced alkalosis, further exacerbating the electrolyte abnormalities. Hypokalemia also may be associated with correction of acidosis or increased uptake of glucose by cells. Acute correction via bolus therapy of mild-moderate hypokalemia is not necessary. Correction of serum K of 2.5-3.4 mEq/dl can usually be achieved gradually by increasing IV or oral potassium supplements from the usual 2-3 mEq/kg/day to the range of 4-6 mEq/kg/day. Severe hypokalemia, with serum K^+ less than 2.5 mEq/ dl, is a risk factor for neurologic or cardiac decompensation and should be corrected using IV infusion guidelines outlined in the "Short Term Potassium Replacement "order set, followed by monitoring of serum K+ to ensure value > 2.5 mEq/dl after intervention. Diuretics should not be given until serum K+ has been corrected above 2.5 mEq/dl.

Chloride Supplements

Chronic diuretic therapy induces hypochloremic metabolic alkalosis with total body potassium depletion. Infants receiving chronic diuretics need chloride supplementation of 2 to 4 mEq/ kg per day in addition to usual nutritional needs. This should be provided as potassium chloride with no sodium chloride provided unless serum sodium < 130 mEq/L or potassium is elevated for age. Serum chloride should be > 90 mg/dL and never maintained < 85 mg/dL. In general, total potassium and sodium chloride supplementation should not exceed 4-5 mEq/kg/d. The combination of furosemide and thiazide are untested and may have a severe effect on electrolytes. Serum chloride less than 85 mEq/dl is a risk factor for cardiac arrest and should be treated. Diuretics generally should not be given until the serum chloride is above 85-90 mEq/dl.

9.3 Hypocalcemia and Hypocalcemic Seizures

Hypocalcemia has two primary forms, usually referred to as early or late onset. Rarely, hypocalcemia is associated with other conditions in the newborn or with exchange transfusion.

Early Hypocalcemia

Early hypocalcemia usually is related to one of the following conditions:

- **Prematurity -** transient hypoparathyroidism or lack of responsiveness of the bone to parathyroid hormone.
- **Infant of diabetic mother** - decreased parathyroid hormone (PTH) or increased calcitonin.
- **Post-asphyxia -** release of tissue phosphorus.
- **Severe intrauterine growth restriction**—lack of calcium transfer across the placenta.

Diagnosis

Calcium (Ca) exists in both the ionized and non-ionized states. Only the ionized fraction maintains homeostasis and prevents symptoms associated with hypocalcemia. Therefore, it is preferred to evaluate ionized Ca directly. The relationship between total and ionized Ca is not linear—total serum Ca is not a reliable predictor of ionized Ca. There is a relatively greater ionized Ca for any total Ca when a patient is very premature (low total protein) or acidotic. Therefore, the greatest risk for hypocalcemia is in large, alkalotic babies.

For very low birth weight infants, an ionized Ca of less than 0.8 mmol/L is considered evidence for hypocalcemia (normal range 0.9 to 1.45 mmol/L).

For infants greater than 1500 grams birth weight, it is advisable to maintain a higher level of both ionized and total calcium. For these infants, an ionized Ca less than 1 mmol/L suggests hypocalcemia, although many infants may not be symptomatic at levels of 0.8 to 1 mmol/L. If total Ca is used, usually a value less than 8 mg/dL indicates hypocalcemia.

Clinical symptoms, including jitteriness and prolongation of the Q-T interval, are not reliable indicators of hypocalcemia.

Hypomagnesemia

The role of magnesium (Mg) in hypocalcemia is poorly defined. Mg deficiency inhibits PTH function and, therefore, it may not be possible to adequately treat hypocalcemia if there is concurrent hypomagnesemia. However, adequate definitions of hypomagnesemia or optimal therapy do not exist. In general, a serum Mg less than or equal to 1.5 mg/dL suggests hypomagnesemia and the need for intravenous Mg therapy (normal range 1.6 to 2.6 mg/dL).

Rapid IV pushes of Mg are not indicated. For maintenance therapy, administer Mg sulfate 25 to 50 mg/kg per dose (0.2 to 0.4 mEq/kg per dose) over at least 2-4 hours twice daily until the serum Mg normalizes (greater than 1.5 mg/dL).

Evaluation

Monitor the ionized Ca of infants who are at risk for hypocalcemia. An ionized Ca should be measured at 24 hours of age and every 12 hours until the infant is receiving Ca either from TPN or from a milk source and has a stable normal ionized Ca value. This usually occurs by 48 to 72 hours of age.

Therapy

Very low birth weight infants - Start treatment when the ionized Ca is less than 0.8 mmol/L in infants whose birth weight is 1500 grams or less. If the infant is asymptomatic, consider beginning TPN as the calcium source as soon as possible. If TPN cannot be started, add Ca gluconate at 500 mg/ kg per day via continuous IV infusion. In general, Ca should not be given intravenously for more than 48 hours without providing phosphorus (P) because of the risk of hypercalcemia. When removing the potassium phosphate from TPN due to concerns about hyperkalemia, it is important to remove the calcium as well if the phosphorus is to stay out of the TPN for longer than 48 hours if sodium phosphate is not used as an alternative.

Larger infants (greater than 1500 grams) - Treatment may be needed for ionized Ca less than 1 mmol/L in larger infants. This is because of the possibility of seizures or other symptoms that have been reported at levels up to 1 mmol/L in full-term infants. Infants who are alkalotic are at high risk for hypocalcemia. If the infant is on oral feeds, intravenous Ca may not be needed but serum Ca and P should be monitored regularly. For infants requiring intravenous therapy, begin therapy with IV Ca gluconate at 500 mg/kg per day given via continuous infusion.

Symptomatic infants of any size - For symptomatic infants (e.g., seizures) of any size, 100 mg/kg of Ca gluconate or 20 mg/kg of Ca chloride may be given over 10 to 20 minutes with concurrent cardiorespiratory monitoring. Administration of IV calcium gluconate should always be followed by administration of maintenance Ca gluconate to the IV solution (500 mg/kg per day).

Late Hypocalcemia

Late hypocalcemia is a frequent entity associated with low serum calcium and high serum phosphorus. It was classically associated with the introduction of whole cow's milk to the diet in the first days of life. Now it is seen in some infants who are fed routine commercial formula. It may present with seizures or be identified on routine testing in asymptomatic infants. Peak age of appearance is 5 to 14 days of life. Although the etiology is not always clear, generally it is believed to be related to transient hypoparathyroidism leading to hypocalcemia and hyperphosphatemia in the presence of a high (relative to human milk) phosphorus intake. An unusual cause is DiGeorge syndrome, which consists of thymic hypoplasia, hypocalcemia, cardiac (usually aortic arch) anomalies and abnormal facies. Any infant presenting with seizures at the end of the first week of life or in the second week of life should be evaluated.

Assessment and Management of Seizures Due to Hypocalcemia in Infants 3 to 10 Days of Age Born at Greater Than 34 Weeks' Gestation

Initial Assessment

After a complete history and physical examination, total calcium, ionized calcium, serum phosphorus, serum magnesium, intact parathyroid hormone, FISH for chromosome 22q deletion and chest radiograph for thymic shadow are recommended. The chest radiograph, parathyroid hormone and FISH can wait until the baby is stable. If sepsis/meningitis is suspected, appropriate evaluation should be done and treatment started with antibiotics and acyclovir, but this may not always be necessary if seizures are likely due to hypocalcemia and the infant is otherwise well. EEG and CT scans can also wait until the calcium therapy has been given and are not needed when the diagnosis is evident based on laboratory values. Anticonvulsant therapy and neurology consultation are not usually indicated. Endocrine consult is optional in the presence of a typical history and if a thymus is seen on CXR.

Intravenous Medication Therapy

After initial laboratory evaluation is performed, give a bolus infusion of calcium gluconate 100 mg/kg IV over 30 minutes. This will provide the patient with approximately 10 mg/kg of

elemental calcium since calcium gluconate is approximately 10% elemental calcium.

- **If a central line is in place, begin calcium gluconate infusion at 1000 mg/kg/day (~100 mg/kg/day of elemental calcium). If central line is not available, calcium gluconate infusion must be limited to 600 mg/kg/day (~60 mg/kg/day of elemental calcium)** regardless of iCa value given the increased risk of extravasation and soft tissue injury. If clinical response is inadequate, then the risks and benefits of obtaining central access to provide higher amounts of calcium should be considered. Ionized calcium should be drawn one hour after the first bolus, then every 4 hours initially. The frequency of sampling can be reduced to every 6-8 hours when iCa is > 1.0 and seizures have stopped.
- If the ionized calcium is less than 1.0 mmol/L after the initial bolus infusion, give an additional bolus infusion of calcium gluconate 100 mg/kg IV over 30 minutes (~10 mg/kg of elemental calcium) and continue calcium gluconate infusion at current rate.
- Correct hypomagnesemia if serum magnesium is less than 1.6 mg/ dl with magnesium sulfate 25 mg/kg IV given over 1 hour. Check serum magnesium after completing the infusion and repeat the same dose every 12 hours until the magnesium level is more than or equal to 1.6 mg/dl. Rarely are more than 2 doses needed.

The calcium infusion should be managed using the following algorithm:

If ionized calcium is 1.00 - 1.20 mmol/L: maintain infusion rate, no need for additional bolus infusions. If no further seizures occur, can start feedings (see below) and start oral supplementation. It is common for seizures to persist until the iCa is greater than 1.00 for 1-2 hours. **Refer to Oral Therapy section.**

When ionized calcium is 1.21-1.30 mmol/L: decrease calcium gluconate infusion to 250 mg/kg/day (~25 mg/kg/day of elemental calcium). If not already started, start feeds and begin oral supplementation. If iCa is 1.21 or greater on two measurements and feeds with oral calcium supplement have been started and tolerated, can stop IV calcium infusion. Refer to Oral Therapy section below for dosing instructions.

When ionized calcium is 1.31 or greater and feeds and oral calcium supplements have been started and tolerated, can discontinue intravenous calcium gluconate infusion if it has not already been stopped. At this point, patient should be on feeds and oral calcium supplementation (usually providing ~50 mg/kg/day of elemental calcium).

Once intravenous calcium infusion has been discontinued, calcium and phosphorus measurements can be reduced to every 8-12 hours.

Oral Therapy

Initiate feeds with Similac® PM 60/40, Gerber Good Start Liquid® or breast milk (all of these are acceptable feedings) when ionized calcium is more than or equal to 1.0 mmol/L and no clinical seizures have occurred within the past 2 hours. Gerber Good Start Liquid® has the lowest phosphorus content of routine infant formulas and is therefore a readily obtained alternative. If family wishes to switch back to another formula, this can usually be done 1-2 weeks after hospital discharge.

Oral calcium supplementation should be initiated with commercially available calcium carbonate suspension at 30 mg/kg/DOSE every 6 hours to provide ~50 mg/kg/DAY of elemental calcium. Since calcium carbonate is a high osmolar product, caution should be exercised in VLBW infants. Enteral medications with high osmolarity are associated with higher risk of necrotizing enterocolitis. To optimize absorption, avoid concomitant use of H_2-antagonists and proton pump inhibitors. Future editions of guidelines may change subject to product availability.

- Pt. may be discharged on Similac® PM 60/40 or Gerber Good Start Liquid® with oral calcium supplementation (providing 25-50 mg/kg/day of elemental calcium), with follow-up by endocrine service or the primary pediatrician 24-48 hours after discharge. Gerber Good Start Liquid® is currently not available at Texas WIC, Similac® PM 60/40 is an alternative option at WIC; however, the availabilities of these formulas is subject to change. Can usually discharge after 24 hours of iCa > 1.3 on oral therapy if reliable follow-up is assured. May be able to stop the oral calcium supplement, monitor for 24 hours and discharge without the need for oral calcium at home.
- If calcitriol is continued at discharge, the patient must have Endocrine Service follow-up. It should be rare that calcitriol is continued after discharge.
  - » The use of calcitriol is at the discretion of the Endocrine Service if they are involved in the patient's care. If begun IV, switch to oral dosing as soon as feeds are started.

9.4 Hypercalcemia or Hyperphosphatemia

The ionized calcium (iCa) should usually be between 0.8 and 1.45 mmol/L in VLBW infants, and between 1.0 and 1.4 mmol/L in larger infants. The maximum iCa usually is 1.40 to 1.45 mmol/L. Hypercalcemia above this level in the neonatal period is usually associated with TPN use, especially in VLBW infants.

Mild hypercalcemia (1.45 to 1.65 mmol/L) or mild hyperphosphatemia (> 9mg/dL) is common and does not warrant specific therapy. If it persists, a small change in the calcium-to-phosphorous (Ca/Phos) ratio (no more than a 20% change in the mmol/mmol ratio) usually will correct this within 48 hours. Under no circumstances should calcium be removed from the TPN for an iCa lower than 1.8 mmol/L.

Infants with moderate hypercalcemia (≥ 1.6 mmol/L) should have their Ca/Phos ratio decreased to about 0.5:1 to 0.8:1. Do not remove all the calcium unless the iCa is greater than 1.8 mmol/L. Hypercalcemia provides no known therapeutic benefit in any condition, especially with levels above 1.6 mmol/L, which may be associated with calcium deposition in various tissues, including the brain.

Avoid withdrawing calcium or phosphorus or markedly changing their ratio for longer than 24 hours. If calcium is

completely removed from the TPN, phosphorous intake generally should be decreased by 50% or deleted, depending on serum phosphorous levels. This should rarely be done for longer than 24 hours, and iCa must be measured every 12 hours if either calcium or phosphorus is reduced by 50% in the TPN.

When the iCa is below 1.45 mmol/L, resume IV calcium at levels similar to usual ratios.

During the first days of life, initiating intravenous calcium therapy in the absence of TPN, or giving supplemental calcium in addition to that provided in TPN, usually is not necessary in non-high-risk groups. There is no evidence that higher levels of calcium are beneficial, and they could pose a substantial risk of inadvertent tissue calcification.

9.5 Hyponatremia and Hypernatremia

Hyponatremia

A serum sodium level below 130 mEq/L is considered hyponatremia and a serum sodium level below 120 mEq/L is referred to as severe hyponatremia. Hyponatremia can be of acute (<24 hours) or chronic onset (>24 hours). Nearly 30% of VLBW infants in the first week and 25-65% in the second week after birth are known to develop hyponatremia. Hyponatremia has been shown to be associated with poor neurodevelopmental outcomes and poor growth.

Changes in a. total body water (TBW) (dilutional hyponatremia resulting from either excess intake or decreased excretion of water), or b. total body sodium (TBNa) (decreased TBNa from either deficient intake or excessive loss of sodium) can result in hyponatremia. Common causes of hyponatremia in relation to fluid status, their common diagnostic markers, and broad treatment plans are mentioned in **Table 9-3.**

Evaluation of urine output, other fluid losses and body weight will help assess the volume status of the infant. Other useful evaluations include paired serum and urine osmolarities and electrolytes.

Optimum treatment of hyponatremia requires evaluating the possible etiology by considering assessment of volume status, the severity of symptoms, and duration of hyponatremia. Hypovolemic states need appropriate replacements of both water and sodium deficits. Normovolemic and hypervolemic states warrant fluid restriction of up to 60% of maintenance fluids either with, or without sodium supplementation. Sodium replacement should take into account the deficit, maintenance, and when possible, ongoing losses of sodium.

Hyponatremic sodium deficit is calculated by using the formula:

Sodium deficit (mEq) = Body weight x 0.7x (desired serum sodium concentration - actual serum sodium concentration).

Generally, the goal of correction of hyponatremia is to increase the serum sodium concentration by no more than 10 mEq/L over a 24-hour period due to the risk of neuronal demyelination Severe hyponatremia (S Na <120 mEq/L) associated with central nervous symptoms such as altered sensorium, vomiting, and seizure require more rapid correction as hyponatremic seizures are resistant to treatment with anticonvulsants. The goal of acute correction in severe hyponatremia with neurologic symptoms is to increase the serum sodium concentration by around 3-5 mEq/L over 2 to 4 hours, resulting in a rate of increase of sodium concentration by no more than 2 mEq/L/hour. This should be followed by a slower correction with a goal increase of serum sodium by no more than 10 mEq/L over 24 hours. Acute correction of rapidly presenting severe hyponatremia (S Na <120 mEq/L) may be achieved by administering intravenous normal (0.9%) saline.

Normal saline should be the first line of choice for treating hyponatremia as hypertonic (3%) saline and normal (0.9%) saline are not interchangeable in terms of safety; therefore, the use of hypertonic (3%) saline should be reserved only for severe hyponatremia with neurologic symptoms. (very low-quality evidence, weak recommendation). It is important to recognize that hypertonic (3 %) saline is extremely hyperosmolar (Osmolarity: 900 mosm/L). This high osmolarity can cause significant electrolyte shifts in the CNS which can increase the risk of neuronal demyelination. Moreover, central line administration for hypertonic (3%) saline continuous infusion is recommended whereas normal (0.9%) saline can be administered via a peripheral line.

Table 9-3. Causes, diagnostic markers and treatment of hyponatremia

Fluid Status	Causes	Diagnosis	Treatment
Hypovolemia	VLBW with renal salt wasting, diuretics, osmotic diuresis (hyperglycemia), adrenal or renal tubular salt-losing disorders, gastrointestinal and skin losses.	Decreased weight, decreased urine output, increased urine osmolarity, signs of dehydration, tachycardia, high BUN, metabolic acidosis, metabolic alkalosis (contraction).	Reduce ongoing sodium loss. Correct sodium and water deficits.
Normovolemia	SIADH, (pain, medications, meningitis, pneumonia, pneumothorax, mechanical ventilation)	Weight gain without edema, decreased urine output, decreased serum osmolarity, increased urine osmolarity, increased urine sodium.	Fluid restriction, Sodium supplementation
Hypervolemia	SIADH, heart failure, renal failure, liver failure, sepsis, HIE, increased maternal free water, iatrogenic administration of excess free water.	Weight gain, edema, decreased urine output, decreased serum osmolarity, increased urine osmolarity, normal or increased urine sodium.	Fluid restriction, Sodium supplementation

Published literature in the use of hypertonic (3%) saline is limited to case series of such treatment in older infants and children; its use in preterm and term newborn infants has not been studied. Hence its use should be carefully considered only in instances of severe hyponatremia with neurologic symptoms. In such instances, a dose of 1 -3 ml/kg over 30 minutes can be considered, following which a serum sodium must be checked 20 minutes after administration. Guidance of a clinical pharmacist with regards to dosing and administration is strongly advised prior to its administration.

During correction of severe hyponatremia or hyponatremia with neurologic symptoms, neurologic assessments should be performed each hour and monitoring of serum sodium should occur every 4 hours or more frequently to assess the rate of serum sodium rise. Titration of sodium chloride infusions should be adjusted based off of the serum sodium values to prevent increases of serum sodium greater than 0.5 mEq/L/hour (a goal increase of no more than 10 mEq/L over 24 hours).

Patients with chronic hyponatremia (>48 hours) can be corrected by a combination of fluid restriction and correction of sodium deficit. Patients presenting with chronic hyponatremia usually undergo cerebral adaptation and are at higher risk for osmotic demyelination if hyponatremia is corrected too quickly. Correction of chronic hyponatremia should be aimed at increase in S. Na of no more than 6-8 mEq/L over 24 hours.

Hypernatremia

Hypernatremia in neonates is defined as serum sodium concentrations > 150 mEq/L. Hypernatremia usually occurs either as a result of a. increased insensible or hypotonic fluid losses (transcutaneous, GI or urinary losses) resulting in a free water deficit, or excessive sodium intake.

While the etiology for hypernatremia in the neonatal period are several, here we address the most common scenarios.

Hypernatremia in VLBW infants: VLBW infants due to increased insensible water and urinary fluid losses particularly within the first week of life, are at a high risk of hypernatremia. The use of humidified incubators has significantly decreased the extent of insensible water loss in this population. Hypernatremia in this high risk group usually suggests free water deficit. Hypernatremia does not always suggest increase in total body sodium concentrations. Infants with hypernatremia often show greater than expected weight loss, tachycardia and metabolic acidosis indicative of the decrease in the extracellular fluid volume. The treatment involves increasing free water fluid intake to facilitate decrease in serum sodium. This can be achieved by supplementing with a 5% or 10% dextrose infusion. Serum concentrations of sodium and glucose should be closely monitored, and the decrease in sodium should be no more than 0.5- 1 mEq/L/hour. Rapid correction of hypernatremia should be avoided given the increased risk for intraventricular hemorrhage. Such infants should, however, continue to receive their recommended daily Na intake. Studies evaluating the use of enteral free water drips in this population have not shown to be beneficial.

Hypernatremia secondary to excessive Na intake: In the NICU, we often use sodium containing infusions to maintain the patency of central venous and arterial catheters. Hence it is important to ensure that the sodium intake does not exceed the patient's daily sodium requirements in a significant manner. These infants may present with excessive weight gain and edema particularly if they have been receiving excessive isotonic/hypertonic fluids. Use of 0.45% NaCl in carrier infusion fluids instead of 0.9% NaCl can limit the amount of sodium delivered in carrier fluids.

The sodium content of various Na preparations used in the NICU are listed below:

0.9% NaCl (NS): 15.4 mEq/100 ml
0.45% NaCl (1/2NS): 7.7 mEq/100 ml
Sodium bicarbonate bolus (4.2%): 0.5 mEq/ml
3% Saline: 51.3 mEq/100 ml

9.6 Metabolic Acidosis

Metabolic acidosis is a frequently encountered problem in the NICU. It is important to determine the anion gap, as it will allow differentiating the etiologies into two categories, gap and non-gap acidosis. Anion gap is calculated as $[Na^+]-([Cl^-] + [HCO3^-])$. Generally, a gap greater than 15 mEq/L is defined as an increased anion gap. Though there are numerous etiologies for metabolic acidosis, the common causes encountered are: 1) lactic acidosis (with increased anion gap) secondary to critical illness, hypoxia, shock, sepsis and 2) Metabolic acidosis seen in VLBW infants as a result of inadequate bicarbonate absorption in their immature kidneys (with normal anion gap). Other examples include renal failure, GI losses from an ileostomy or chronic TPN use in VLBW babies. These infants have persistent normal anion gap metabolic acidosis without marked elevation in lactate levels.

Many preterm infants, especially those ≤ 1500g, benefit from addition of acetate to their TPN or, uncommonly, base supplementation (such as Bicitra®) in their oral diet. Typically, 1-2 mEq/100 ml of sodium or potassium acetate are added each day to TPN. Need for a higher concentration is rare but, if necessary, care providers should take note of the added cation in determining total sodium and potassium needs. Under no circumstances should sodium bicarbonate be added to TPN that includes calcium as sodium bicarbonate in the presence of calcium increases the risk for precipitation.

Use of Sodium Bicarbonate in Metabolic Acidosis

- Treatment of acidosis in neonates using sodium bicarbonate has been around for many years. However, evidence that correction of acidosis with sodium bicarbonate improves outcome of cardiopulmonary dysfunction remains lacking. Conversely, increasing evidence suggests potential adverse effects of sodium bicarbonate administration. Several retrospective studies have reported a strong association between rapid infusions of bicarbonate and IVH in premature infants. Human and animal studies demonstrate impaired myocardial and circulatory function, increase cerebral blood volume, worsening intracellular acidosis and diminished tissue oxygen delivery in association with bicarbonate administration.

Several lines of evidence suggest a much more limited role for this agent.

- Acidosis associated with respiratory distress in neonates is mainly respiratory (due to hypercarbia), or mixed. Infusion of bicarbonate in the face of impaired ventilation induces production of additional CO_2 that cannot be removed. This CO_2 diffuses into the intracellular space and worsens intracellular acidosis.
- No human studies have demonstrated a beneficial effect of bicarbonate on survival or any other outcome following CPR. The NRP no longer recommends use of buffers during neonatal resuscitation.
- Effect of bicarbonate infusion on blood pH, if any, is transient.
- No studies have demonstrated increased survival or reduced morbidity in neonates with respiratory distress receiving sodium bicarbonate.
- If a true metabolic acidosis is present, it is a result of renal or GI tract loss of base, hydrogen ion load in excess of renal excretory function, edema or generation of organic acids such as lactate. None of these underlying disorders is corrected by sodium bicarbonate. The underlying mechanism itself should be the target of therapeutic intervention.

Based upon current evidence, we do not recommend use of sodium bicarbonate in neonates with acute cardiopulmonary disease and a base deficit except in exceptional circumstances. Acute circumstances in which infusion of sodium bicarbonate may be appropriate include management of certain cardiac patients, symptomatic hyperkalemia, babies with severe lactic acidosis associated with circulatory insufficiency (while attempting to stabilize circulatory function) or initial management of a severe organic acidemia.

Suggested Reading

1. Doherty E.J. (2017). Fluid and Electrolyte Management, In Eichenwald E.C., Hansen A. R., Martin C.R., Stark AR. (Eds.), Cloherty and Stark's Manual of Neonatal Care, 18th Edition.
2. Somers M.J., Traum A.Z., (2019). Hyponatremia in children. In Kim M.S. (Ed.), UpToDate. Retrieved April 12, 2019.

Section 10: Nephrology

Editors: Catherine Joseph and Joseph Garcia-Prats

10.1 Acute Kidney Injury

Renal Physiology

At birth, serum creatinine (SCr) is typically equal to the concentration in the mother. In neonates, SCr is influenced by several factors, including the presence of maternal creatinine, varying degrees of creatinine reabsorption in the proximal tubules, overall lower glomerular filtration rates (GFRs), and maturational differences.

In term infants, creatinine declines in 1-2 weeks of life to its nadir (SCr 0.2 to 0.4 mg/dL)

In very preterm infants (GA <32 weeks), SCr may have a slight increase after birth, most likely due to low GFR and tubular reabsorption of creatinine, followed by a slower decline over two months. **Table 10-1** shows data regarding expected GFR in preterm infants and at 2 weeks of age.

Table 10-1. Serum creatinine values for very preterm infants (gestational age less than 33 weeks)

AGE	50th percentile value [mg/dL]	95th percentile value [mg/dL]
7 days		
25-27 weeks GA	0.87	1.23
28-29 weeks GA	0.84	1.18
30-33 weeks GA	0.66	0.95
14 days		
25-27 weeks GA	0.75	1.10
28-29 weeks GA	0.69	1.02
30-33 weeks GA	0.57	0.84
1 month		
25-27 weeks GA	0.48	0.72
28-29 weeks GA	0.41	0.64
30-33 weeks GA	0.35	0.57
2 months		
25-27 weeks GA	0.31	0.51
28-29 weeks GA	0.33	0.58
30-33 weeks GA	0.25	Data not available

Acute Kidney Injury (AKI)

Acute kidney injury (AKI) is a sudden impairment in renal function that leads to dysregulation in the fluid and electrolyte balance of the body as well as impaired waste excretion.

Definition of AKI

Despite its limitations, creatinine is the standard used for the diagnosis of AKI in all populations. The most commonly used is the KDIGO Neonatal AKI definition. Published in 2013, it accounts for a change in serum creatinine level from a previous baseline, includes urine output criteria, and has 3 stages accounting for AKI severity **Table 10-2**.

While AKI in neonates is usually non-oliguric, newborns can develop oliguric kidney injury and be at risk for developing fluid overload. Hence to diagnose AKI, infants do not need to meet both (SCr and UOP) criteria.

Epidemiology of AKI/Mortality

Using the KDIGO classification, recent evidence from a large multi-center epidemiologic study1 showed that the incidence of AKI in hospitalized neonates was 43% in those <29 weeks GA, 18% in those between 29 and 36 weeks GA, and 37% in those >36 weeks GA. AKI is independently associated with increased mortality and longer hospitalizations in the newborn population. Hence early recognition is crucial to identify potentially reversible factors and provide supportive care to prevent complications.

Risk factors for AKI:

- Prematurity: low nephron number
- Perinatal asphyxia
- Low birth weight
- Sepsis
- Congenital heart disease (e.g.) in peri/postoperative period
- ECMO
- Nephrotoxin exposure: aminoglycosides, iodinated contrast, indomethacin, amphotericin, acyclovir
- Renal anomalies

Evaluation of AKI

Assessment should include review of **maternal creatinine** and medication profile and a thorough assessment of fluid status (BW, current weight, I/O, net fluid balance and UOP)

Labs - Upon initial assessment, labs should include: Chem10, CBC, albumin, drug levels (such as vancomycin and gentamicin) and UA with microscopy.

Table 10.2. Neonatal AKI KDIGO Definition

STAGE	Serum Creatinine	Urine Output
0	NO change in SCr or rise < 0.3 mg/dL	>0.5 mL/kg/h
1	SCr rise ≥ 0.3 mg/dL within 48 hr or rise ≥1.5-1.9 times reference[a] SCr within 7 days	<0.5 mL/kg/h for 6-12 h
2	SCr rise > 2-2.9 x reference SCr	<0.5 mL/kg/h for >12 h
3	SCr rise >3 x reference SCr or SCr >2.5[b] mg/dL or receipt of dialysis	<0.3 ml/kg/h ≥24 h or anuria for ≥ 12 h

a. Reference SCr will be defined as lowest previous SCr value
b. SCr value of 2.5 mg/dL represents <10ml/min/1.73m^2

Table 10-3. Causes of AKI

Pre – Renal [80%]	Renal/Intrinsic [10-11%]	Post-Renal [3-5%]
• Inadequate renal perfusion • Hypovolemia • Hypoperfusion • Hypoxia	• Nephrotoxic agents: o Indomethacin, o ibuprofen, o aminoglycosides, o iodinated contrast • Renal vein thrombosis • Pyelonephritis	• Posterior urethral valves • Neurogenic bladder • Urethral stenosis • Ureteropelvic junction obstruction

Fractional excretion of Sodium (FeNa) - In term infants, FeNa can be useful in differentiating pre-renal from intrinsic AKI. FeNa < 2% is suggestive of pre-renal AKI.

$$\text{FeNa: } \frac{100 \times (\text{Serum Cr} \times \text{Urine Na})}{(\text{Serum Na} \times \text{Urine Cr})}$$

However, in premature infants this test can be unreliable owing to tubular immaturity with FeNa values ranging from 2-6%.

Imaging - Renal ultrasound is recommended to assess baseline structure and evaluate for congenital anomalies. If vascular thrombosis in renal vessels is suspected, doppler studies should be performed.

Management of AKI

- Mostly supportive with management of the underlying causes: sepsis, hypotension, congenital heart disease, hypovolemia, vascular thrombosis, nephrotic syndrome
- Consider placing a urinary catheter to document urine output.
- Fluid management is based on the underlying cause of AKI

Pre-renal AKI - Address risk factors such as hypotension and hypovolemia. Consider fluid resuscitation with NS bolus only if hypovolemia is suspected. If there is a response, continue judicious fluid resuscitation until infant is euvolemic based on weight, serum Na and UOP. Otherwise avoid further fluid boluses if there is continued oliguria to limit worsening fluid overload.

Intrinsic AKI - With oliguria or anuria, limit fluid intake to insensible water losses in addition to any ongoing outputs (e.g. urine, gastrointestinal, drains). Daily insensible losses in newborns increases with decreasing birth weight (BW).

Post-renal AKI - Fluid management should take into consideration post-obstructive diuresis which occurs once the underlying obstruction is relieved.

Medications:

- Discontinue potassium containing fluids/feeds
- Withdraw nephrotoxic medications and avoid further use if possible.
- Adjust medication dosages for renal dysfunction when indicated

Nutrition:

- Continue EBM/DEBM. Renal formulas such as Similac® 60/40 can be considered if hyperkalemia or hyperphosphatemia worsen.
- Fortification should be considered in consultation with Renal Dietician as caloric concentration can significantly affect electrolyte composition. Protein restriction is not recommended in AKI. It is recommended that these infants continue to meet the minimum required protein intake during AKI.

Hypertension - Fluid overload or intrinsic renal disease can contribute to hypertension in the setting of AKI. Use of diuretics judiciously in addition to fluid restriction can help with fluid overload.

Electrolyte abnormalities:

- **Hyperkalemia** can be a life-threatening complication. Refer to **Ch 9.2-Hyperkalemia and Hypokalemia** for further management.
- **Metabolic acidosis** - In addition to treating the underlying cause, bicarbonate supplementation is frequently required
- **Hyperphosphatemia** - related to dietary intake and or cell/tissue breakdown. Can be managed with renal formulas and if needed, phosphate binders in consultation with Renal Dietician.

Prognosis

For infants who had AKI, weekly monitoring of renal function tests is recommended until it returns to baseline. Closer monitoring may be required with additional acute illness or nephrotoxic exposure as susceptibility to AKI increases after one episode. Data in children show increased risk of chronic kidney disease with AKI, especially when it is severe and/or recurrent. KDIGO guidelines recommend nephrology evaluation of AKI survivors within three months after the onset of AKI to assess for resolution and/or the development of chronic kidney disease.

AKI and Renal Replacement Therapy (RRT)

RRT modalities support waste removal, electrolyte and acid-base stability, and fluid removal/balance in the setting of AKI. In the neonatal population, the available RRT include acute peritoneal dialysis (PD), hemodialysis (HD) and continuous renal replacement therapy (CRRT).

Generally, acute RRT provides renal support for conditions that are considered reversible. However, in certain cases this can be difficult to ascertain early in the course of illness. For this reason, providers may consider a time-limited trial of therapies to facilitate decision making based on reversibility or non-reversibility of the condition and assess the future course of illness.

Listed in the next several sections are the different modalities of RRT. The choice of modality will be determined by (1) patient characteristics, (2) therapy goals, as well as (3) renal providers' expertise.

Indications for renal replacement therapy:

- Fluid overload-worsening and refractory to diuretic therapy
- Hyperkalemia and metabolic acidosis not responding to medical therapy

- Inability to tolerate fluid restriction due to high fluid intake for medication intake, blood products or adequate nutrition
- Uremic encephalopathy or pericarditis
- Removal of dialyzable toxin
- Hyperammonemia in the case of inborn errors of metabolism

Considerations for all RRT

Size Qualifications:

- Infants >2 kg are potential candidates for peritoneal dialysis provided there are no other contraindications
- Infants > 3 kg are possible candidates for hemodialysis and/or CRRT. In babies 2-3 kg, consideration of HD or CRRT are determined in consultation with the nephrologist on a case by case basis.
- These size-based guidelines are subject to modification especially with availability of newer dialysis machines that are designed for neonates.

Nutritional Considerations:

- Neonates receiving RRT may need specialized formulas or TPN modifications
- RRT removes water soluble vitamins, requiring supplementation
- A Renal Dietitian should be involved in determining nutritional needs (calories and protein)

Medications Management:

- RRT may effect medication delivery or clearance depending on the drug properties
- All medications should be reviewed for dosage adjustment, frequency and timing of administration

Peritoneal Dialysis (PD)

PD is generally considered the optimal dialysis modality for neonates for slow removal of fluid and solutes. PD uses the peritoneal membrane, which overlays the vessels surrounding the visceral and parietal surfaces in the abdomen, acts as a semipermeable membrane for fluid and solutes. We use commercially available dialysate solution composed of varying concentrations of dextrose that provide the osmotic gradient to facilitate fluid removal. Dialysis fluid is instilled into the peritoneal cavity and allowed to dwell for a prescribed time and then drained. This process is repeated via intermittent (12-16 hours/day) or continuous mode (24 hours/day) depending on the needs of the neonate.

Prescription - Nephrologist orders composition of dialysate/catheter use/cycle regimen.

- **Peritoneal dialysis fluid-** instilled intraperitoneally composed of dextrose-based solutions to create osmotic ultrafiltration
- **Catheter:** straight or swan neck peritoneal dialysis catheters can be used. The choice of catheter is determined by nephrologist and pediatric surgeon. After catheter placement, if possible, we attempt a dialysis free period for ~1-2 weeks to permit healing and minimize chances of leaking.
- Hourly dialysis cycles performed on a manual set up with small fill volumes
- The dialysis catheter dressing changes and exit site care are conducted by the renal dialysis nursing team **ONLY**

Most Common Complications:

- Inadequate fluid or solute removal
- Poor filling or draining: possible catheter dysfunction
- **Peritonitis -** Fever or cloudy peritoneal fluid are signs of peritonitis. Peritoneal fluid should be sent by dialysis RN for cell counts and cultures. Nephrology team to determine treatment
- **Leaking -** Can be around catheter or in the subcutaneous plane seen as swelling and/or lack of ultrafiltration. Renal team should be notified when suspected. To prevent this, we try to let catheter heal before use and start with low volumes.
- **Hernia -** risk factors include patent processus vaginalis and high intraabdominal pressure

Contraindications to PD:

- Diaphragmatic hernia/defects
- Intraabdominal surgeries
- NEC
- Gastroschisis
- Bladder Exstrophy
- Other conditions that have compromised the peritoneum

Hemodialysis (HD)

HD is accomplished by removing the blood via catheter, filtering the blood through a dialyzer, and returning the processed blood back to the patient. HD is technically challenging in neonates due to the limitation of the current HD machine technology. However, HD can be done safely and effectively in neonates with careful consideration.

HD Specific Considerations:

- **Fluid restriction -** In infants with oliguric AKI, fluid restriction is based on the maximum fluid removal possible for an HD treatment. This is absolutely necessary for HD to minimize the potential for hypotension associated with fluid removal.
- Heparin delivery during HD is necessary for maintenance of the circuit to deliver adequate clearance
- Some medications need to be administered after HD and supplemental dosing might be necessary.

Nephrologist will order dialysis prescription:

- **Catheter** - Dual Lumen 7 Fr or 8 Fr. Preferred location is Right IJ
- Blood priming the HD circuit is necessary due to the large extracorporeal volume. Smallest available HD circuit is ~70 mL

Most Common Complications:

- **Hypotension -** Frequently secondary to fluid removal requirements
- Catheter dysfunction
- **CLABSI** - High risk for infection, HD catheters are only managed by Renal RN(s)

Contraindications:

- Inability to establish vascular access
- Patients requiring multiple inotropes or vasopressor for blood pressure support
- Patients without realistic life expectancy due to acutely life-limiting severe underlying conditions

Continuous Renal Replacement Therapy (CRRT):

CRRT is similar to HD, accomplishing fluid and electrolyte control by removing the blood via catheter, filtering the blood through a dialyzer, and returning the processed blood back to the patient. However, in CRRT fluid and electrolyte corrections are done much slower, and CRRT runs continuously until able to transition to other RRT or renal recovery. As with HD, CRRT is technically challenging in neonates, as we currently use machines designed for adult use. However, CRRT is successfully done with careful consideration and modifications.

CRRT Specific Considerations:

- Hypotension is common at the start of CRRT and with subsequent circuit changes, therefore the **renal attending/APP AND the NICU APP/fellow/attending** must be present at the bedside for each procedure initiation. Clinicians need to anticipate hypotension and have a well-planned strategy to manage hypotension.
    - MAP goals need to be reviewed with NICU team prior to CRRT start. Review recent labs- serum Ca, HCO3 and pH.
    - Keep the infant warm with initiation and while on CRRT to decrease chances of bradycardia
    - Have IV calcium chloride or calcium gluconate doses, 5% albumin and dopamine at bedside prior to initiation
    - If newborn is not on vasopressors, have them ordered and set up in line to start infusion if hypotension does not resolve with IV calcium
    - If hypotension develops-give a dose of IV calcium.
    - If not responding, recommend a bolus of 5% Albumin [5-10 ml/kg]. Give sodium bicarbonate 1meq/kg as a bolus dose in addition if indicated.
    - Start/titrate vasopressor support to meet earlier defined MAP goals.
- Generally, neonates on CRRT MUST receive at least 2.5 gm/kg of protein to account for losses via CRRT
- CRRT uses regional anticoagulation with citrate. Therefore, careful monitoring of calcium is essential. The delivery rates for citrate and calcium are titrated per the appropriate protocol
- Fluid removal rates are modified based on patient response AND must include the renal team

Prescription:

- All aspects of this are ordered by a nephrologist
- **Catheter -** Dual Lumen 7 Fr or 8 Fr. Preferred location is Right IJ
- **Blood priming** the CRRT circuit is necessary due to the large extracorporeal volume. Smallest available circuit is 165 mL
- **Modality -** Continuous veno-venous hemodialfiltration (CVVHDF) combines both convective and diffusive dialysis, thus both dialysate and replacement fluids are required, and both small and middle molecules are cleared
- **CRRT Solutions -** Standardized solution help maintain electrolyte
- **Net UF (Fluid removal rates) -** NOT to exceed 1-2 mL/kg/hour.
- **Net UF goals** are determined every morning and modified as needed in collaboration with renal team. ONLY renal can change the UF goals
- **Laboratory Schedule -** Mandatory: CMP with phos/mag BID; Ionized Calcium (Circuit, Patient) Q 8 hours

Discontinuing CRRT Considerations (Scheduled and NON-Scheduled):

- Routine circuit changes are performed every 3 days
- If the circuit must be discontinued due to clotting/access/procedures, it is **IMPERATIVE** to evaluate all infusion rates. They may likely be decreased after a discussion with renal team. All fluids with potassium should be stopped.

Most Common Complications:

- Similar to hemodialysis procedure. In addition, citrate accumulation evident by elevated serum calcium and normal or low ionized calcium. The renal team will modify treatment as necessary.

Contraindications:

- Inability to establish vascular access

10.2 Chronic Kidney Disease

Definition

Chronic kidney disease (CKD) is universally defined as abnormalities of kidney structure **or** function with glomerular filtration rate (GFR) < 60 ml/min/1.73m2 for greater than 3 months. GFR criteria to define CKD does not apply to children < 2 years of age irrespective of etiology. Developmental renal anomalies account for 30-50% of children with CKD/ESRD, and infants, while born with normal serum Cr for age, can still meet the definition of CKD by structural abnormalities and can be classified within the first few days of life. Furthermore, since normal GFR in newborns is less than 60 ml/min/1.73m2 and increases to adult GFR by 2 years of age, age appropriate GFR needs to be taken into account to define normal kidney function and chronic kidney disease in an infant **(Table 10-4 and Table 10-5).**

Table 10-4. Glomerular filtration rate (GFR) in healthy infants as assessed by inulin clearance

Age	Mean GFR± SD (ml/min/1.73 m2)
Preterm babies	
1-3 d	14.0 ± 5
1-7 d	18.7 ± 5.5
4-8 d	44.3 ± 9.3
3-13 d	47.8 ± 10.7
8-14 d	35.4 ± 13.4
1.5 -4 mo	67.4 ± 16.6
Term babies	
1-3 d	20.8 ± 5.0
3.4 d	39.0 ± 15.1
4-14 d	36.8 ± 7.2
6- 14 d	54.6 ± 7.6
15-19 d	46.9 ± 12.5
1-3 mo	85.3 ± 35.1

Adapted by permission from Springer Nature Customer Service Center GmbH: Springer Nature, Pediatric Nephrology, Glomerular filtration rate measurement and estimation in chronic kidney disease, George J. Schwartz, et al, © 2007.

Incidence

Neonatal CKD - estimated incidence 1:10,000 live births with 50% or greater being preterm.

Neonatal End Stage Renal Disease (ESRD) - estimated incidence 0.045 cases per million population per year.

Medical Management

All these measures are focused on promoting growth and development in the infant.

Nutrition - Due to periods of rapid growth during infancy, it is important to provide optimal macro and micronutrients. NG or G tube placement are commonly required early on in neonates with CKD to overcome oral aversion, provide adequate protein and caloric intake, and administer medications. GERD and gastric dysmotility are not uncommon and medications can be used but required adjustment based on GFR. Serial assessment of daily weight and monthly length and head circumference are needed. A multidisciplinary team approach consisting of both neonatal and nephrology team as well as dietitian is key to meet the changing needs in this vulnerable population to ensure growth while maintaining metabolic control.

Fluid & Electrolyte Management - Infants with underlying renal disease can be either oliguric or polyuric depending the etiology and degree of renal impairment. Polyuria is often seen with dysplastic kidneys necessitating higher than normal fluid intake in order to prevent dehydration. Due to tubular dysfunction, sodium chloride and bicarbonate supplementation is frequently needed to maintain a positive sodium balance and correct acidosis. Base supplementation to correct acidosis can be provided via supplemental acetate in TPN or oral/enteral sodium citrate. Unlike neonates with age-appropriate kidney function who typically also require a positive potassium balance, those with CKD frequently require a potassium restricted formula (or EBM) and at times potassium binders to overcome hyperkalemia as many neonates with CKD are only able to tolerate ~ 1-1.5 meq/kg/day of potassium.

Table 10-5. KDIGO classification schemata for CKD for ages less than 2 years

Neonatal CKD Classification	Glomerular Filtration Rate
Normal GFR	GFR ≤ 1SD below the mean
Moderately reduced GFR	GFR > 1SD to ≤ 2SD below the mean
Severely reduced GFR	GFR > 2SD below the mean

Adapted from: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150

Table 10-6. Etiology of CKD/ESRD in neonate

Diagnosis	Incidence
Congenital Anomaly of Kidney and Urinary Tract (CAKUT) includes renal hypoplasia/dysplasia/ PUV/VUR/MCDK/ VACTERL	55%
Cystic kidney disease	13%
Congenital nephrotic syndrome (CNS)	6%
Renal cortical necrosis	11%

Adapted from: van Stralen KJ, et al; ESPN/ERA-EDTA registry; IPPN registry; ANZDATA registry; Japanese RRT registry. Survival and clinical outcomes of children starting renal replacement therapy in the neonatal period. Kidney Int. 2014 Jul;86(1):168-74. doi: 10.1038/ki.2013.561. Epub 2014 Feb 5. PMID: 24499775.

Table 10-7. Evaluation of neonatal CKD

Test	Utility/Assessment
Basic Metabolic Panel/chem 10	Renal function (BUN/Creatinine) & electrolyte imbalance
Renal bladder ultrasound	Structural anomaly and size of kidney
Voiding cystourethrogram (VCUG)	Obstruction (PUV/ureterocele) and VUR
Nuclear DMSA scan	Function and shape kidney
Nuclear MAG-3 scan	Obstruction of UVJ/UPJ
Genetic testing	ARPKD/nephronophthisis/CNS

Anemia - Anemia frequently is multifactorial in etiology. Decreased erythropoietin levels, iron deficiency, inflammation, blood loss due to frequent blood draws, and secondary hyperparathyroidism all contribute to anemia of CKD. Treatment includes erythropoietin stimulating agents (ESA) and iron supplementation in attempts to avoid frequent blood transfusions to reduce sensitization for future transplant and bone marrow suppression. Goal hemoglobin thresholds for blood transfusions vary in the neonatal period. ESA however are used to target Hgb 10-12 and are frequently initiated after the first 6-8 weeks of life.

Bone Mineral Homeostasis - Calcium and phosphorous supplement along with vitamin D is often needed. In infants with CKD on a low potassium formula or receiving dialysis, phosphorus supplementation is frequently initiated to maintain serum phosphorus 4.5-7. Vitamin D analogues like calcitriol and sometimes calcimimetics like cinacalcet are required for management of secondary hyperparathyroidism to promote normal bone growth.

Renal Replacement Therapy

Indications for initiation of renal replacement therapy in the neonatal period include electrolyte abnormalities, oliguria/fluid

overload, and poor growth unamenable to medical management. While transplant is the modality of choice for management of pediatric ESRD, an infant needs to be at least 8-10 kg and 75-80 cm for successful kidney graft placement. Options for chronic renal replacement therapy in the neonatal period include peritoneal dialysis and hemodialysis.

Peritoneal dialysis (PD) is the modality of choice for management of neonatal ESRD. PD requires placement of a PD catheter in the peritoneal cavity positioned in the pelvis by a pediatric surgeon skilled in access placement. On PD, nutritional goals need to be reassessed due to higher sodium and protein loss through PD ultrafiltrate. Adjustment in dialysate glucose concentration using commercially available dialysate bags and is often needed to maintain euvolemia and hemodynamic stability. Once at adequate fill volumes, infant can be transitioned to an automated cycler machine and begin preparations for caregiver training and home dialysis.

Hemodialysis (HD) is often required as a bridge to PD or as a long-term modality in select newborns. Despite significant advances in technology, hemodialysis, although feasible in neonates, remains challenging due to complication with vascular access placement, blood loss, hemodynamic instability, temperature dysregulation and need for more frequent dialysis.

Ethical consideration - CKD and ESRD management entails long term and multiple levels of complexity of care frequently with additional comorbidities including presence of non-renal congenital anomalies, neurocognitive delays, and pulmonary hypoplasia which can contribute to ethical distress and should be addressed with the families via ongoing support and a multidisciplinary team approach frequently including Renal, Neonatology and Palliative care.

10.3 Neonatal Hypertension

Definition

Defining a normative blood pressure in neonates is complex as the hemodynamic status of infants is influenced by birthweight, gestational age, postnatal age, and size for gestational age. Blood pressures at birth are influenced by all of these factors, with the smallest and most premature infants having the lowest blood pressures at birth. As demonstrated in **Table 10-8,** careful consideration must be given to all of these factors when defining a normal range of blood pressure in the neonate.
After approximately 2 weeks of life, the rapid hemodynamic changes that accompany the transition to postnatal life slow down, and normal blood pressure can be estimated by postmenstrual age as defined in **Table 10-9**. Hypertension is defined as repeated blood pressure measurements above the 95th percentile; repeated values above the 99th percentile are considered severe hypertension.

Intra-arterial monitoring is the gold standard for blood pressure measurement. However, automated oscillometric measurements can provide valuable clinical information if multiple measurements are trended over time, cuff size has a width to

Table 10-8. Change in systolic, diastolic, and mean blood pressure during the first month of life in infants classified by estimated gestational age[1]

Average BP <28 weeks

Postnatal Day of life	Systolic BP	Diastolic BP	Mean BP
1	42	26	31
2	43	27	33
3	44	28	34
4	45	31	36
5	46	33	37
6	47	34	38
7	49	35	41
30	62	42	48

Average BP 29-32 weeks

Postnatal Day of life	Systolic BP	Diastolic BP	Mean BP
1	48	32	37
2	51	34	40
3	53	35	42
4	55	36	44
5	57	37	45
6	58	38	46
7	59	40	47
30	71	47	56

Average BP 33-36 weeks

Postnatal Day of life	Systolic BP	Diastolic BP	Mean BP
1	56	36	44
2	57	37	45
3	59	38	46
4	61	40	47
5	62	40	48
6	64	41	49
7	65	41	49
30	73	50	56

Average BP >37 weeks

Postnatal Day of life	Systolic BP	Diastolic BP	Mean BP
1	63	40	47
2	64	41	48
3	65	42	50
4	66	43	51
5	67	44	52
6	70	45	53
7	71	46	54
30	76	50	59

[1]Adapted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature Pediatric Nephrology Pejovic, Bijana, Amira Peco-Antic, and Jelena Marinkovic-Eric. "Blood Pressure in Non-Critically Ill Preterm and Full-Term Neonates." Pediatric Nephrology 22.2 (2007): 249–257. ©2007.

Table 10-9. Systolic, mean and diastolic blood pressure for infants after 2 weeks of life postmenstrual age

Postmenstrual Age	Blood pressure	50th percentile	95th percentile	99th percentile
44 weeks	SBP	88	105	110
	MAP	63	80	85
	DBP	50	68	73
42 weeks	SBP	85	98	102
	MAP	62	76	81
	DBP	50	65	70
40 weeks	SBP	80	95	100
	MAP	60	75	80
	DBP	50	65	70
38 weeks	SBP	77	92	97
	MAP	59	74	79
	DBP	50	65	70
36 weeks	SBP	72	87	92
	MAP	57	72	77
	DBP	50	65	70
34 weeks	SBP	70	85	90
	MAP	50	65	70
	DBP	40	55	60
32 weeks	SBP	68	83	88
	MAP	49	64	69
	DBP	40	55	60
30 weeks	SBP	65	80	85
	MAP	48	63	68
	DBP	40	55	60
28 weeks	SBP	60	75	80
	MAP	45	58	63
	DBP	38	50	54
26 weeks	SBP	55	72	77
	MAP	38	57	63
	DBP	30	50	56

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arm circumference ratio in the range of 0.45–0.55, and users of automated blood pressure devices are familiar with the limitations of their own equipment as it may vary between manufacturers. When using an oscillometric device in the evaluation of a potentially hypertensive neonate, readings are most reliable if taken under the following conditions: patient can be prone or supine, after placing cuff wait 15 minutes prior to taking measurement, take measurement 1.5 hours after feeding or after an intervention/procedure, take while infant is asleep or quietly awake, measure on the upper right extremity, and take three readings at two minute intervals.

Etiologies

There are many potential etiologies of neonatal hypertension. When evaluating a neonate for hypertension, careful consideration must be given to both the neonatal and maternal past medical history. Factors including maternal hypertension and maternal medication history, neonatal medication history, history of neonatal intra-arterial catheter placement are among the many important considerations in evaluating potential etiologies of neonatal hypertension. The three most common causes of neonatal hypertension are umbilical artery thrombi, bronchopulmonary dysplasia, and coarctation of the aorta. There are numerous other etiologies for hypertension in the neonate which are outlined in **Table 10-10.**

Signs and Symptoms

With mild blood pressure elevation, the infant is often asymptomatic. Hypertension is most often detected on routine monitoring. However, cases of symptomatic hypertension often present concurrently with signs of other serious medical conditions including apnea, increased tone, tachypnea, tachycardia, cyanosis, mottling, lethargy, vomiting, irritability, abdominal distension, failure to thrive, and feeding intolerance. Life-threatening complications of neonatal hypertension include cardiovascular collapse from cardiogenic shock, congestive heart failure, and neonatal seizures. In cases of primary renal disease, signs of significant hypertensive disease include hematuria and hypertensive retinopathy.

Diagnosis

Multiple accurate and reliable blood pressures obtained over time exceeding the 95th percentile blood pressure for the infant's post-menstrual age are necessary to diagnose hypertension in an infant, which can be especially challenging when using an oscillometric device. Crying, feeding, and even non-nutritive sucking have all been demonstrated to contribute to elevated blood pressures in infants. When elevated blood pressure is first noted, the infant's activity must be observed and documented at the time of the measurement. When using oscillometric devices, blood pressure should be measured with a proper sized cuff, and the infant should be allowed to rest 15 minutes after placement of the cuff. The measurement should be in the right upper extremity while the infant is lying down ≥ 1.5 hours after a procedure or a feed. In general, the more severe the blood pressure, the fewer measurements needed to confirm the diagnosis.

Imperative to the diagnosis of hypertension is identifying an underlying cause or etiology of the hypertension starting with the history and physical examination. The prenatal and perinatal history should be reviewed for pregnancy complications, maternal hypertension, maternal medications, delivery events, neonatal history including medications and umbilical arterial line history, and conditions or syndromes associated with hypertension, e.g. Williams syndrome.

On physical exam, four-extremity blood pressures should be obtained to evaluate for coarctation of the aorta, but an echocardiogram is required to confirm the diagnosis. The infant should be examined for dysmorphic features, neurologic findings, hypertensive retinopathy, congestive heart failure, abdominal bruits, and abdominal masses suggesting renal pathology.

Laboratory evaluation and imaging studies should be guided by the history and physical exam, but often includes urinalysis, electrolytes, BUN, creatinine and a renal ultrasound. Doppler flow studies on the renal ultrasound are helpful to evaluate the renal vessels, but if there is a high index of suspicion for renal artery stenosis, a negative result should be followed up with a CT angiogram or MR angiogram. Further studies can include thyroid studies, aldosterone, cortisol, and renin. An echocardiogram is important to evaluate for coarctation of the aorta and for potential complications from hypertension (such as depressed cardiac function). See **Table 10-11** for additional studies to consider.

Management

Treatment of hypertension in the infant should be directed towards correcting the underlying cause. However, in cases of severe

Table 10-10. Etiologies for Hypertension in the Neonate

Neurologic	Cardiovascular	Pulmonary	Adrenal
• Intraventricular hemorrhage • Subdural hematoma • Pain • Cushing's disease • Neonatal seizures • Birth asphyxia • Hyperthyroidism • Neural crest tumor • Cerebral angiomas • Familial dysautonomia	• Post-PDA ligation • Ductal aneurysm • Coarctation of the aorta • Umbilical artery catheterization	• Bronchopulmonary dysplasia • Chronic lung disease • Pneumothorax • Congenital neuroblastoma of the lungs	• Congenital adrenal hyperplasia • Primary hyperaldosteronism • Pseudohypoaldosteronism type II • Adrenal tumors • Adrenal hemorrhage • Pheochromocytoma
Renal Parenchymal Disease	**Reno-Vascular Disease**	**Acquired Renal Conditions**	**Medications**
• Obstructive uropathy • Congenital malformations • Polycystic kidney disease • Multicystic-dysplastic kidney disease • Tuberous sclerosis • Ureteropelvic junction obstruction • Unilateral renal hypoplasia • Congenital nephrotic syndrome • Glomerulonephritis • Pyelonephritis • Wilms tumor • Mesoblastic nephroma • Parenchymal Renal Tumors	• Renal artery thrombosis • Renal vein thrombosis • Renal artery stenosis • Thromboembolism • Idiopathic arterial calcification • Renal artery compression	• Acute tubular necrosis • Cortical necrosis • Obstruction (stones) • Hemolytic uremic syndrome • Interstitial nephritis	• Hypercalcemia • Fluid overload • TPN • Maternal drug exposure (e.g. Cocaine, Heroin) • Vitamin D toxicity • Neonatal steroid administration • Inotropes • Methylxanthine/ • Theophylline

Table 10-11. Diagnostic testing in neonatal hypertension

Routine studies	Additional studies, if needed
• Urinalysis +/- culture • CBC with platelet count • Electrolytes • BUN, creatinine • Chest x-ray • Renal ultrasound with Doppler	• Thyroid studies • Aldosterone • Renin • Cortisol • Urine VMA/HVA • Echocardiogram • Abdominal/ pelvic ultrasound • VCUG • Arteriogram • Renal angiography • Nuclear scan (DTPA/MAG3)

BUN blood urea nitrogen, CBC complete blood count, HVA homovanillic acid, VMA vanillylmandelic acid, DTPA diethylene triamine pentaacetic acid, MAG3 mercaptoacetyltriglycerine

hypertension, initiation of antihypertensive medication may be required prior to completing the diagnostic evaluation.

Continuous intravenous (IV) infusion of antihypertensive medication is recommended in infants with acute severe hypertension. The continuous infusion allows for close titration of the medication to prevent rapid reduction in blood pressure which could result in cerebral ischemia and hemorrhage. Premature infants may be particularly susceptible to the consequences of rapid reduction in blood pressure due to periventricular circulation immaturity. When using continuous IV antihypertensive therapy, blood pressure should be closely monitored either via arterial catheter or frequent cuff measurements to allow for appropriate dose titration. Intermittent IV antihypertensive medications, such as hydralazine or labetalol, can be used in infants with mild to moderate hypertension especially when oral medications are not an option. **(Table 10-12)**

For the asymptomatic infant, oral medications can be used as first line agents. When choosing the type of agent, the underlying cause of hypertension and other co-morbidities should be taken under consideration. For example, beta blockers should be avoided in a patient with chronic lung disease. However, diuretics may be beneficial to those patients with chronic lung disease to not only control blood pressure but also improve their pulmonary status. Calcium channel blockers such as amlodipine are generally safe first line medications for

oral treatment of hypertension. Angiotensin converting enzyme inhibitors (ACEi) use in neonates is controversial because of the potential effect on nephrogenesis. Nephrogenesis is complete around 34-36 weeks of gestation but nephron maturation continues. Therefore, the use of ACEi is usually reserved for infants > 44 weeks corrected post-menstrual age. **See Table 10-12** for a list of antihypertensive medications.

Rarely, a procedural intervention is required for treatment of hypertension if medical management alone is not successful or in cases of aortic coarctation or severe renal artery stenosis. Endovascular intervention for renal artery stenosis may be prohibited by the size of the infant, and a multi-disciplinary approach to those patients is necessary. Rarely, nephrectomy could be considered in those patients.

10.4 Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

Introduction

The CAKUT represent a heterogeneous and wide range of disorders involving the kidney and the collecting system. The pathogenesis is likely to be multifactorial involving both environmental exposure (maternal diabetes, antibiotics, ACE inhibitors etc.) and genetics. Early recognition during the neonatal period is important for prognosis.

Incidence

CAKUT are among the most common fetal anomalies ranging from 20-30% of all the fetal genetic abnormalities in the antenatal period. CAKUT represents ~30-50% of the etiology of pediatric chronic kidney disease and 25% of end stage renal disease in adults.

Renal Parenchyma Malformations

Definitions and Presentation (Fig 10-1)

Agenesis - defined as failure of kidney to develop, it may happen bilaterally or unilaterally. Invariably fetuses who have bilateral agenesis have poor prognosis and generally demonstrate Potter Sequence facies as a result of oligohydramnios or anhydramnios during pregnancy. Most patients are born with severe lung hypoplasia and most patients will die in the first 24 hours postnatally. Unilateral renal agenesis may result in compensatory hypertrophy of the

Table 10-12. Selected medications for treatment of neonatal hypertension

Drug	Class	Route	Dose	Comments
Severe, symptomatic hypertension				
Nicardipine	calcium channel blocker	IV Infusion	0.5 - 5 mcg/kg/min	usually requires a large volume of infusion
Labetalol	alpha and beta Blocker	IV Infusion	0.25 - 3 mg/kg/hr	use with caution in patients with BPD or heart failure
		IV bolus	0.2 - 1 mg/kg/dose q 4-6 hrs	
Sodium nitroprusside	direct vasodilator	IV infusion	0.5 - 10 mcg/kg/min	potential for thiocyanate toxicity with prolonged use (> 72 hrs) or in renal failure
Hydralazine	direct vasodilator	IV bolus	0.25 - 1 mg/kg/dose q 4-6 hrs	
Asymptomatic hypertension				
Amlodipine	calcium channel blocker	Oral	0.05 - 0.3 mg/kg/day divided BID	may cause reflex tachycardia or peripheral edema
Propranolol	beta blocker	Oral	0.25 - 1 mg/kg/dose q 8 hrs; Max 8 - 10 mg/kg/DAY	avoid in BPD, monitor heart rate; commercially prepared oral solution available
Labetalol	alpha and beta blocker	Oral	0.5 - 1 mg/kg/dose BID-TID; Max 10 mg/kg/DAY	avoid in heart failure and BPD
Hydralazine	direct vasodilator	Oral	0.25 - 1 mg/kg/dose q 6 - 8hrs; Max 7 mg/kg/DAY	may cause tachycardia
Lisinopril	ACE inhibitor	Oral	0.07 - 0.6 mg/kg/day divided QD-BID	monitor serum creatinine and potassium; avoid use until at least 44 weeks corrected post-menstrual age
Enalapril	ACE inhibitor	Oral	0.08 - 0.6 mg/kg/day divided QD-BID	monitor serum creatinine and potassium; avoid use until at least 44 weeks corrected post-menstrual age
Captopril	ACE inhibitor	Oral	< 3months: 0.01 - 0.5 mg/kg/dose TID; Max 2 mg/kg/DAY; > 3months 0.15 - 0.3 mg/kd/dose TID; Max 6 mg/kg/DAY	first dose may cause drop in BP; monitor serum creatinine and potassium; avoid use until at least 44 weeks corrected post-menstrual age
Clonidine	central alpha agonist	Oral	5 - 10 mcg/kg/day TID; Max 25 mcg/kg/day	may cause mild sedation

Figure 10-1: Schematic description of parenchymal kidney malformations

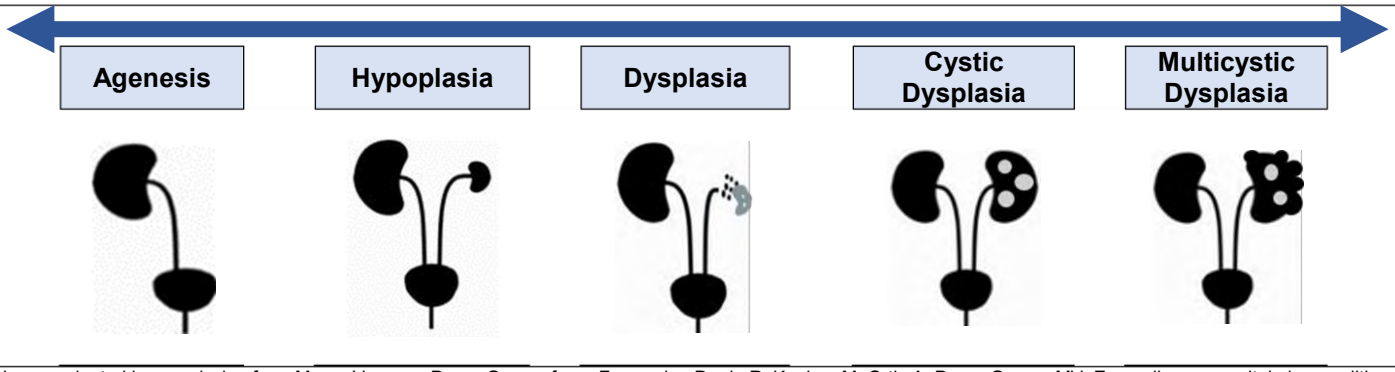

Image adapted by permission from Marua Vanessa Perez-Gomez from: Fernandez-Prado R, Kanbay M, Ortiz A, Perez-Gomez MV. Expanding congenital abnormalities of the kidney and urinary tract (CAKUT) genetics: basonuclin 2 (BNC2) and lower urinary tract obstruction. Ann Transl Med 2019;7(Suppl 6):S226. *doi: 10.21037/atm.2019.08.73.* ***Auda Plaud Gonzalez, 2020***

contralateral kidney and can be associated with ipsilateral malformations of the reproductive tract.

Hypoplasia-refers to small kidneys with reduced number of functional-normal nephrons due to reduced branching morphogenesis. Histologically, it may demonstrate oligomeganephronia because of the associated enlargement and compensation of the available functioning units and secondary glomerulosclerosis. The diagnosis is made presumptively based on appearance on renal US and clinical normal renal function. These patients may be at higher risk of developing Chronic Kidney Disease in their lifetime due to a decreased number of nephrons

Dysplasia/Cystic Dysplasia - contrary to hypoplasia, this refers to malformed kidney tissue elements in a disorganized manner. It can be caused by primarily branching morphogenesis defects or secondary to vesicoureteral reflux (VUR). If bilateral dysplasia exists, it may be suspected with history of oligohydramnios in pregnancy or may be identified incidentally when screening patients with dysmorphic phenotypes. Most of the times, it is incompatible with life. Dysplasia can also occur in the entire kidney or a portion of the kidney and can also be associated with defects in the contralateral kidney (50-70%)

Multicystic Dysplasia - is a form of severe renal dysplasia, involving several non-communicating cysts **without functional parenchyma**. 25% of the time the contralateral kidney is found to have VUR. Prognosis is similar to patients with solitary kidneys.

- **Approach and post-natal evaluation-** This will depend on the degree of the anomaly. If the patient has a solitary kidney (unilateral renal agenesis, unilateral multicystic dysplastic) or **unilateral anomaly**, based on prenatal evaluation, then a repeat post-natal renal US is indicated to confirm the diagnosis. This may be done **after the first 48 hours of life, typically within the first week or prior to discharge** (Grade 1C, strong recommendation). If the anomaly involves **both kidneys,** then a renal US should be done during the **first 24-48 hours.** (Grade 1C, strong recommendation). Further imaging will depend on initial renal US. Renal function should be assessed by checking serum creatinine and BUN after the first 24hors. Patients will need consultation with renal specialists and may need to have nutrition adjustment based on renal clearance, potentially diet restrictions if needed in conjunction with Renal Service Dietician.

Urinary Collecting System Anomalies (Figs. 10-2 and 10-3)

Hydronephrosis - Refers to the dilatation of the renal pelvis and calyces of varying degrees due to stagnation of urine or reflux. It is commonly diagnosed prenatally during fetal imaging (US, MRI), 1-5% of all pregnancies. Hydronephrosis

Figure 10-2: Schematic description of urinary collecting system anomalies

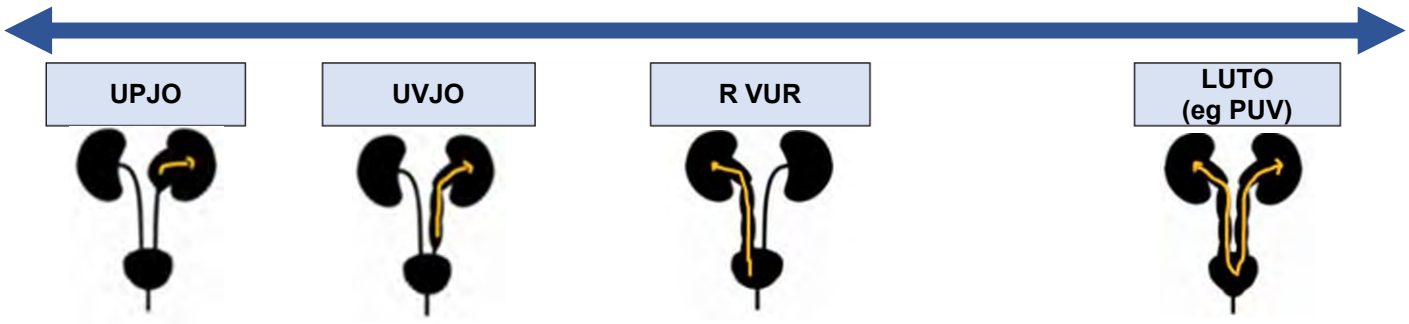

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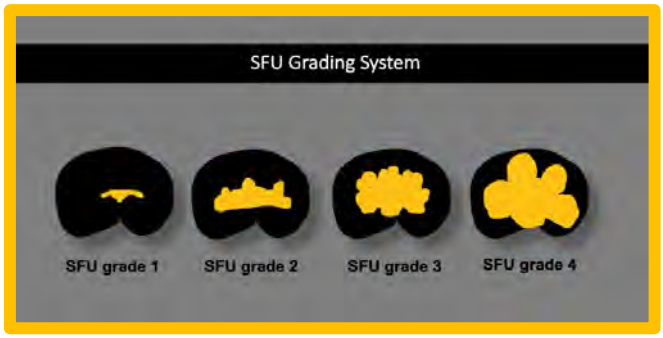
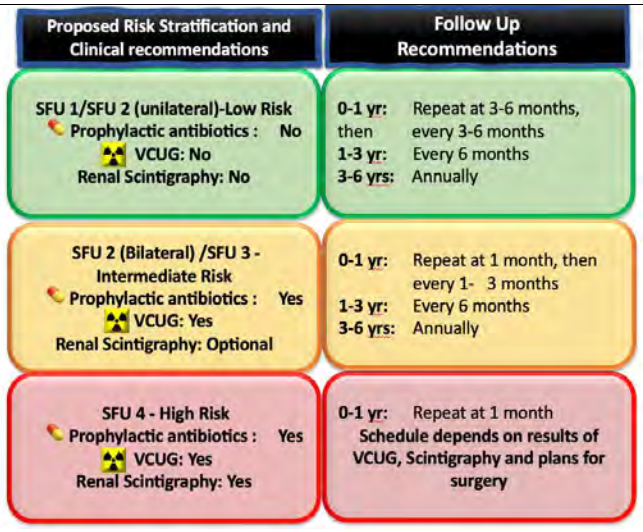
Figure 10-3. Hydronephrosis classification



Adapted by permssion from Springer Nature Customer Service Centre GmbH: Nature Reviews Neurology in Timberlake MD, Herndon CD. Mild to moderate postnatal hydronephrosis--grading systems and management. ©2013. ***Auda Plaud Gonzalez, 2020***



Adapted from: Nguyen HT, Herndon CD, Cooper C, Gatti J, Kirsch A, Kokorowski P, Lee R, Perez-Brayfield M, Metcalfe P, Yerkes E, Cendron M, Campbell JB. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol. 2010 Jun;6(3):212-31. doi: 10.1016/j.jpurol. 2010.02.205. Epub 2010 Apr 15. PMID: 20399145. ***Auda Plaud Gonzalez, 2020.***

reflects a spectrum of disease that includes cases with physiological transient findings to potentially surgical emergencies in the early neonatal period. Bilaterally findings suggest more severe pathologies. In short, it is important to establish the diagnosis in order to intervene in a timely manner to prevent complications associated with it, including increased risk of urinary tract infection (UTI) and damage to the renal parenchyma and nephropathy by persistent obstruction.

- **Transient physiological -** the majority of patients, up to 44-88%, with antenatal hydronephrosis ultimately resolve. This may be due to early immature anatomy as narrowing of the ureteropelvic junction or natural kinks and folds that occur early in the development that resolve as the patient matures.
- **Vesicoureteral Reflux (VUR)-** defined as the retrograde flow of urine from bladder to the ureter. Clinical presentation is within a spectrum of varying degrees of hydro-ureteronephosis, ~10-20% of antenatal hydronephrosis may be secondary to VUR. This may be due to inadequate closure of the ureterovesical junction which happens as a normal anti-reflux mechanism when bladder contracts and the ureteral bladder segment is closed during voiding by the bladder muscles. It is important to note that a normal postnatal US does not exclude entirely the possibility. It can be diagnosed by retrograde flow of radiopaque contrast during a voiding cystourethrogram (VCUG). VUR can be associated with UTI.
- **Ureteropelvic Junction Obstruction (UPJO) -** refers to pelvicalyceal dilatation in the absence of ureteral dilatation due to an intrinsic narrowing at the ureteropelvic junction. It happens 1:500 of live births, most commonly occurs as a unilateral defect, usually partial obstruction. Only ~20-25% require surgical intervention.
- **Ureterovesical Junction (UVJO) -** is the site where the ureter enters the bladder. This back pressure can result in hydroureter, and then hydronephrosis. This may be secondary to a megaureter, which may represent an abnormality at the distal ureter with formation of an aperistaltic segment or secondary to abnormalities in insertion of ureter.
- **Bladder outlet obstruction (Posterior Urethral Valves [PUV], Urethral strictures) -** PUV Refers to a congenital blockage of the male posterior prostatic urethra due persistent urogenital membranous folds. The incidence is ~1/5000-8000 male births and is about 10% of antenatal hydronephrosis. Typically, these patients present with bilateral hydroureteronephrosis, thickened walled bladder and varying degrees of renal parenchyma abnormalities, which may lead to varying degrees of renal dysfunction. On the US, the "keyhole" sign in the bladder neck tends to be pathognomonic.

  Urethral stenosis/atresia refers to varying degrees of obstruction at the level of the urethra which may lead to a similar phenotype as PUVs and may require initial surgery or bladder catheterization initially to allow for decompression.

Approach and Post-Natal Evaluation

Although no absolute consensus exists as to the best way to approach the patient with antenatal hydronephrosis, there are some general principles to management.

- Severe antenatal hydronephrosis or bilateral hydronephrosis, evaluation with postnatal US must be early after birth, within 24-48 hours due to risk of obstruction that may need further intervention (Grade 1C). The Society of Fetal Urology has proposed a postnatal evaluation algorithm based on stratification for risk of renal deterioration, infection or need for surgery and clinical management accordingly.
  - **Bilateral Hydroureteronephrosis-** may represent a lower urinary tract obstruction, such as PUV, therefore initial Foley catheter placement to drain bladder is the first step. This may be done in consultation with Urology. Blood chemistries must be done at least daily to monitor for possible electrolyte derangements such as hyperkalemia. These patients are at risk of tubular dysfunction given longstanding obstruction and tubular damage; this may manifest as polyuria with renal salt wasting.

Figure 10-4: Schematic description of position defects anomalies

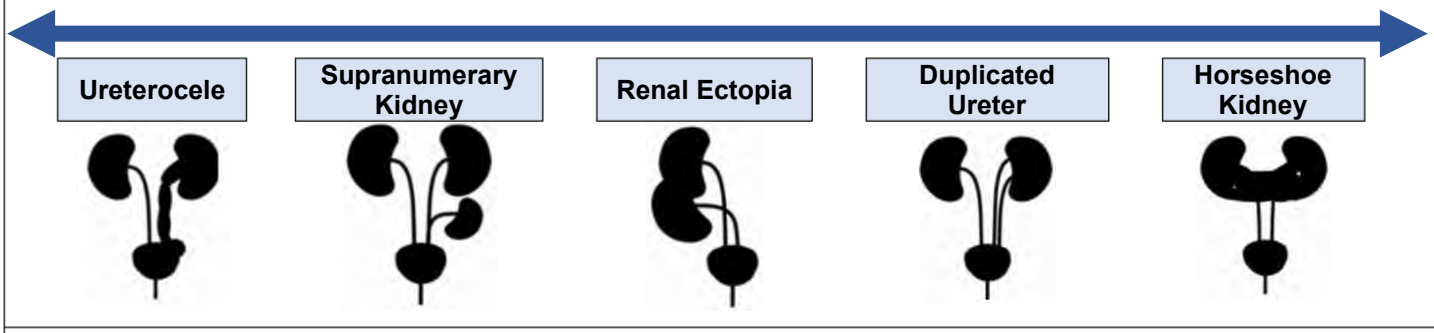


Image adapted with permission by Maria Vanessa Perez-Gomez from: Expanding congenital abnormalities of the kidney and urinary tract (CAKUT) genetics: basonuclin 2 (BNC2) and lower urinary tract obstruction. Ann Transl Med 2019;7(Suppl 6):S226. doi: 10.21037/atm.2019.08.73. ***Auda Plaud Gonzalez, 2020***

Position Defects (Fig 10-4)

Duplication or Supernumerary Kidneys- these refer to the existence of >2 kidneys, usually associated with own collecting system, vasculature and encapsulated renal parenchyma. These are very rare, with <100 cases reported in the literature. May be associated with ectopic ureters draining to different structures such as vagina.

Horseshoe Kidney- These refers to the fusion of renal parenchyma that leads to abnormal ascent of the kidneys to a more superior position. Typically, parenchyma is normal, but there may be associated reflux or obstruction. It is the most common fusion anomaly (1/400)

Crossed Fused Ectopia- in contrast to a horseshoe kidney, refers to a kidney that has crossed the midline and fused to the contralateral kidney, it is less common.

- This is second most common position anomaly (1/2000), the kidney has crossed the midline and fused with the contralateral kidney. The crossed kidney is usually smaller compared with the orthotopic kidney.

Malrotation- Refers to abnormal rotation along the long axis with the hilum often facing anteriorly with an incidence rate 1/500.

Ureterocele, ectopic ureter and duplicated ureter-the ureterocele is a saccular dilatation of the terminal segment of the ureter inside the bladder, these may cause obstruction at the insertion site. Normally the ureter inserts at the bladder trigone, which prevents kinking and obstruction. An ectopic ureter may be inserted at any point in the urinary tract and even at other organs such as ureter or vagina. Duplicated ureters may occur as spectrum ranging from a complete duplication where both ureters drain into the bladder or partial duplication draining at varying points with only one ureter draining the bladder, these are more common in females than males (2-4:1). These may lead to obstruction and or VUR and therefore may be at risk for UTI.

Approach and Post-Natal Evaluation

Similar to previous pathologies, if there is an abnormality on the antenatal US, the postnatal evaluation should include a renal US in the first week, or prior to discharge from the hospital to confirm the diagnosis and to evaluate for potential obstruction. Further evaluation will depend on the findings of the initial evaluation. If there is concern for hydronephrosis or is there is development of UTI, then a VCUG should be performed (Grade 1C, strong recommendation).

10.5 Genetic Renal Disorders

Polycystic Kidney Disease

Definition

Presence of cysts in the kidney. Autosomal recessive polycystic kidney disease (ARPKD) is commonly seen in the neonatal period with enlarged echogenic kidneys, hypertension, and renal dysfunction. ARPKD is a congenital hepatorenal fibrocystic syndrome which can cause significant renal and liver-related morbidity and mortality in children. ARPKD may result in oligohydramnios and pulmonary hypoplasia. Thirty percent of the affected patients will die in neonatal period or within the first year of life due to respiratory insufficiency. Long term survival of these infants has improved to greater than 80% with neonatal respiratory support and renal replacement therapies.

Incidence

The incidence of ARPKD is estimated at 1:10,000 to 1:40,000 live births.

Diagnosis

Antenatal diagnosis - A presumptive diagnosis of ARPKD after 24 weeks GA is based on the presence of characteristic findings of markedly enlarged echogenic kidneys with poor corticomedullary differentiation along with oligo or anhydramios. It is unusual to see discrete large renal cysts on prenatal imaging (>10mm) in ARPKD. When discrete cysts are noted, other differential diagnoses such as dominant polycystic kidney disease and multicystic dysplasia should be considered.

Family history - As ARPKD is inherited in a recessive fashion, the parents of an infant suspected to have ARPKD are heterozygous carriers of a pathogenic variant and as a result without disease. It is important for parents of a child with suspected ARPKD to undergo renal ultrasound to exclude renal cysts. Presence of renal cysts would suggest diagnosis of dominant polycystic kidney disease.

Postnatal diagnosis - Neonatal presentation of severe ARPKD is oligohydramnios, massively enlarged kidneys, respiratory distress, and impaired kidney function. Neonates with severe ARPKD could rapidly progress to end-stage renal disease in their childhood. An abdominal US is recommended for evaluation of kidneys and liver, if not conclusive MRI or CT.

Characteristics of abdominal US in ARPKD include large echogenic kidneys with poor corticomedullary differentiation and coexisting liver disease. Liver US findings include hepatomegaly, increase echogenicity and dilation of peripheral intrahepatic ducts and main bile ducts. Infants often have severe respiratory distress owing to underlying pulmonary hypoplasia. The marked renal enlargement can contribute to respiratory distress and feeding difficulty. These infants have significant renal dysfunction after birth and are at risk for acute kidney injury, electrolyte abnormalities such as hyponatremia and hypertension.

Molecular confirmation - molecular confirmation should be sought by performing genetic testing for *PKHD1* and rarely *DZIP1L*

Management

Requires initial stabilizing respiratory function by mechanical ventilation and the possible need for bilateral or unilateral nephrectomy if massive kidney enlargement impaired diaphragmatic excursion. The amount of urine that neonate makes (oliguria or anuria) dictates whether peritoneal dialysis is required within first day of life. These patients are often at risk for acute kidney injury and hypertension which needs monitoring and treatment. Treatment of biliary dysfunction is focused on malabsorption of nutrients and fat-soluble vitamins and the risk of ascending cholangitis. Administration of synthetic bile acids and early recognition and treatment of ascending cholangitis. Patients may require portosystemic shunting and/or consideration of liver transplant. Patients with end stage renal disease (ESRD) and severe portal hypertension may be candidate for dual renal and liver transplantation.

Congenital Nephrotic Syndrome

Definition

The presence of nephrotic syndrome at birth or within first three months of life. It is characterized by nephrotic range proteinuria (typically more than 2000 mg/L), hypoalbuminemia (serum albumin concentration less than 2.5 g/dL), edema, and hyperlipidemia

Incidence

The incidence of congenital nephrotic syndrome (CNS) is 1 to 3 per 100,000 children. Congenital nephrotic syndrome begins in infancy and usually leads to end-stage renal disease by childhood.

Etiology

Congenital nephrotic syndrome in children less than 3 month of age can be either due to genetic or non- genetic causes.

Genetic causes - Almost 80% of CNS have a monogenic cause for their disease. The genetic mutations are in proteins that regulate the glomerular filtration barrier.

Secondary/non-genetic causes - Infantile lupus, congenital syphilis, congenital toxoplasmosis, membranous nephropathy or idiopathic nephrotic syndrome are less common causes of congenital nephrotic syndrome.

Clinical Features

Antenatal/Perinatal presentation - Prenatal diagnosis of CNS is suggested by elevated maternal serum α-fetoprotein (MSAFP) obtained in routine second-trimester screening.

Postnatal presentation - Generalized edema develops within the first week of life in 70-80% of infants. In addition, owing to protein losses they are prone to recurrent infection, poor weight gain and thromboembolism which can be a presenting feature.

Diagnosis

- Assessment of quantitative measurement of protein excretion based upon a timed 24-hour urine collection. Typically, infants with CNS will have >2000 mg/L of urine protein in 24 hr. period.
- Blood tests: electrolytes, creatinine, blood urea nitrogen, cholesterol, albumin and complement C3. Severe hypoalbuminemia is common [<1.5 g/dl].
- Renal imaging by ultrasound- typically show enlarged, echogenic kidneys with poor corticomedullary differentiation.
- Evaluation for secondary causes such as congenital infections to rule out treatable causes of nephrotic syndrome.
- Genetic testing is indicated to detect monogenic causes.
- They are risk for hypogammaglobinemia, hypothyroidism and hypercoagulable state owing to urinary protein losses so will need lab monitoring and evaluation of these as indicated.

Management

Consultation with the Renal Service early in the management of these patients is strongly encouraged. The genetic forms of congenital nephrotic syndrome are typically resistant to immunosuppression including steroids. In patients with persistent proteinuria, salt and fluid restriction, and diuretics alone or in combination with daily intravenous 25% albumin are needed to control edema and maintain serum albumin above 2.5 g/dl. Infants are on a high calorie and high protein diet and often require thyroid supplements to treat hypothyroidism. In addition, proteinuria is managed medically with addition of an ACE inhibitor and/or indomethacin.

Eventually, most of these children undergo unilateral/bilateral nephrectomies in early childhood and transition to renal replacement therapy until they are old enough to undergo renal transplantation.

10.6 Nephrocalcinosis

Definition

Nephrocalcinosis (NC) is defined as the deposition of calcium, either as calcium phosphate or calcium oxalate, within the interstitium of the kidney.

Incidence

Reported as low as 7% to as high as 64% of premature infants with gestation ages younger than 32 weeks or birthweights less than 1.5 kg.

Presentation

Newborn infants with NC are mostly asymptomatic and NC is an incidental finding when imaging is performed for other reasons. Renal radiographs and renal US are sufficient to diagnose NC. Renal US may also obtained when NC is suspected on high risk patients, such as very low birth infants,

microscopic or gross hematuria, patients on chronic loop diuretic therapy, patients with bronchopulmonary dysplasia.

Etiology

Medullary NC is a consequence of hypercalciuria. Increased urinary calcium load arises either through increased calcium absorption (extra-renal causes) or impaired calcium reabsorption within the renal tubule. In neonates, especially preterm and small for gestation infants their immature renal tubules manifest impaired calcium reabsorption and calcium wasting. Paracellular absorption of calcium in the thick ascending limb is dependent on the sodium reabsorption via the furosemide sensitive NKCC2 cotransporter and chronic use of furosemide in premature infants with bronco-pulmonary dysplasia put them at risk for hypercalciuria and NC.

Acidosis is a risk factor for NC especially in premature infants. Only unbound calcium or calcium salts are filtered by the glomerulus. Binding of calcium is pH dependent, and acidosis decreases bound calcium increasing the filtered calcium load. Acidosis may also stimulate calcium release from bone to act as a buffer. Finally, acidosis may decrease urinary citrate (a stone inhibitor) excretion.

Other causes of increased calcium excretion in neonates include: the use of glucocorticoids, caffeine/theophylline, supplementation of vitamin D, calcium and or sodium supplementation. Finally, there are genetic conditions that may feature NC due to hypercalciuria within their clinical phenotype. Monogenic causes of NC should be considered in term infants with NC and also in premature infants when risk factors described above are not present

Diagnosis

Laboratory Studies

- Serum creatinine, electrolytes, calcium, magnesium, phosphate
- If hypercalcemia: check 25 (OH) Vit D, 1, 25 (OH)2 vitamin D and parathyroid hormone level
- Urinary calcium/Creatinine ratio (normal value in infant < 6 months: <0.8 mg/mg);

Urine pH and urine electrolytes to calculate anion gap

- Urinary oxalate levels and plasma oxalate
- Other work up as indicated if any monogenic causes suspected

Options for Management

Assess modifiable factors:

- If related to loop diuretics: Consider reducing dose as much as possible and or consider discontinuation. If not possible to discontinue consider the combination of loop diuretics with thiazides
- Dietary intake of calcium and phosphate should be reduced specially TPN dependent infants

Treatment for specific disorders in consultation with Nephrology:

- Distal RTA should be treated with alkali therapy:
- William Beuren syndrome: Restricting calcium as well as increase fluid intake
- Thiazide diuretics should be considered for hypercalciuria as indicated.

Follow up and Outcome

Neonatal NC should be followed up in 1-2 months by repeating renal US and assess progression of NC. Urolithiasis is rarely found in former preterm infants at least in short term follow up in 1-2 years. Most cases associated due to prolonged loop diuretics resolve with time after discontinuation of diuretics. Cases due to genetic form or secondary to tubulopathies should be monitored periodically for progression of NC and if untreated will progress to chronic kidney disease and in some instances to ESRD.

10.7 Renal Tubular Acidosis

Definition

Renal Tubular Acidosis (RTA) refers to a group of disorders characterized by normal anion gap, hyperchloremic metabolic acidosis without impairment in glomerular filtration. It is either due to inherited or acquired defect that affects the kidney's ability to reabsorb bicarbonate or excrete acid.

Pathophysiology

The pulmonary and renal buffer systems tightly regulate acid-base balance. In the kidney the tubules are in charge of this regulation. The glomerulus freely filters bicarbonate (HCO_3^-), and up to 80% is reabsorbed in the proximal tubule (by secretion of protons by Na^+/H^+ exchangers and proton pumps). The next 15% is absorbed in the thick ascending loop of Hele and the rest in the distal tubule. The distal tubules are responsible for acid secretion (H^+) via the production of ammonia and titratable acids that are hydrogen bond to sulfuric and phosphoric acid.

In the extreme premature neonates, the bicarbonate reabsorption threshold is as low as 14 mEq/L, whereas, in the preterm infant, it is around 18mEq/L, and around 21mEq/L in the term infant. The lower bicarbonate levels are due to immature Na^+/H^+ exchanger, H^+ ATPase, Na-K ATPase and carbonic anhydrase type 4. As such, the more premature the infant, the more HCO_3^- is wasted in the urine, contributing to lower serum bicarbonate and metabolic acidosis. With time, all patients with transient RTA will achieve tubular maturity and correction of acidosis.

Incidence

Inherited forms of RTA are extremely rare in the pediatric population. The most common cause of acquired normal anion gap, hyperchloremic metabolic acidosis is diarrhea. In neonates, owing to physiologic immaturity of renal tubules, they have decreased ability reabsorb HCO3 and excrete acid which leads to a transient metabolic acidosis. This improves with time as most infants can acidify their urine by six weeks of age.

There is limited data on the prevalence of transient RTA in the preterm population. However, in Japan, a retrospective chart review found that 80% of preterm infants born less than 30 weeks developed transient RTA within the first seven days of life.

Types of RTA

RTA can be distinguished based on clinical and pathophysiological into three types: Type I (Distal), Type II

Table 10-13. Types of renal tubular acidosis

	Type 1 Distal RTA	Type 2 Proximal	Type 4
Pathophysiology	Impaired H^+ excretion in distal tubule (decrease H+ ATPase)	HCO_3- wasting in proximal tubule	Impaired H+ & K+ excretion in distal tubule due to Aldosterone deficiency or resistance
Serum HCO_3	Low (<10mEq/L)	Low-normal (10-20mEq/L)	Almost normal (18-22mEq/L)
Metabolic acidosis	Severe	Acid base balance but lower set point.	Mild. Hyperkalemia
Potassium	Low – Urine losses	Low-normal	High
Urine pH	Alkaline > 5.3	Acidic	Acidic <5.5
Hypercalcemia/ Nephrocalcinosis	Present	No	No
Bone disease	Yes - Rickets	Yes	No
Other findings	Hearing loss (AR) Renal stones	Can have global proximal tubule dysfunction (wasting Na, K, Phos, glucose, protein)	
Causes	Primary • Inherited o AR mutation in H + ATPase pump on the alpha-intercalated cell associated with sensorineural hearing loss. o AD: not associated with hearing loss. Sickle cell disease. Ehlers Danlos Sd. • Drugs o Amphotericin o ifosfamide o NSAIDs o Foscarnet o lithium	Primary • Diseases causing Fanconi syndrome: o Cystinosis o Tyrosinemia o galactosemia o Lowe's syndrome o Wilson Syndrome • Drugs o gentamycin o tetracyclines o ifosfamide o acetazolamide	Aldosterone deficiency/resistance: • Congenital adrenal hyperplasia • Addison disease • Adrenal insufficiency • Urinary obstruction • UTI • pseudo-hypoaldosteronism type I and II • fetal alcohol syndrome Drugs: • ACEI • NSAIDs • Ketoconazole • spironolactone

(Proximal), and Type IV (Hyperkalemic). Previously, a fourth type of RTA, RTA Type 3, a combination of Type 1 and 2 was described that after long-term follow-up showed improvement in urinary loss of bicarbonate; it is now considered a Type I RTA. All RTAs have normal anion gap hyperchloremic metabolic acidosis. Clinical symptoms are unspecific, vomiting, polyuria, dehydration, lethargy and FTT are the most common symptoms.

Diagnosis

RTA is diagnosed by a normal anion gap metabolic acidosis in the presence of normal renal function and no diarrhea. Anion Gap is calculated as $Na^+ + K^+ - (Cl^- + HCO_3^-)$ and normal values are between 12 and 20. Urinary anion gap is not used in neonates because their physiologic tubular immaturity renders this calculation inaccurate.

Tests that are important for the evaluation include:

- Venous blood gas is important to evaluate the acid base balance along with compensatory mechanism like in PCO2
- **Urinalysis -** A bag specimen will be sufficient
  - o **pH:** Type 1 RTA has alkaline urine and Type 2 and 4 RTA have acidic urine.
  - o **Leukocyte esterase and nitrites -** can be suggestive of UTI associated with Type 4 RTA. Will need a sterile specimen for urine culture to confirm.
  - o **Proteinuria and/or glucosuria -** can be present in Type 2 RTA from global proximal tubular dysfunction.
  - o Urine calcium/creatinine ratio for hypercalciuria present mainly in Type 1RTA.
  - o **Urine citrate:** low in Type 1 RTA
- **Blood work-** Renal function tests including BUN, creatinine, sodium, chloride, calcium, phosphorus, are important. Aldosterone levels for aldosterone deficiency in Type 4 RTA.
- **Imaging -** Renal ultrasound to evaluate for nephrocalcinosis that is frequently seen in RTA type 1, obstruction in RTA 4. Skeletal X rays to rule out rickets can be considered.

- Audiometry (AR RTA1) and ophthalmology (AR RTA2) evaluation.
- **Genetic testing -** Genetic testing is recommended specially if patient has other signs and symptoms that suggest primary or syndromic causes of RTA. Important to obtain family history.

Treatment

- Assess for and treat any secondary causes of RTA. For e.g. withdrawal of contributing medications or treatment of UTI
- **Alkali supplementation -** Goal is to attain close to normal serum bicarbonate for age.
  - Patients with Type I RTA generally require low doses ranging from 1-3mEq/kg/day.
  - Patients with Type II RTA require much higher doses, 10 mEq/kg/day into q4-6 hours. It is also important to identify and treat underlying causes of Fanconi syndrome, if present.
  - Oral route is preferred, when possible.
    - HCO_3^- deficit = (Target HCO_3^- level – Serum HCO_3^- level) x weight (kg) x 0.4.
  - Alkali therapy decreases proximal citrate reabsorption and increases downstream delivery of citrate thereby reversing hypercalciuria, reducing the rate of kidney stone formation and prevents or ameliorates nephrocalcinosis.
- Treat Hypokalemia - In Type 1 RTA, Initial therapy should aim to correct hypokalemia before treating acidosis as potassium will be moved intracellularly with acidosis correction and hypokalemia will deteriorate.
- In infants with Fanconi syndrome and global proximal tubule dysfunction, there is risk of severe hypophosphatemia and vitamin D deficiency. They have an ongoing need for phosphate and vitamin D supplementation.
- Type IV RTA is often is accompanied by hyperkalemia and will need management of that as outlined in chapter **Chapter 9.2 Hyperkalemia and Hypokalemia**. In addition to bicarbonate supplementation, treating the underlying cause like urinary obstruction, UTI or adrenal insufficiency is important.

Outcome

Transient forms of RTA associated with tubular immaturity have good prognosis and resolve over time. In all forms of RTA, adequate supplementation with alkali can help achieve normal growth and prevent bone disease. Early treatment prevents nephrocalcinosis and nephrolithiasis that can occur in Type 1 RTA. All inherited forms of RTA are at risk for chronic kidney disease over time. Follow up with renal clinic after discharge from NICU in recommended.

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Section 11: Neurology

Editors: Lakshmi Katakam and Christopher J. Rhee

11.1 Encephalopathy

'Neonatal encephalopathy' is defined as neurologic dysfunction in earliest days of life in an infant born at or beyond 35 weeks. It can manifest as altered level of consciousness, seizures, apnea, or depressed tone and reflexes. "Hypoxic Ischemic Encephalopathy" or HIE is a term used to describe neonatal encephalopathy that is secondary to hypoxic-ischemic brain injury. More specifically, when HE occurs secondary to an acute perinatal insult, it is referred to as "Perinatal Hypoxic Ischemic Encephalopathy."

Neonatal encephalopathy may be due to a number of different underlying etiologies:

- Metabolic abnormalities (hypocalcemia, hypoglycemia)
- Toxins (hyperammonemia, kernicterus)
- Inborn errors of metabolism
- Intracranial hemorrhage
- Cerebral infarction
- CNS developmental anomalies (holoprosencephaly)
- Infections (sepsis, meningitis, CNS TORCH infection)
- Spinal cord injury
- Neuromuscular disorder

The cause of the encephalopathy is not always immediately evident, and should not automatically be ascribed to perinatal depression or hypoxic ischemic injury without a structured assessment of perinatal risk factors and physical exam findings. However, peripartum risk factors such as placental abruption, feto-maternal hemorrhage, maternal hypotension/shock, prolonged labor, multiple births, chorioamnionitis, placental insufficiency, and IUGR should increase the suspicion for perinatal hypoxic ischemic injury.

Evaluation

Evaluation of an infant presenting with encephalopathy requires an in-depth review of maternal history, pregnancy related complications, details of labor and delivery as well as delivery room resuscitation. In addition, physical exam, particularly a thorough neurologic examination is key for assessing the nature and severity of injury.

Laboratory evaluation of an infant with encephalopathy includes CBC with differential, blood glucose, serum calcium, magnesium, electrolytes, blood culture, as well as CSF profile and culture. Depending on degree of suspicion for metabolic disease, additional studies such as serum ammonia, serum and CSF lactate, serum and CSF amino acids, and urine organic acids may be warranted. Evaluation of the placenta can also provide key information for identifying etiology of encephalopathy.

EEG monitoring for seizure detection and imaging studies such as head ultrasound and magnetic resonance imaging (MRI) of Brain should be considered in this patient population.

11.2 Hypoxic Ischemic Encephalopathy (HIE)

HIE is a term used to describe neonatal encephalopathy that is secondary to perinatal insult and resulting hypoxic-ischemic brain injury. It has a dramatic impact on mortality and neurological morbidity. According to one estimate, 40% of the infants with moderate encephalopathy and 100% of those with severe encephalopathy either die or develop neurosensory impairment.

Pathophysiology

Adequate cerebral blood flow is necessary to deliver oxygen and glucose to the fetal brain and maintain homeostasis and meet cellular energy demands. When disruption in cerebral blood flow occurs as a result of risk factors such as placental abruption, prolapse of umbilical cord or uterine rupture, it causes disruption of oxygen/glucose delivery to brain and results in energy failure and neuronal cell death. First, primary energy failure and necrosis occur, followed by a complex biochemical cascade that leads to secondary energy failure and apoptosis. The sequence of neuronal injury is described below (**Table 11–1**).

Diagnosis

While there is no gold standard test for diagnosis of HIE, we rely on perinatal risk factors, birth and delivery room resuscitation history, and patient's neurological exam to assess for encephalopathy. Sarnat staging is frequently used to assess

Table 11–1. Sequence of neuronal injury in hypoxic-ischemic encephalopathy (HIE)

Acute phase	Latent phase	Secondary phase	Tertiary phase
↓CBF + ↓ Glucose → anaerobic metabolism → ↓ATP and ↑lactic acid Intracellular accumulation of sodium, water, and calcium Cell releases excitatory amino acid glutamate	1 to 6 hours after injury Recovery of oxidative metabolism Inflammation and continuation of the activated apoptotic cascades More severe the insult, the shorter the latent period	6 to 15 hours after the injury Cytotoxic edema, excitotoxicity, and secondary energy failure Nearly complete failure of mitochondrial activity Clinical deterioration in neonates with moderate to severe injury Seizures typically occur in this phase	Months after the insult Late cell death, remodeling of the injured brain, and astrogliosis

the severity of encephalopathy and the modified Sarnat classification is recommended for evaluating infants with suspected HIE to delineate the severity of encephalopathy, decide on treatment options, and provide prognostic information. While initial neurological exam is important for diagnosis and for therapeutic considerations, it is also important to perform sequential neurologic assessments to monitor the evolution of symptoms related to encephalopathy (**Table11–2**). The worst neurological exam of an infant or the highest Sarnat stage reached by an infant can be predictive of long-term outcomes. Examples of normal and abnormal neurological exam findings can be found at: https://people.stanford.edu/wusthoff/neurologic-exam-neonates-suspected-encephalopathy-0. Once candidacy for therapeutic hypothermia has been determined and the window for therapeutic hypothermia has passed, it is no longer necessary to continue serial modified Sarnat scoring. However, it is important to continue to do a thorough neurologic exam on a daily basis when patient is undergoing therapeutic hypothermia.

Treatment

Usual care for neonates with HIE is supportive in nature and involves correcting metabolic and electrolyte disturbances, stabilizing pulmonary and hemodynamic parameters, treating seizures, and monitoring closely for multi organ dysfunction. In addition, infants with signs of encephalopathy, specifically in the context of perinatal depression, should be evaluated for treatment with therapeutic hypothermia in a timely manner.

11.3 Therapeutic Hypothermia

Using a cooling blanket, infant's core temperature is lowered to 33.4 degrees Celsius for 72 hours and provide total body cooling (TBC). The mechanism of action by which TBC affects brain injury is hypothesized to be as follows. Decreasing the body temperature in turn reduces the cerebral metabolic rate, attenuates release of excitatory amino acids, improves uptake of glutamate, lowers production of free radicals, and reduces cytotoxic edema and apoptosis.

Eleven international multicenter randomized clinical trials, including a total of 1,505 infants, have affirmed the safety and efficacy of therapeutic hypothermia as a therapy for HIE in newborns ≥36 weeks resulted in reduction in the mortality and/or major neurodevelopmental disability. The first trial, the CoolCap Study, which employed selected head cooling and used amplitude-integrated EEG (aEEG) abnormalities as entrance criteria, showed improved survival without severe disability (once newborns with severe aEEG abnormalities were excluded). The NICHD trial, using whole body hypothermia reported improved survival without severe disability in treated infants at 18 months of age. Importantly, benefits observed at 18–22 months of age persist to early school age, as shown in the CoolCap and NICHD follow-up trials. An expert panel convened by the NICHD concluded that therapeutic hypothermia, if offered, needs to be performed using a rigorous set of criteria and a published protocol (strong recommendation, high quality evidence)

Therapeutic hypothermia is available in the TCH NICU and the following screening process can be used to methodically evaluate a patient suspected to have HIE and determine candidacy for total body cooling **(Table11–3).** Use the table/checklist to review inclusion and exclusion criteria and assess severity of encephalopathy. Only infants who meet the criteria for gestational age, age, and have neurological exam consistent with **moderate-to-severe encephalopathy** based on modified Sarnat exam should be treated with TBC. If it is unclear if infant is a candidate or if there are special circumstances, please discuss these with unit's medical director. For infants with mild encephalopathy, serial neurological exams should be performed every hour until the 6 hour window for TBC expires **(Table 11-3).**

Even though many recent studies have reported that mild hypoxic ischemic encephalopathy has been associated with increase in risk of abnormal neurodevelopmental outcomes and abnormal brain imaging, the safety and efficacy of treating infants with mild HIE with whole body hypothermia has not been established. Among 341 infants with mild HIE who were enrolled in observational studies and RCTs, 25% were noted to have abnormal neurodevelopmental outcome. However, a meta-analysis of these studies shows there is no definitive evidence that therapeutic hypothermia is beneficial. According to a 2018 systematic review by Conway et al. "Within the RCT studies, data was available for 91 infants with mild HIE; 45 cooled and 46 uncooled. Abnormal outcome in the cooled and uncooled groups was 29% and 37% respectively, with an odds ratio of 0.67 (95% CI: 0.28 to 1.61, p = 0.59). While the available data is showing a trend in the direction of therapeutic hypothermia, this trend was not significant and therefore not robust enough to guide therapy." Based on this information, at this time we do not recommend routine use of therapeutic hypothermia for infants with mild HIE due to low quality evidence and potential for harm (strong recommendation, very low quality evidence).

TBC should be initiated within 6 hours of birth. When receiving patients from another hospital, passive cooling should be initiated at the referral hospital after the infant has been evaluated and determined to be a candidate for therapeutic hypothermia by having all heat sources removed from the infant. Initial neurologic exam to qualify for passive cooling should be done at least 1 hour after birth to allow an adequate amount of time for transitioning. It is critical to monitor temperature every 15 minutes to prevent overcooling. Active servo-controlled therapeutic hypothermia (with continuous rectal temperature monitoring) is available to be used during transport from the referral hospital to the TCH NICU.

For placement of the esophageal probe, measure the distance from the tip of the nose to the earlobe to the xyphoid process then subtract 2 cm from the length to approximate distance to lower esophagus. Confirm placement with a 2 view x-ray with ideal placement of the tip in the lower esophagus above the stomach. Infants are cooled to 33.5°C esophageal core body temperature for 72 hours using a servo-controlled cooling blanket system. The incubator or radiant warmer heat source is turned off throughout the procedure. During rewarming esophageal and skin temperature is monitored continuously. Rewarming is done slowly with 0.5°C increases in servo "set temp" every hour until set point reaches 36.5°C for 1 hour. Then the radiant warmer is turned on with servo set point 0.4°C above the infant's skin temperature. When the skin temperature reaches 36.5–37°C, the infant is returned to standard NICU temperature control care.

Table 11–2. Serial neurological exam worksheet

Neurological Exam					Enter the highest score in each category of neurological exam					
					Date and Time of Serial Exams					
Category	Normal (Score 0)	Encephalopathy								
		Mild (Score 1)	Moderate (Score 2)	Severe (Score 3)	1st	2nd	3rd	4th	5th	6th
Level of Consciousness	Awake, alert, fixes on visual stimuli	Irritable, hyperalert	Lethargic	Stupor or coma						
Spontaneous Activity	Frequent spontaneous movements	Increased activity, jittery	Decreased activity	No activity						
Posture	Extremities flexed in toward the trunk	Slight distal flexion, slight extension	Distal flexion, complete extension	Decerebrate						
Tone	Normal	Normal or slightly increased	Hypotonic	Flaccid						
Primitive Reflexes Suck	Strong coordinated suck	Uncoordinated	Weak or unsustained	Absent						
Primitive Reflexes Moro	Complete Moro	Exaggerated	Incomplete	Absent						
Autonomic System Pupils	Reactive	Dilated	Constricted	Dilated, deviated, unequal, or unreactive to light						
Autonomic System Heart Rate	Normal	Tachycardia	Bradycardia	Variable (heart rate is not constant and varies widely)						
Autonomic System Respiration	Normal	Regular	Periodic breathing	Apnea (mechanical ventilation)						
Seizure Activity	None	None	Yes	Yes	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Overall Assessment of Encephalopathy	Presence of moderate or Severe encephalopathy is defined as seizures **or** presence of signs in at least 3 of 6 categories in neuro exam (a score of 2 or above in 3 of the categories above)				Normal ☐ Mild ☐ Mod ☐ Severe ☐	Normal ☐ Mild ☐ Mod ☐ Severe ☐	Normal ☐ Mild ☐ Mod ☐ Severe ☐	Normal ☐ Mild ☐ Mod ☐ Severe ☐	Normal ☐ Mild ☐ Mod ☐ Severe ☐	Normal ☐ Mild ☐ Mod ☐ Severe ☐
Qualification for Total Body Cooling	Does patient meet criteria for Gestational age, Age, biochemical profile and have exam findings suggestive of moderate or Severe encephalopathy?				**YES** ☐ **NO** ☐	**YES** ☐ **NO** ☐	**YES** ☐ **NO** ☐	**YES** ☐ **NO** ☐	**YES** ☐ **NO** ☐	**YES** ☐ **NO** ☐

Table 11–3. Screening for total body cooling			Meets Criteria?
Gestational Age	Newborn infants ≥ 36 weeks should be screened using the following criteria		Yes ☐
Age	Less than 6 hours of age at the time of assessment		Yes ☐
Biochemical Criteria	A. **IF BLOOD GAS IS AVAILABLE** Cord pH or first postnatal blood gas (done within 1 hour of life) pH ≤ 7.0 OR Base Deficit on cord pH or first postnatal blood gas ≥ 16mEq/L	B. **IF BLOOD GAS IS NOT AVAILABLE OR pH 7.01 to 7.15 OR base deficit 10 to 15.9 mEq/L** Acute Perinatal event* AND one of the following: 1)An Apgar score ≤ 5 at 10 minutes OR 2)Continued need for ventilation initiated at birth and continued for ≥ 10 minutes *abruptio placenta, cord prolapse, severe FHR abnormality (variable/late decelerations)	Yes for (A) ☐ **OR** Yes for (B) ☐ (must meet criteria for either A or B)

Neurological Exam

	Category	Normal (Score 0)	Mild Encephalopathy (Score 1)	Moderate Encephalopathy (Score 2)	Severe Encephalopathy (Score 3)	Highest Score in Each Category
#1	**Level of Consciousness**	When awake, alert, fixes on visual stimuli	Irritable, hyperalert	Lethargic	Stupor or coma	
#2	**Spontaneous Activity**	Frequent spontaneous movements	Increased activity, jittery	Decreased activity	No activity	
#3	**Posture**	Extremities flexed in toward the trunk	Slight distal flexion, slight extension	Distal flexion, complete extension	Decerebrate	
#4	**Tone**	Normal	Normal or slightly increased	Hypotonic	Flaccid	
#5	**Primitive Reflexes Suck**	Strong coordinated suck	Uncoordinated	Weak or unsustained	Absent	
	Primitive Reflexes Moro	Complete Moro	Exaggerated	Incomplete	Absent	
#6	**Autonomic System Pupils**	Reactive	Dilated	Constricted	Dilated, deviated, unequal, or unreactive to light	
	Autonomic System Heart Rate	Normal	Tachycardia	Bradycardia	Variable (heart rate is not constant and varies widely)	
	Autonomic System Respiration	Normal	Regular	Periodic breathing	Apnea (mechanical ventilation)	

Seizure Activity?	Yes ☐
Overall Assessment of Encephalopathy	Moderate or Severe Encephalopathy is defined as seizures **or** presence of signs in at least 3 of 6 categories in neuro exam (a score of 2 or above in 3 of the categories above) Mild ☐ Moderate ☐ Severe ☐
Exclusion Criteria	Known chromosomal anomaly? Major congenital anomalies? Severe IUGR (<1800 grams BW)? No ☐
Qualification for Total Body Cooling	Does patient meet criteria for gestational age, age, biochemical profile and have exam findings suggestive of moderate or severe encephalopathy? **YES ☐ NO ☐**

Management of Patient Undergoing TBC

Respiratory

- Most infants will require assisted ventilation due to poor respiratory effort
- However, they will likely need low support since there is usually no intrinsic lung disease in majority of the cases
- Avoid hypocarbia and hyperoxia to minimize further brain injury
- Monitor for evidence of pulmonary hypertension

Cardiovascular

- Expect to see asymptomatic sinus bradycardia (with heart rate between 80-100 bpm)
- Monitor BP closely
- Consider vasoactive medications for treatment of hypotension
- Consider echo to more thoroughly evaluate cardiac function and right sided pressures (if suspecting pulmonary hypertension)
- Monitor for arrhythmias

Fluids and Electrolytes

- Start with 40-60 ml/kg/d and adjust based on urine output and renal function
- Avoid fluid boluses
- Follow electrolytes (calcium, potassium, magnesium), creatinine, and urine output closely Monitor blood glucose closely
- Avoid replacement with bicarb if possible (as lactic acidosis will likely correct with time)
- NPO during the duration of TBC and TPN for nutrition

Hematology

- Monitor for evidence of coagulopathy and treat based on symptomatology

Infectious Disease

- Strongly consider infection as a cause of encephalopathy and obtain a blood culture on admission and begin antibiotics (ampicillin and gentamicin)

Dermatology

- Reposition infant every 2 hours while cooled to prevent skin breakdown

Neurologic

- Follow serial neuro exams to monitor for changes in severity of encephalopathy
- Consult Neurology service
- Monitor for clinical and electrographic evidence of seizures with continuous EEG monitoring
- Treat Seizures in consultation with Neurology service
- Treat pain, shivering, irritability with Morphine (load with 0.1 mg/kg and then begin continuous infusion at 0.01 mg/ kg/hour and adjust dose as needed)
- Neonatal brain MRI with MRS for day 5–6 (NO CONTRAST)
- HUS can be used to evaluate for intracranial hemorrhage and for measuring resistive indices, as a marker of cerebral edema

Access

- UAC needed for continuous monitoring of BP
- UVC needed for fluids, medications, and nutrition
- PICC or PAL as needed
- On admission: CBC with diff, ABG, DIC panel, Chem 10, ionized calcium, LFTs, blood culture, point of care glucose
- Daily labs: repeat labs as necessary based on clinical picture

Outcomes

In infants with HIE, improved (or normal) EEG and improved (or normal) neurologic exam (by 7 days of age) in general are good prognostic indicators. Long-term developmental and neurologic follow-up is indicated in all cases of neonatal encephalopathy. Outcome studies from the major cooling trials have indicated that whole body hypothermia is safe, is associated with improved survival and reduced neurodevelopmental disability at 18 months, and the benefits noted at 18 months seem to persist to early school age.

NICHD Neonatal Research Network RCT of whole-body hypothermia for neonatal HIE noted the rate of death or moderate or severe disability at 18 to 22 months of age was 62% in the control group versus 44% in the hypothermia group (p=0.01), with a mortality rate of 37% and 24% respectively (p=0.08). The rates of moderate or severe CP were 30% in the control and 19% in the hypothermia group, with corresponding rates of blindness of 14% versus 7% and hearing impairment of 6% versus 4%. Childhood outcomes study of these patients was done at 6-7 years of age and rate of death or severe disability was 41% in hypothermia group vs. 60% in control group at the time of follow up (p=0.03). Among children in the trial who had moderate or severe disability at 18 months, the corresponding rates at 6-7 years of age was 15 of 17 (88%) in the hypothermia and 18/19 (95%) in the control group.

Infants receiving whole body cooling should be referred to the TCH Desmond Developmental Center for long-term follow up and to the Pediatric Neurology Clinic. If admitted to the Woodlands campus, developmental and neurologic follow-up should occur in the Woodlands.

11.4 Seizures

Overview and Pathogenesis

A seizure results from an abnormal, synchronous discharge of a population of neurons. This discharge is the result of a failure of neuronal ATP-dependent sodium-potassium pumps leading to persistent cell depolarization. Since energy is required to power the pump, a deficiency in cerebral energy substrates (glucose and oxygen) can lead to seizure activity. Increased availability of glutamate (an excitatory

neurotransmitter) with hypoxemia, ischemia, and/or hypoglycemia can also lead to seizures. Deficit of inhibitory neurotransmitters (e.g., pyridoxine dependency) is another cause of neonatal seizures. Finally, membrane alterations leading to increased sodium permeability (e.g., hypocalcemia and hypomagnesemia) can lead to neonatal seizures.

Neonates are especially prone to seizures because the mechanisms that lead to the inhibition of seizure activity are not yet fully developed. Neonatal seizures appear clinically different than seizures in children and adults due to this immaturity. Further, seizures do not progress as they do in older individuals because dendritic/axonal branching and synaptic connections are not fully developed. Since myelination is also not yet complete in cortical efferent systems, seizures may occur without motor manifestations. These types of seizures are often referred to as subclinical seizures (or electrographic seizures); seizures that appear on an EEG without overt clinical manifestations.

The short-term result of a prolonged seizure, due to decreased ATP, release of excitatory amino acids, and cardiopulmonary compromise is neuronal death. Further, recurrent neonatal seizures can render the brain more susceptible to the development of epilepsy later in life. The long-term effects of recurrent seizures are altered neurodevelopment. Thus, prompt identification and immediate treatment of seizures is important.

Diagnosis

The diagnosis of neonatal seizures cannot rely on accurately recognizing them. There is a high rate of subclinical and subtle seizures in neonates due to immaturity of the central nervous system and inability to propagate motor manifestations. The most common etiologies of neonatal seizures are listed in **Table 11–4**. Seizures with motor manifestations can be categorized as: subtle, clonic, tonic, and myoclonic. Subtle seizures are simply motor or autonomic changes that are not better described as clonic, tonic, or myoclonic seizures. Examples of subtle seizures include sustained opening of the eyes with fixation, chewing, other oral-buccal-lingual movements, pedaling motions, and apnea. An EEG is helpful in determining if episodes concerning for seizures are epileptic or non-epileptic. Clonic seizures can be focal or multifocal and involve rhythmic jerks, usually 1–3 jerks per second, with the rate declining with progression of the seizure. Tonic seizures can be focal, multifocal, or generalized, and involve sustained posturing of a limb or tonic extension of extremities. Myoclonic seizures are best described as sudden jerks of muscle groups and can be focal, multifocal, or generalized. Myoclonic seizures can be distinguished from clonic seizures because of the faster speed of the myoclonic jerk and predilection for flexor muscle groups.

Neonatal seizures should be distinguished from jitteriness which is non-epileptic activity. Jitteriness can appear as tremor-like movements and can be secondary to anoxic brain injury, drug withdrawal, or electrolyte abnormalities. Unlike neonatal seizures, jitteriness usually does not involve an abnormality of gaze or eye movement, and the movements in jitteriness are usually exquisitely stimulus-sensitive and can be stopped with passive flexion.

Work-up

The work-up and management of neonatal seizures begins with the H&P. Information provided in the H&P should help in narrowing down the differential diagnosis, and thus dictate the proper work-up. It is imperative that the work-up include evaluation of easily treatable (and reversible) conditions, such as hypoglycemia, electrolyte disturbances, and infectious meningitis/encephalitis. Thus, a typical work-up for neonatal seizures includes:

- Serum glucose, sodium, potassium, calcium, phosphorous, and magnesium
- CSF with cell count and differential, gram stain, culture, protein, and glucose

A continuous EEG (CEEG) will be useful in determining whether "abnormal movements" are associated with electrographic seizures. Importantly, treatment of suspected epileptic activity should not be delayed until CEEG is performed. A CEEG will also be useful in identifying subclinical seizures in those receiving neuromuscular blockade. Finally, CEEG is useful in defining the interictal

Table 11–4. Most common etiologies of neonatal seizures

Etiology	Differential
Hypoxic Ischemic encephalopathy	
Intracranial hemorrhage	Intraventricular hemorrhage
	Primary subarachnoid bleed
	Subdural/epidural hematoma
Central nervous system infection	Bacterial meningitis
	Viral encephalitis
	Intrauterine infection (TORCH)
Infarction	Ischemic necrosis (stroke)
	Venous thrombosis
Metabolic derangements	Hypoglycemia
	Hypocalcemia
	Hypomagnesaemia
	Hypo/hypernatremia
Inborn error of metabolism	Amino acids disorders
	Organic acids disorders
	Urea cycle disorders
	Mitochondrial disorders
	Peroxisomal disorders
	Pyridoxine dependency
Others	Chromosomal anomalies
	Congenital abnormalities of the brain
	Neurodegenerative disorders
	Benign neonatal convulsions
	Benign familial neonatal convulsions
	Drug withdrawal or intoxication
	Unknown etiologies

background features which are of value in estimating prognosis. The American Clinical Neurophysiology Society has produced a Guideline on Continuous Electroencephalographic Monitoring in Neonates which delineates the clincal disorders that carry a high-risk for neonatal seizures and warrant CEEG monitoring **(Table 11–5).**

An MRI of the brain should also be obtained to assess for epileptogenic lesions (areas of anoxic brain injury, cortical malformations, disorders of neuronal migration, etc.). If there is concern for anoxic brain injury or a metabolic disease, magnetic resonance spectroscopy (MRS) should also be performed. Also, a cranial ultrasound can detect major intracranial hemorrhages and structural abnormalities, but may not detect superficial cortical hemorrhage, such as subarachnoid bleeding.

If the above work-up fails to identify the etiology of neonatal seizures, then specific serum, urine, and CSF tests should be performed (e.g., serum amino acids and urine organic acids) to rule out inborn errors of metabolism or genetic conditions.

Treatment

Initial Treatment

Securing the airway and providing adequate oxygenation and ventilation, as well as cardiovascular and metabolic support, are crucial in the management of an infant with seizures. Appropriate antibiotic therapy should be initiated if infection is suspected, and metabolic derangements corrected, if present:

Hypoglycemia – (Ch 3.4 Hypoglycemia)

Hypocalcemia – (Ch 9.4 Hypocalcemia)

Recurrent seizures that are not immediately due to correctable causes warrant the prompt use of an anti-epileptic drug (AED). The optimal AED for neonatal seizures is unknown. Published studies comparing phenobarbital to phenytoin as initial therapy did not show any difference in efficacy. However, because phenytoin has a very narrow therapeutic range (levels need to be measured frequently), it is not well absorbed orally in the newborn or young infant, in addition to concerns for cardiotoxicity with Fosphenytoin, it is recommended to use phenobarbital as the initial drug of choice. If treatment with phenobarbital does not eradicate seizures, an additional drug may be considered. If the infant is clinically stable and the seizures are brief and/or infrequent, the addition of another drug may carry higher risks than the seizures per se.

The suggested order of drug therapy for the acute management of neonatal seizures is listed below:

First-line:

Phenobarbital (Strong recommendation, very low quality evidence): 20 mg/kg given intravenously at a rate of 1–2 mg/kg/min. Two additional 10 mg/kg doses (total phenobarbital dose of 40 mg/kg) can be given, if needed. Obtain a level 2 hours after the loading dose. The desired phenobarbital level is 20–40 mcg/mL. Be aware of respiratory depression associated with administration of phenobarbital that may warrant intubation.

Second-line:

Midazolam (Weak recommendation, very low quality evidence): given as an initial intravenous bolus of 0.15 mg/kg. An additional intravenous bolus dose of 0.1–0.15 mg/kg can be given 5–10 minutes later, while awaiting other AEDs. Respiratory depression necessitating intubation may occur.

Table 11-5. Examples of clinical scenarios conferring high risk of neonatal seizures

Clinical syndrome of acute neonatal encephalopathy
Neonatal depression from suspected perinatal asphyxia (chronic or acute)
After cardiopulmonary resuscitation
Cardiac or pulmonary risks for acute brain injury and clinical encephalopathy
Significant respiratory conditions such as severe persistent pulmonary hypertension
Need for ECMO
Congenital heart defects requiring early surgery using cardiopulmonary bypass
CNS infection
Laboratory confirmed meningoencephalitis
Suspected CNS infection, such as clinical evidence in setting of maternal chorioamnionitis, funisitis, group B streptococcus or HSV colonization
CNS trauma
Intracranial subarachnoid, subdural or intraventricular bleeding
Clinical encephalopathy and suspicion for CNS injury, for example, maternal trauma, traumatic delivery, prolonged second stage of labor, or suspected nonaccidental trauma
Inborn errors of metabolism (suspected or confirmed)
Perinatal stroke (suspected or confirmed)
Sinovenous thrombosis (suspected or confirmed)
Premature infants with additional risk factors
Acute high-grade intraventricular hemorrhages
Very low birth weight with clinical concern for encephalopathy
Genetic/syndromic disease involving CNS
Cerebral dysgenesis on neuroimaging
Dysmorphic features or multiple anomalies with microencephaly

ECMO, extracorporeal membrane oxygenators; CNS, central nervous system; EEG, electroencephalography; HSV, Herpes simplex virus

Adapted with permission from Wolters Kluwer Health, Inc.: Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, Nguyen S, Wusthoff CJ, Clancy RR. The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. J Clin Neurophysiol. 2011 Dec;28(6):611-7. https://journals.lww.com/clinicalneurophys/Citation/2011/12000/The_American_Clinical_Neurophysiology_Society_s.12.aspxs

Midazolam can also be administered as an infusion if the initial bolus does not abort the seizure, at a rate of 0.1–0.4 mg/kg/hr. Midazolam is preferable in the sick neonate, especially if intubated.

Fosphenytoin (Weak recommendation, very low quality evidence): 20 mg/kg given intravenously at a rate of 0.5–1 mg/kg/min. Obtain a level 2 hours after the loading dose. The desired total phenytoin level is 15–20 mcg/mL (must adjust for albumin level). Hypotension and cardiac arrhythmias have occurred with Fosphenytoin administration. This drug should be avoided in cardiac patients.

Third-line:

Levetiracetam: 60 mg/kg given intravenously at a rate of 2–5 mcg/kg/minute. Maintenance dosing with levetiracetam can be

used at 20–60 mg/kg/day divided three times daily. In 2019, Gowda et al published results from a randomized controlled trial of Levetiracetam versus Phenobarbital for neonatal seizures in which they compared the safety and efficacy of these two drugs as first line agents. 100 neonates (0-28 days) with clinical seizures were randomized to receive either Levetiracetam (20 mg/kg) or Phenobarbital (20 mg/kg) intravenously. Clinical cessation of seizures were noted in 43 (86%) and 31 (62%) neonates in Levetiracetam and Phenobarbital group, respectively (RR 0.37; 95%CI 0.17, 0.80, P<0.01). 10 neonates from the Phenobarbital group were noted to have adverse events (hypotension in 5, bradycardia in 3 and requirement of mechanical ventilation in 2 neonates) and no adverse events reported in Levetiracetam group. However, EEG monitoring and serum drug levels were not monitored, and there was no long-term follow up of patients enrolled in the study. In 2020, another randomized controlled trial of Levetiracetam and Phenobarbital was published by Sharpe et al. In this multicenter, randomized, blinded, controlled, phase IIb trial, 80% of patients (24 of 30) randomly assigned to Phenobarbital remained seizure free for 24 hours, compared with 28% of patients (15 of 53) randomly assigned to Levetiracetam (RR 0.35; 95% CI 0.22, 0.56; P = 0.001;). More adverse effects were seen in subjects randomly assigned to phenobarbital (not statistically significant). These two RCTs show differing results, but the RCT by Sharpe et al is more generalizable since it was based on electrographic evidence of seizure and therefore able to include the population with subclinical seizures. Further studies are necessary to better understand the efficacy of Levetriracetam as the first line agent for treating neonatal seizures.

Pyridoxine (Strong recommendation, very low quality of evidence) Pyridoxine-dependent epilepsy is an inborn error of metabolism that is characterized by recurrent seizures in the neonatal period that do not respond to conventional AEDs but respond to pyridoxine (Vitamin B6). If pyridoxine-dependent epilepsy remains in the differential in an acutely seizing infant, it is reasonable to provide IV doses of pyridoxine (1–5 doses of 100 mg (there is a risk for respiratory failure) followed by maintenance dosing of oral pyridoxine at 15–30 mg/kg/day or up to 200 mg/day in neonates. Treatment with oral pyridoxine should be continued until negative biochemical or genetic testing excludes pyridoxine-dependent epilepsy. It is important to discontinue pyridoxine when no longer needed given that the side effect of long-term use is peripheral neuropathy.

Neurology should be consulted on for every neonatal seizure and a formal consultation to the Epilepsy Service is needed for refractory neonatal seizures and neonatal status epilepticus.

Outcome and Duration of Treatment

Because etiology may be the most important factor that determines neurodevelopmental outcome, it is not clear if treating the actual neonatal seizure decreases the risk for poor outcome. Two Cochrane reviews raised doubts about the benefits of treating each seizure. The first review in 2001, updated in 2004, concluded that, “at present there is little evidence from randomized controlled trials to support the use of any of the anticonvulsants currently used in the neonatal period.” The second review in 2007 concluded that, “at the present time, AEDs given to term infants in the immediate period following perinatal asphyxia cannot be recommended for routine clinical practice, other than in the treatment of prolonged or frequent clinical seizures.” In addition, there is a growing body of data from animal models of seizures that certain AEDs used to treat neonatal seizures may produce widespread neuronal apoptosis. Given the lack of sufficient evidence for improved neurodevelopmental outcome and the potential for additional brain injury with anticonvulsant therapy, care should be exercised in selecting which infants warrant treatment.

Although duration of therapy depends on the underlying illness and the physical examination, it is recommended that ongoing treatment be limited to one agent, if possible, and be administered for the shortest possible time period.

11.5 Cerebral Hemorrhage and Infarction

Periventricular, Intraventricular Hemorrhage (PIVH)

Periventricular, intraventricular hemorrhage (PIVH) is 1 of 2 major neuropathologies of prematurity and is a major cause of death in premature infants. The overall frequency of PIVH has remained constant over the past 10 years and is reported to affect approximately 28% of all VLBW infants. Because no epidemiological data are available, the true incidence in the US is unknown. The severity of PIVH is inversely proportional to gestational age and birth weight, occurring in 40% of infants with birth weight 500–750 g compared to 20% of infants 1001–1250 g. Approximately 50% of PIVH occurs within the first postnatal day, and virtually all occurs within 1 week of birth. Because the majority of babies who incur PIVH are asymptomatic, screening with HUS is routinely practiced.

The pathogenesis of PIVH is poorly understood, but is thought to encompass intravascular, vascular and extravascular factors. Intravascular factors include fluctuating systemic blood pressure, an increase or decrease in cerebral blood flow, an increase in cerebral venous pressure and platelet and coagulation disturbance. Vascular factors include the tenuous integrity of the germinal vascular bed and its vulnerability to hypoxic-ischemic injury. Extravascular factors include the excessive fibrinolytic activity that is present in the germinal matrix.

The site of the majority of PIVH is the subependymal germinal matrix, a primitive vascular network that is most prominent between 28 and 34 weeks gestation and which involutes by term gestation.

PIVH is classically graded as I to IV:

- **Grade I** – hemorrhage contained within the germinal matrix.
- **Grade II** – IVH with no ventricular dilatation/distension.
- **Grade III** – IVH with ventricular dilatation/distension.
- **Grade IV** – parenchymal hemorrhage. This lesion is rarely bilateral and often is referred to as a periventricular hemorrhagic infarction (PHI).

The risk of PIVH in term infants is low (<1% of live births) and the hemorrhage usually originates from either the choroid

plexus or the germinal matrix overlying the roof of the fourth ventricle.

Notable sequelae of PIVH are post-hemorrhagic hydrocephalus (PHH) and porencephaly. PHH occurs in approximately 25% of infants with PIVH, while porencephaly is noted in 5–10%, all of whom incurred a grade IV PIVH.

It is recommended that all premature infants <30 weeks' gestation undergo a screening HUS at 7–10 days of age (Strong recommendation, moderate quality evidence). If ventricular dilatation is noted, serial HUSs at weekly intervals are warranted to ascertain if ventricular dilatation is static or progressive. If ventricular dilatation is not noted on the initial scan and there are no extenuating reasons to do a repeat HUS sooner, a follow up HUS at 36–40 weeks postmenstrual age is recommended. A brain MRI to delineate the presence and extent of periventricular leukomalacia (PVL) is preferable to the HUS, if it can be obtained without having to heavily sedate the infant.

The management of PHH is aimed at maintaining low intracranial pressure and normal perfusion of the brain, as well as decreasing axonal stretch during early development. Repeated lumbar or ventricular punctures have not been shown to arrest the development of symptomatic hydrocephalus. Because elevated protein levels and high red blood cell counts in the ventricular fluid, as well as small infant size, are associated with an increased risk of shunt obstruction, several temporizing measures have been employed, including the placement of continuous external ventricular drainage, implantation of a ventricular access device to allow intermittent safe ventricular drainage (reservoir), or creation of a temporizing shunt construct draining fluid into the subgaleal space. Ventricular access devices and ventriculo-subgaleal shunts have unique advantages and disadvantages but are superior to continuous external drainage because of the high rate of ventriculitis associated with the latter. The decision regarding the need for a shunt usually is delayed until the protein content in the ventricular fluid has decreased and an infant weighs approximately 1500 g.

Mortality in infants with severe PIVH (grade III–IV) is about 20%. In infants with grade IV PIVH, >50% of survivors develop PHH. Long- term outcome depends both on the severity of the IVH and associated white matter lesions.

Periventricular Leukomalacia (PVL)

PVL is the most common neuropathology of prematurity. Unlike Grade IV PIVH, a lesion that is unilateral, PVL is symmetrical. The spectrum of PVL ranges from large cystic lesions located at the external angles of the lateral ventricles to microscopic areas of focal necrosis scattered throughout the deep cortical white matter.

The overall frequency of PVL is unknown, because the vast majority of the lesions cannot be detected with commonly used cranial imaging techniques. Studies using sophisticated MRI techniques suggest that 70% of premature infants have some degree of PVL with 20% having moderate to severe lesions. The pathogenesis of PVL is poorly understood but is thought to involve multiple interacting pathways operating to injure the immature white matter. Risk factors for PVL include twin gestation, nosocomial infection, PIVH, PDA, and NEC. In addition, late preterm infants who undergo cardiac surgery and those with congenital diaphragmatic hernias are at increased risk. The optimal time to screen for PVL is at 36–40 weeks' postmenstrual age. As stated above, a brain MRI to delineate the presence and extent of PVL is preferable to the HUS if it can be obtained without having to heavily sedate the infant. The hallmark of PVL is spastic diplegia; however, long-term outcome depends on the extent of PVL and any associated lesions.

Erythropoietin for Neuroprotection in Preterm Infants

Previous studies including a 2017 meta-analysis suggested that erythropoietin might improve neurodevelopmental outcomes in preterm infants. The PENUT trial published in 2020 was a large randomized, double-blind, placebo-controlled study, which evaluated the safety and efficacy of early, high-dose erythropoietin for neuroprotection. The trial enrolled 941 infants born between 24 weeks and 27 weeks gestational age who were randomized to receive either high dose erythropoietin or placebo. At the 2-year follow-up, babies treated with erythropoietin did not have improved neurodevelopmental outcomes – defined as decreased incidence of cerebral palsy or improved cognitive score on Bayley-III testing – compared to babies who received the placebo. Based on these study results, we do not recommend the use of erythropoietin for neuroprotection in preterm infants.

Perinatal and Neonatal Stroke (Term and Near-Term Infant)

The term "perinatal stroke" describes localized or multifocal infarction/ necrosis within an area of cerebral vascular distribution that may occur between 20 weeks' gestation and 28 days after birth. Approximately 80% of these are ischemic in origin, with the remainder due to cerebral venous thrombosis or hemorrhage. Causes include vascular malformations, coagulopathies, prothrombic disorders, trauma, infections and embolic phenomenon. The broader category of "intracranial hemorrhage" shares many of the same etiologies. Perinatal stroke mostly occurs in term or near term infants and the definition excludes the spectrum of SEH-IVH in preterm infants. The lesions are prone to cavitation within the brain and are a common cause of cerebral palsy in term and near term infants.

Estimated incidence of perinatal stroke is 1 in 2,300–5,000 births. The infarction may be either arterio-ischemic or veno-occlusive in nature. Arterial infarctions are typically unilateral and appear as wedged-shaped lesions in the distribution of the anterior, middle and/or posterior cerebral artery with approximately 60% occurring in the area of the left middle cerebral artery. Venous infarctions usually are located in deep cortical grey matter, specifically the thalamus. Infants commonly present with seizures, apnea or poor feeding in the early neonatal period but may be asymptomatic. Perinatal and birth history is often unremarkable. Prompt diagnostic workup is important because antithrombotic therapy may be appropriate in selected circumstances.

MRI is the imaging modality of choice but CT may be more accessible in the acute setting. Detailed family history and pathologic examination of placenta and umbilical cord is recommended. Additional work up depends upon clinical circumstances but usually includes EEG and Neurology Service consultation. Evaluation for infection may be

indicated. No consensus exists regarding routine evaluation for coagulopathies and prothrombotic disorders. Cost/benefit ratio of such testing has not been established. In neonates with stroke, consideration should be given to Hematology Service consultation to help determine appropriate patients for selective studies or intervention.

A clinical guideline for diagnosis and management of ischemic stroke in children has been developed by the TCH Evidence-Based Outcomes Center and is available on the physician web site. Though informative, this guideline excludes patients <1 month of age.

Published outcome studies suggest that approximately half of affected infants will have a major disability. The most common abnormality is hemiplegia and/or motor asymmetry. Approximately a third of the infants have a deficit in vision, usually a field cut, and about 15% will develop seizures. The outcome for an infant depends on the type, extent and location of the lesion.

Traumatic Birth Injuries (Nervous System)

Trauma to the head, nerves, and spinal cord can be divided into extracranial hemorrhage (cephalohematoma and subgaleal), intracranial hemorrhage (subarachnoid, epidural, subdural, cerebral and cerebellar), nerve injury (facial, cervical nerve roots including brachial plexus palsy, phrenic nerve injury, Horner syndrome and recurrent laryngeal injury), and spinal cord injury. Potential causes include a rigid birth canal, a large baby relative to the size of the birth canal, abnormal fetal presentation (breech, face, brow, and transverse lie) and instrumented deliveries. Caesarean delivery does not eliminate the risk of trauma, especially if vaginal delivery with forceps and/or vacuum extraction was attempted before delivery.

Head Trauma

Cephalohematoma (Ch 12.5-Extracranial Swelling)

Skull Fractures (Ch 12.8-Neuromusculoskeletal)

Subgaleal Hemorrhage (Ch 12.5-Extracranial Swelling)

Intracranial Hemorrhages

Intracranial hemorrhage is rare but can be seen with vacuum extraction or forceps assisted delivery. The incidence ranges from 1 in 600–1000 live births. The types of hemorrhage include epidural, subdural, subarachnoid, and to a lesser extent intraventricular and/or intraparenchymal.

The clinical presentation is variable and depends on the type, location, and extent of the hemorrhage. For infants with signs of increased intracranial pressure (full fontanel, hypertension, bradycardia, and irregular breathing) close observation for signs of herniation is warranted, and a neurosurgical consult obtained if decompression is needed.

Brachial Palsies and Phrenic Nerve Injury (Ch 12.8 Neuromusculoskeletal)

Spinal Cord Injury

Spinal cord injury can be caused by excessive traction or torsion during delivery. Infants with spinal cord injury usually are delivered by breech extraction or require mid-forceps application. Rarely, spinal cord injury can result from vascular occlusion of the spinal cord after umbilical catheterization or from venous air embolism.

Clinical presentation includes respiratory failure, weakness, and hypotonia. Neurologic signs may include:

- paralysis with areflexia in the lower extremities and variable involvement of the upper extremities depending on the level of injury,
- diaphragmatic breathing,
- presence of a sensory level,
- distended bladder,
- patulous anus, and
- Horner syndrome

Later findings include the development of spasticity and hyperreflexia. Formal imaging should include spinal MRI, though ultrasound and spine radiographs can be used to rule out surgical lesions such as hematomas or dysraphisms.

Treatment is primarily supportive and includes mechanical ventilation, maintenance of body temperature, bowel and bladder care, prevention of infection, and appropriate physical therapy.

At the time of initial presentation, stabilization of head and neck while consulting a neurosurgeon and neuroradiologist is mandatory to avoid worsening of the injury.

Outcome

Outcome is related to the persistence of neurologic signs during the first few postnatal days. Infants exhibiting some spontaneous respiratory effort by 24 hours have a good chance of having independent daytime breathing and good motor function.

11.6 Neural Tube Defects

Neural tube defects (NTD) are among the most common birth defects, ranking second after congenital heart disease. The etiology of NTDs is unknown and most cases are isolated. NTDs can occur as part of syndromes either in association with chromosomal abnormalities or because of environmental factors. The incidence of NTDs is reduced by folic acid supplementation before and during pregnancy. NTDs encompass a spectrum of malformations that include anencephaly, encephalocele, meningomyelocele, and spina bifida occulta, the latter being the most common and least severe of NTDs. Anencephaly is characterized by the absence of the cranial vault, as well as part or most of the cerebral hemispheres. An encephalocele is a hernia of part of the brain and the meninges through a skull defect, usually in the occipital area. Spina bifida is a defect in the vertebral column through which the spinal cord and the meninges might herniate creating a meningomyelocele.

The incidence of meningomyelocele in the US is 0.2–0.4/1000 live births. The Eastern and Southern regions have higher incidences than the West and females are more affected than males. The recurrence risk is 1.5–3% with 1affected sibling and 5.7–12% with 2 affected siblings. Associated anomalies include hydrocephalus, Chiari II malformation, hydrosyringomyelia, or

spinal arachnoid cyst. Nerve damage can continue postnatally, if the lesion is not managed appropriately.

Prenatal Surgery

A multicenter, randomized controlled trial of prenatal vs. postnatal repair of myelomeningocele demonstrated that prenatal surgery reduced the need for shunting, improved motor outcomes and neurocognitive function at 30 months when surgery was performed <26 weeks' gestation. The greatest benefit was seen in neonates with ventricle size <10mm at the time of fetal repair. The trial was stopped for efficacy of prenatal surgery. However, the prenatal surgery was associated with maternal risks (placental abruption, spontaneous rupture of membranes and uterine dehiscence) and fetal risks (preterm delivery, RDS and apnea). This surgery is currently available in the TCH Fetal Center (Strong recommendation, high quality evidence).

Immediate Management

- Avoid latex gloves at all times.
- Place the infant in the prone position immediately after delivery to avoid traumatic injury to the defect and spinal cord.
- Cover the lesion with non-adhesive gauze wet with sterile Ringer's Lactate or saline and plastic wrap to create a barrier from the environment and decrease fluid loss.
- Notify the neurosurgical service.
- Amoxicillin is recommended (10 mg/kg/day) for UTI prophylaxis.
- Infants who require resuscitation at delivery and need to be supine should be placed on a doughnut shaped cushion to support the defect.

Evaluation

The infant should be examined thoroughly with emphasis on the neurologic examination (spontaneous movement, muscle strength, sensory level, deep tendon reflexes, and anocutaneous reflex). Imaging studies are needed to ascertain the level of the defect and any associated anomalies (hydrocephalus, Chiari malformation, tethered cord). Fronto-occipital circumference needs to be measured daily and serial HUSs are recommended to monitor the progression of hydrocephalus, especially since most infants will require a shunt device. Once the infant can be placed supine, a urological evaluation, including a renal ultrasound and VCUG, need to be done. Based on the clinical course and physical examination further diagnostic tests may be needed. The evaluation of infants who underwent fetal surgery to close a NTD is the same.

Discharge planning

Infants with NTDs require the services of many specialists and disciplines. All infants should be referred to the Spina Bifida Clinic at TCH, a multidisciplinary clinic staffed by neurosurgeons, urologists, orthopedists and PM&R physicians. Services available at the clinic include social services, nutrition, OT and PT. A physician from the clinic should be contacted before discharge to meet with the family. The role of a clinician treating such patients is not limited to the traditional medical treatment, but also includes preparing the parents to adapting to their children's disabilities.

Outcomes

Occipital encephalocele – mortality is 40–50%, and only about 15% of survivors will have a normal outcome.

Postnatal Meningomyelocele Repair – mortality is 15-30%; 30% IQ <80; 50% will not be able to live independently

Fetal Meningomyelocele Repair – coordination and gait deficits still present but at significantly lower rate than postnatally repaired; 30% still need maximal assistance with life tasks; no improvement in bowel/bladder incontinence have been shown compared to postnatal repair.

11.7 Substance-Exposed Infants

Background

Exposure of infants *in utero* to both prescription and illicit drugs has risen over the past 10 years. This rise corresponds with the Institute of Medicine recommendation to treat pain as a public health priority. This shift in the focus on pain management has led to more liberal use of prescribed opiates in pregnant women for complaints such as back pain. There has also been an increase in illicit use of opioids (OxyContin, heroin, and fentanyl) and medication assisted treatment (MAT) programs (e.g., methadone and buprenorphine maintenance clinics). Opioid abuse has also shifted from a primarily inner city or low socioeconomic population to include all demographic and socioeconomic groups. Infants born to mothers with a history of chronic opioid use during pregnancy, illicit or MAT, are at risk for withdrawal after birth. In Texas, 35–50% of infants exposed *in utero* to opiates will have withdrawal symptoms. Co-exposure to nicotine and psychiatric medications increase the risk for withdrawal requiring pharmacotherapy due to an overlap of withdrawal symptoms from these medications with opioid withdrawal; with a 30% increased risk with one medication and 50% increase in risk with 2 or more medications taken.

Pathophysiology

Opiate drugs are low molecular weight, polar, and water soluble. They easily cross the placenta and the blood-brain barrier of the fetus. Opiates also have a prolonged half-life in the fetus as compared to adults or older children. When the infant is separated from the placenta during the birth process, the discontinuation of the opioid may result in the Neonatal Abstinence Syndrome (NAS). Current terminology for symptomatic withdrawal in opiate exposed infants is "Neonatal Opioid Withdrawal Syndrome" or NOWS.

Presentation

NOWS produces a constellation of symptoms primarily involving the neurologic and gastrointestinal systems. Neurologic symptoms include tremors, irritability, and excessive crying. Excoriation of extensor surfaces or nasal tip results from excessive movement creating friction against bedding. Seizures can occur but are rare. The cry is high-pitched, shrill, and persists for excessive lengths of time. These infants have decreased sleep cycles. GI symptoms include excessive sucking behaviors, voluminous eating or

difficulty eating, and diarrhea. The large feeding volumes can exacerbate the loose stools and lead to excoriation in the diaper and perianal area. The pain of skin breakdown can worsen the crying episodes. Vomiting and excessive stools may inhibit growth. Other symptoms include sneezing, nasal stuffiness, fever, sweating and tachycardia.

Maternal Drug and Alcohol History

A thorough history of maternal drug, alcohol, and tobacco use during pregnancy is essential to management of the drug-exposed newborn. If a history is not available (i.e., previously obtained by clinic or obstetrician), interview the mother to obtain the following information:

Specific drugs or types of drugs:

- **Illicit**: heroin, PCP, cocaine, etc.
- **Prescription drugs**: tranquilizers, opioids (pentazocine, hydromorphone, methadone, buprenorphine), diet pills, nicotine replacement, etc.
- **Over-the-counter**: dextromethorphan, bromides, etc.
- **Pattern of use** (amount, frequency, route, duration of drug use, with detailed history especially during last trimester of pregnancy).
- **Treatment** (involvement in drug treatment or voluntary dose reduction during pregnancy).

Nursery Admission

Infants with intrauterine exposure to drugs (identified by maternal history or positive urine drug screen) other than marijuana or cocaine should be admitted to Level 2 NICU. Infants with intrauterine exposure only to marijuana or cocaine are admitted to the Level 1 nursery but should be screened as all other drug-exposed babies. Common indications for toxicology testing in the neonate include no or limited maternal prenatal care, placental abruption, intrauterine growth restriction, a history of substance use disorder, or a positive drug screen during pregnancy. First-line workup for suspicion of drug-exposed infants should begin with a meconium drug screen with the first stool. Meconium will reflect drug use after 20 weeks, is more sensitive than urine, and results will return in a few days. The most reliable results require collection of meconium free of urine.

Urine screen (15–20 mL) can also be done; however, it only reflects exposure in the previous 48 hours. Umbilical cord segment testing is commercially available, but not routinely done in most BCM-affiliated nurseries.

Observation of opiate exposed infants for the presence of withdrawal is essential. A scoring system such as the modified Finnegan has long been used to document signs and symptoms, lending consistency to the parameters being evaluated and scored providing a tool to guide management decisions. All infants should be scored every 3 hours immediately after a feeding with the modified Finnegan Scoring System.

A newer functional scoring system called the Eat-Sleep-Console (ESC) approach has been reported to be beneficial. It is best paired with rooming-in with moms who are engaged in substance use treatment and interested in parenting their baby but can also be used for babies in the Level 2 nursery using alternate cuddlers. While mom or a human contact is the primary treatment, every 3 to 4 hours baby's nurse checks in with mom and/or other family caregiver to discuss how baby is eating, sleeping, and consoling during the entire time period. Baby does not need to be moved, undressed or examined to make this assessment. Babies having difficulties should first be supported to maximize all non-pharmacologic treatments available. Pharmacologic treatment of the infant should be based on infant function and comfort. Up to 3 PRN doses of morphine may be provided before moving to standing dosing as well as rapid weaning of the medication dose which is part of this approach. Babies rooming in should be moved to Level 2 for monitoring for 3-4 hours once medication is given.

Table 11–6. Onset, duration, and frequency of NAS caused by various substances

Drug	Onset, hours	Duration, days
Heroin	24-48	8-10
Methadone	48-72	up to 30 or more
Buprenorphine	36-60	up to 28 or more
Prescription opioids	36-72	10-30
SSRI	24-48	2-6
TCA's	24-48	2-6
Methamphetamines	24	7-10

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In 2018, the two largest studies to date reported the impact of ESC from quality improvement projects. Grossman et al. showed in 287 opioid exposed infants, the average length of stay decreased from 22 to 6 days, pharmacologic treatment with morphine was decreased by over 80% and costs associated with hospitalization also decreased significantly. In addition, Wachman et al. reported in 240 opioid exposed infants, pharmacologic treatment decreased by 47%, adjunctive agent use decreased by 31%, hospitalization rates decreased by 6 days, and total opioid treatment was reduced by 3.5 days. While the quality of evidence is very low, it may be worthwhile to consider this intervention when proper training and education has occurred (Weak recommendation, very low-quality evidence).

At-risk asymptomatic infants need to be observed for 4-7 days for opioid-exposed infants. However, a select group of patients may be discharged after 48–72 hours of observation if the following criteria are met:

- No maternal drug use during last trimester, or a history of cocaine or marijuana use only.
- Infant urine screen is negative, or it is positive only for cocaine or marijuana.
- Maternal HIV, hepatitis B, and RPR status known; appropriate evaluation and treatment completed.
- Consider asking Obstetricians to test for Hepatitis C if there is a history of maternal IV drug exposure.
- Infant is AGA or LGA and ≥37 weeks' gestation.
- No dysmorphic features.

- CPS has cleared patient for discharge or mom engaged in treatment with a plan of safe care in place.

Neonatal Opioid Withdrawal Syndrome

Treatment Protocol

The use of weaning protocols decreases the duration of pharmacological treatment, decreases length in hospital stay, and decreases the use of adjunctive drug therapy.

Non-Pharmacologic Treatment

Non-pharmacological interventions should be maximized before pharmacological interventions are initiated. Non-pharmacological inventions include frequent skin to skin, swaddling or containment, decreased sensory and environmental stimulation - clustering care and exposure to minimal light and noise. Frequent small volume feedings with higher calories may also be helpful. Encourage breastfeeding if it is not contradicted per guidelines. Rocker-beds have not shown to be beneficial and are therefore not recommended. Only vertical rocking (and not horizontal) should be used. When scores increase despite non-pharmacological interventions, pharmacological intervention should be initiated with either morphine or phenobarbital depending on the substances exposed to.

Pharmacologic Treatment

Morphine (strong recommendation, high quality evidence) is the most common first-line medication for NOWS. Treatment should be initiated if an infant has 3 consecutive scores >8 OR average of 8 or higher of 3 scores OR 1 score >12 (after verifying there was no confounding reason for the 1 elevated score). Scores <8 indicate that symptoms are controlled.

Initiation Dose: Morphine 0.05 mg/kg/dose q 3 hours PO

Escalation Dose: May increase morphine by 0.03 mg/kg/dose q 3 hours PO until symptoms are controlled, as demonstrated by average scores decreasing to <8 in 24 hours

Stabilization Dose: Maintain the same dose for at least 48 hours, with scores <8 before weaning.

Weaning Phase: Wean the dose by 10% of the original dose every 24 hours. Use 10% as the weaning factor for the rest of the treatment. Do not weight adjust the medication. Do not adjust or change the frequency of the medication. Keep frequency every 3 hours due to the short half-life of morphine. Morphine can be discontinued when the dose is <0.02 mg/kg/dose. If an infant has been very difficult to wean, or if has been on morphine for a prolonged period, in rare circumstances, interval can be weaned before discontinuation.

Backsliding: If infant has 2 consecutive NOWS scores >8 during the weaning process, assure that non-pharmacological measures are optimized before going back to the previous dose at which the patient was stable. If the infant's scores remain elevated (even after physical exam to ensure nothing else is wrong/bothering the infant), either weight adjust medication and/or continue to increase dose in a stepwise fashion until patient's scores are ≤8. Once stabilized on a new dose for minimum of 48 hours, resume 10% wean but consider weaning at less frequent intervals, e.g., q 48 hours instead q 24 hours.

Adjunctive Treatment

Phenobarbital is used by a majority of practitioners as an adjunctive agent when the morphine dose has reached >0.3 mg/kg/dose and scores are still >8; OR unable to wean morphine for >3 consecutive days OR/AND if polysubstance exposure is suspected or confirmed. Phenobarbital is also used as the drug of choice for NON-Opiate-NAS. Phenobarbital will not improve gastrointestinal symptoms associated with NOWS. There are many different recommendations for the dosing and weaning of phenobarbital. Phenobarbital levels of 20–30 mcg/mL have been proven to be effective in the treatment of NOWS. **Maintenance Dose**: 5 mg/kg/day divided q 12 hours.

Weaning Phase: The current dose should be maintained until scores are <8 for 3 days. Wean by 10% every 24 hours or 20% every 48 hours until the medication is discontinued entirely.

Clonidine can be used for adjunctive management of withdrawal symptoms. Monitoring blood pressure is recommended with Clonidine as it can cause hypotension with use and rebound hypertension when discontinued.

Initial: 0.5-1.5 mcg/kg PO every 4-6 hours

Maintenance: Increase over 1 to 2 days to target dose to target 3-5 mcg/kg/day divided every 4-6 hours

Weaning Phase: Taper **dose** by 25% of the total daily dose every other day

Feeding Guidelines:

General:

- Breastfeeding is encouraged when appropriate.
- Caloric needs may be as high as 150–250 cal/kg/day
- Frequent small volumes of hypercaloric (22–24 cal/oz) feeding or breastmilk every 2-3 hours may help minimize hunger and improve growth.
- Soy or "specialized formula" (Similac Sensitive) may improve feeding tolerance.

Breastfeeding is encouraged in the following situations:

- Mother stable on medication assisted treatment - methadone or buprenorphine - regardless of dose
- Substance use treatment provider endorses the Mother is engaged in recovery
- Mother plans to continue substance use disorder treatment during the postpartum period
- Negative maternal urine toxicology testing at delivery, except for prescribed medications
- Consistent prenatal care

Breastfeeding is discouraged in the following situations:

- Medical contraindication to breastfeeding (such as HIV, HSV lesion on the breast or HCV with cracked or bleeding nipples)
- No or limited prenatal care in the setting of substance use disorder
- Relapsed into illicit/licit substance use within 30 days prior to delivery (including marijuana or cocaine)

- Positive maternal urine toxicology testing for illicit substances at delivery (including marijuana or cocaine)
- Inability to engage in substance use disorder treatment
- No confirmed plans for postpartum substance use disorder treatment
- Demonstration of other indicators of active substance use disorder

Discharge

Patients must be monitored and observed for ≥48 hours off medications before discharge. An appointment with the primary physician must be secured before discharge to ensure proper follow-up. If a baby's drug screen is positive, the case should be referred to ~~Harris~~ County Children's Protective Services (CPS). If the case has been referred to CPS, notify CPS before allowing the baby to leave the hospital. ECI referral is highly recommended.

11.8 Pain Assessment and Management

The goal of pain management is to minimize procedural, post-operative or disease-related pain. **(Table 11–7)**

Assessment

Pain assessment is essential for optimal pain management. Pain should be assessed on admission and at regularly defined intervals throughout an infant's hospitalization. Developmental maturity, behavioral state, previous pain experiences and environmental factors all may contribute to an inconsistent, less robust pattern of pain responses among neonates and even in the same infant over time and situations. Therefore, what is painful to an adult or child should be presumed painful to an infant even in the absence of behavioral or physiologic signs. This general rule, along with the use of a valid and reliable instrument, should be used to assess pain.

Pain can be most effectively assessed using a multidimensional instrument that incorporates both physiologic and behavioral parameters. Multidimensional instruments with evidence of validity, reliability, and clinical utility include:

- PIPP, Premature Infant Pain Profile,
- CRIES, Crying, Requires increased oxygen administration, Increased vital signs, Expression, Sleeplessness, and
- NIPS, Neonatal Infant Pain Scale.

Physiologic measures should be used to assess pain in infants who are paralyzed for mechanical ventilation or who are severely neurologically impaired. Because the use of paralytic agents masks the behavioral signs of pain, analgesics should be considered

Non-pharmacologic Pain Management

Non-pharmacologic approaches may be used for minor to moderately stressful procedures to help minimize pain and

Table 11–7. Suggested management of procedural pain in neonates at Baylor College of Medicine affiliated

Procedure	Pacifier	Sucrose	Swaddling, Containment, or Facilitated Tucking	Local Anesthetic	Opioids	Other
Heel lance, venipuncture	✓	✓	✓			Consider venipuncture in full-term and older preterm infants; skin-to-skin contact with mother.
Percutaneous inserted venous catheter			✓	✓	✓	
Percutaneous arterial puncture/catheter	✓	✓	✓	✓		
Peripheral arterial or venous cutdown	✓	✓	✓	✓	✓	
Surgical central line	✓		✓	✓		Consider general anesthesia.
Umbilical arterial or venous catheter	✓	✓	✓			Avoid placement of hemostat clamps on skin around umbilicus.
Lumbar puncture	✓	✓		✓		Use careful physical handling.
Subcutaneous or intramuscular injection	✓	✓	✓			Give drugs intravenously whenever possible. Consider acetaminophen prophylactically for immunizations.
ET intubation (nonemergent)			✓		✓	
ET suction	✓		✓			
Nasogastric-orogastric tube	✓		✓			Gentle technique and appropriate lubrication.
Chest tube	✓	✓		✓	✓	Consider thoracentesis before chest tube insertion. Anticipate need for intubation and ventilation.
Circumcision	✓	✓	✓	✓		Dorsal penile nerve block, subcutaneous ring block, or caudal block using plain or buffered lidocaine. Consider acetaminophen for postoperative pain.
Ongoing analgesia for routine NICU care and procedures	✓	+/–	✓		✓	Avoid long-term sedation. Avoid midazolam. Minimize stress from environmental sound and light levels in the NICU.

Adapted from: Walden M. Breaking News: Managing Procedural Pain. NeonatalNews.Net July 2002;3(1):1,2.

stress while maximizing an infant's ability to cope with and recover from the painful procedure. All aspects of care-giving should be evaluated for medical necessity to reduce the total number of painful procedures to which an infant is exposed. Behavioral measures that may be employed to manage minor pain experienced by the infant include:

- Hand-swaddling technique known as facilitated tucking (holding the infant's extremities flexed and contained close to the trunk).
- Pacifiers for nonnutritive sucking (NNS). NNS is thought to modulate the transmission or processing of nociception through mediation by the endogenous non-opioid system.
- Sucrose is used to relieve neonatal pain associated with minor procedures such as heel stick, venipuncture, intravenous catheter insertion, eye exam, immunization, simple wound care, percutaneous arterial puncture, lumbar puncture and urinary catheter insertion. Studies demonstrate that a dose of 24% sucrose given orally about 2 minutes before a painful stimulus is associated with statistically and clinically significant reductions in pain responses. This interval coincides with endogenous opioid release triggered by the sweet taste of sucrose. Pain relief is greater in infants who receive both NNS and sucrose. The following dosing schedule is recommended:
    - Infants <35 weeks corrected age: 0.2 mL/dose every 2 minutes up to 3 doses; maximum dose for 1 procedure = 0.6 mL.**
    - Infants ≥35 weeks or more corrected age: 1 mL/dose every 2 minutes up to 3 doses, maximum dose for 1 procedure = 3 mL.**
    - Kangaroo care (skin-to-skin contact) has been found to be beneficial for pain associated with heel sticks in preterm infants ≥32 weeks' postmenstrual age.

** Per pain protocol only 3 series of doses may be given in one 24-hour period. Additional doses will require an additional physician's order.

Pharmacologic Pain Management

Pharmacologic approaches to pain management should be used when moderate, severe or prolonged pain is assessed or anticipated. Pharmacologic approaches in the NICU primarily consist of systemic analgesic therapy (opioid and non-opioid). Sedatives, including benzodiazepines and barbiturates, do not provide pain relief and should only be used when pain has been ruled out.

Opioids remain the most common class of analgesics administered in the NICU, particularly morphine sulfate and fentanyl citrate. The following dosages are based on acute pain management; neonates with chronic pain, or during end-of-life. Longer dosing intervals often are required in neonates <1 month of age due to longer elimination half-lives and delayed clearance of opioids as compared with adults or children >1 year of age. Efficacy of opioid therapy should be assessed using an appropriate neonatal pain instrument. Prolonged opioid administration may result in the development of tolerance and dependence.

Tolerance to opioids usually is managed by increasing the opioid dose. Neonates who require opioid therapy for an extended period of time should be weaned slowly. Refer to **Weaning Opioid Guidelines in this chapter.**

Morphine Sulfate

- **Intermittent IV dose –** 0.05–0.1 mg/kg over 5 to 10 minutes every 4–6 hours
- **Intermittent PO dose**
    - **Neonates:** 0.08–0.1 mg/kg every 4–6 hours
    - **Infants <6 months**: 0.08–0.1 mg/kg q3–4 hours
    - **Infants >6 months:** 0.2–0.5 mg/kg every 3–4 hours
- **Continuous IV infusion dose –** loading dose is 0.05–0.1 mg/kg over 5 minutes followed by a continuous infusion of 0.01–0.02 mg/kg/hour as a starting dose. The infusion should be titrated by no more than 0.02 mg/kg/hour every 30 minutes. If up-titration is necessary, a bolus is likely needed.

Fentanyl Citrate

- **Intermittent IV dose** – 1–2 mcg/kg/dose over 5 minutes every 2–4 hours
- **Continuous IV infusion dose** 0.5–1.0 mcg/kg/hour as a starting dose. Drip can be titrated by no more than 1 mcg/kg/hour every 30 minutes.

While opioid-induced cardiorespiratory side effects are uncommon, neonates should be monitored closely during opioid therapy to prevent adverse effects.

Acetaminophen

Acetaminophen is a non-steroidal anti-inflammatory drug commonly used short-term for mild to moderate pain in neonates. Intermittent dose and interval is based on the age and weight of the patient. Refer to hospital formulary for dosing.

If the oral route is unavailable, the rectal route is an alternative option for infants. Intravenous acetaminophen is also an option for pain relief in a patient who is NPO. Rectal administration has a longer duration of action than the intravenous route.

Procedural Pain Management

Newborn infants, particularly those born preterm, are routinely subjected to an average of 61 invasive procedures from admission to discharge, with some of the youngest or sickest infants experiencing >450 painful procedures during their hospital stay. These frequent, invasive, and noxious procedures occur randomly in the NICU and many times are not routinely managed with either pharmacologic or non-pharmacologic interventions. The International Evidence-Based Group for Neonatal Pain provides guidelines for preventing and treating neonatal procedural pain. Suggested strategies for the management of diagnostic, therapeutic and surgical procedures commonly performed in the Baylor-affiliated hospital NICUs are summarized in **Table 11–7.**

Weaning Opioid Guidelines

Opioid tolerance and dependence may occur in neonates with *in utero* exposure. More frequently in our unit, it occurs in neonates who receive analgesic therapy postnatally. Most of the time, patients receive opioids for a duration that necessitates weaning before discontinuation. This can be accomplished by

weaning from the original therapy or converting the patient to oral therapy (especially if patient no longer requires a central line for any other therapy). Weaning generally occurs over a similar duration to the patient's exposure to opioids.

Opioid Weaning Options

If risk factors for pain remain and/or an infant has elevated pain scores or exhibits physical and/or behavioral signs of pain, opioid weaning will be deferred and pain will be managed.

There are 3 opioid weaning options (based on duration of opioid therapy and/or dosage during therapy):

- **Short-term opioid therapy** (<3 days for fentanyl and <5 days for morphine):
  - **Therapy can be discontinued without weaning.**
- **Intermediate** opioid therapy (3–5 days to 2 weeks)
  - Must wean before discontinuing. How much to wean and how quickly depends on duration, dose, and patient clinical factors (e.g., pulmonary hypertension. Stop NAS monitoring 48 hours after opioid has been discontinued if NAS scores remain ≤7.
- **Long-term** opioid therapy (>2 weeks and/or maximum fentanyl >10 mcg/kg/hour or morphine >0.1 mg/kg/hour)
  - Wean opioid as described under intermediate weaning option,

OR

Convert patient to oral morphine if patient can tolerate oral therapy, continuous infusion dose is low enough for conversion, and central line can be removed. Be cautious when converting fentanyl to morphine in young infants; the conversion factors are different than those for older patients. Conversion to methadone should only be considered in patients who are not dependent upon their opioid for sedation and who require long-term weaning. The long half-life of methadone does not make it ideal for use in patients who can be weaned quickly.

The pharmacist should determine the weaning factor (calculated by taking the percentage that is going to be weaned and multiplying it by the original dose) which will be the amount that the dose will be decreased. This weaning factor will not change throughout the weaning process even as the doses overall become smaller. The weaning factor should be a straight mg dose (not mg/kg because the weight changes during the treatment). Use the modified Finnegan scoring system to monitor withdrawal in the patient. **CAUTION:** this scoring system is only validated for newborns so it must be interpreted cautiously when used for older babies. Review what signs/symptoms the patient is being scored for and determine if that is appropriate behavior for that age. An alternative withdrawal scoring scale may be necessary for patients >28 days of life.

11.9 Vein of Galen Malformation (VGAM)

Vein of Galen malformation is caused by a failure of the fetal Vein of Markowski to involute at 11–12 weeks' gestational age. Persistence leads to abnormal venous connections and dilation beyond 11-12 weeks' gestation, leading to dilation of the Vein of Markowski which consequently drains into the Vein of Galen. Blood quickly flows from the arterial vessels directly to low resistance venous systems without a capillary bed in between causing rapid circulation, high venous blood volumes, and venous pressure. Cardiac output is shunted toward the VGAM (as much as 80%) leading to poor systemic perfusion and blood supply. To compensate for the VGAM steal phenomenon, heart rate and total blood volume increase. Over time, this leads to high output cardiac failure.

Signs and Symptoms of VGAM

- High output cardiac failure
- Compromised coronary artery perfusion
- ↑ Pulmonary blood flow and venous return
- ↑ Pulmonary vascular resistance
- ↑ R to L shunt across the ductus arteriosus (if patent)
- Prerenal injury
- Hepatic insufficiency
- ↑ Venous return/CVP
- ↑ Intracranial pressure

Evaluation of VGAM

Evaluation of an infant presenting with VGAM includes imaging of the VGAM itself as well as assessment of end organ injury secondary to decreased systemic perfusion.

- If at TCH Woodlands, transfer infant to the TCH main campus West Tower level 4 NICU
- An echocardiogram should be ordered STAT to evaluate cardiac function
- A head ultrasound should be ordered STAT even if brain MRI or CT scan has been done to provide a baseline for future serial HUS comparisons
- An MRI of the brain without contrast should be ordered to evaluate the size of the VGAM (when the infant is stable and after initial evaluation and treatment)
- Obtain a full liver and coagulation panel to evaluate for hepatic insufficiency and synthetic function
- Obtain serum BUN and creatinine due to risk of pre-renal injury secondary to decreased systemic perfusion
- A STAT EEG must be ordered as many neonates with VGAM have subclinical seizures which is an important prognostic indicator

- Daily FOCs should be ordered to monitor for hydrocephalus
- Consults: Cardiology, Neurology, Neurosurgery, Interventional Neuroradiology (STAT, do not wait until morning)
- The Bicêtre Score must be calculated to determine if the patient is a candidate for palliative care only (<8), emergent embolization (8–12), or medical management with delayed embolization (>12). **(Table 11–8)**
    - If Bicêtre Score is between 8–12, emergently call Neurosurgery and Interventional Radiology for evaluation of an emergent embolization (Do not wait until morning)
    - If Bicêtre Score is <8, call Palliative Care Service, and discuss with colleagues if treatment is indicated

Medical Management

For patients with a Bicêtre Score >12 medical management consists of the following:

- Cardiac preload reduction strategies such as diuretics and fluid restriction
- Inotropic support to increase contractility and cardiac output
- Regular monitoring of liver function and coagulation studies with transfusion of blood products as needed
- Regular monitoring of renal function and urine output
- Daily FOC measurements and neurologic examinations

Endovascular Embolization

Endovascular embolization has become the standard of care treatment for VGAM and has led to improved neurologic outcomes. The goal is not to completely occlude the entire VGAM, but a large enough component to restore satisfactory circulatory physiology and minimize vascular steal of systemic organs and neighboring areas of developing brain. Selection and timing of embolization is challenging and the current best scoring system is the Bicêtre Score. A recent meta-analysis of endovascular embolization (treatment timing according to Bicêtre score) showed improved neurologic outcome in >60% of neonates treated (Strong recommendation, high quality evidence).

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Table 11–8. Bicêtre neonatal evaluation score[a]

Points	Cardiac function	Cerebral function	Respiratory function	Hepatic function	Renal function
5	Normal	Normal	Normal	—	—
4	Overload, no medical treatment	Subclinical, isolated EEG abnormalities	Tachypnea, finishes bottle	—	—
3	Failure; stable with medical treatment	Non-convulsive intermittent neurologic signs	Tachypnea, does not finish bottle	No hepatomegaly, normal hepatic function	Normal
2	Failure, not stable with medical treatment	Isolated convulsion	Assisted ventilation, normal saturation FIO^2 <25%	Hepatomegaly, normal hepatic function	Transient anuria
1	Ventilation necessary	Seizures	Assisted ventilation, normal saturation FIO^2 >25%	Moderate of transient hepatic insufficiency	Unstable diuresis with treatment
0	Resistant to medical therapy	Permanent neurological signs	Assisted ventilation, desaturation	Abnormal coagulation, elevated enzymes	Anuria

[a] EEG, electroencephalogram; FIO^2, fractional inspired oxygen. Maximal score = 5(cardiac) + 5 (cerebral) + 5 (respiratory) + 3 (hepatic) +3 (renal) = 21.

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Section 12: Newborn Care

Editors: Catherine Gannon and Tiffany McKee-Garrett

12.1 Routine Care

Introduction

Clinical issues in normal newborns provide challenges different from those that occur in the intensive care nursery, yet they are just as important. The physician should begin with a firm understanding of the transitional period and then progress to understanding normal findings and common abnormalities.

Transitional Period

Infants undergo a complex sequence of physiologic changes as they make the transition from intrauterine to extrauterine life. This transition is successful in almost all infants, although some may have cardiopulmonary abnormalities that require intervention.

Every effort should be made to facilitate 24-hour rooming-in of baby with mother. Observation of the healthy infant during the transitional period may occur in the mother's room with intermittent assessment by nursing personnel.

Bathing

A newborn's first bath is usually given during the first day of life when stability through the transitional period has been demonstrated, including normal blood glucose values for babies at risk for hypoglycemia. Before the umbilical cord falls off, a newborn should have sponge baths only. Thereafter, infants can be placed directly into warm water (warm to touch on the inside of one's wrist or elbow). In general, the first bath should be as brief as possible, in a warm room, and using mild, non-perfumed soaps.

Cord Care

Keeping the umbilical cord clean and dry is as effective and safe as using antiseptics and shortens the time to cord separation. Evidence does not support the use of frequent alcohol applications for routine cord care.

To reduce maternal concerns about cord care, health care providers should explain the normal process of cord separation, including appearance and possible odor. The parents should be instructed to keep the umbilical cord open to the air for natural drying and to use only water at the base of the cord to remove any discharge that may develop. The umbilical cord usually separates from the abdomen 6 to 14 days after birth.

Eye Care

As part of the initial newborn exam, the eyes are examined for reaction to the light, pupil size, general alignment and appearance of the conjunctiva and cornea. If mucopurulent material is produced from the lacrimal puncta when the lacrimal sac is pressed against the bones of the nose and medial orbital wall, there might be an obstruction of the nasolacrimal system. Repeated massage of the lacrimal sac at the medial canthal area serves to flush out the stagnant tears and decrease the risk of infection. A congenital dacryocystocele can manifest as a firm, medium-sized, bluish mass adjacent to the medial canthus. This distended lacrimal sac is filled with mucoid material and can become secondarily infected. Conservative management with topical or systemic antibiotics and massage is often successful, and referral to ophthalmology is recommended. The bulbar and palpebral conjunctivae are normally moist and pinkish. Redness or exudate is abnormal and may indicate infection.

Eye Prophylaxis and Vitamin K Administration

The incidence of gonococcal disease is approximately 0.3 cases per 1000 live births. Gonococcal conjunctivitis was the leading cause of infant blindness before the introduction of ocular prophylaxis by Credé in 1881, and it remains an important neonatal disease in developing countries. Ocular prophylaxis to prevent ophthalmia neonatorum is mandated in all 50 states. Texas Health and Safety Code, §81.091, requires a physician, nurse, midwife or other person in attendance at childbirth to provide ocular prophylaxis to prevent ophthalmia neonatorum. Appropriate prophylaxis includes the application of a 1 to 2 cm ribbon of 0.5% erythromycin to the eyes within 2 hours of birth. The erythromycin should **not** be flushed from the eye. After 1 minute, excess ointment can be wiped off.

All newborns are given vitamin K1 (phytonadione) as an IM dose of 0.5 to 1.0 mg within the first 6 hours of life. Vitamin K is essential for the formation of clotting factors II, VII, IX, and X. Fetal vitamin K is derived from the mother; however, placental transfer of the vitamin is poor. A newborn obtains vitamin K from the diet and putrefactive bacteria in the gut. Therefore, production of the vitamin is dependent upon the initiation of feeding. Vitamin K levels in breastmilk are low, even in mothers who are taking supplements. In a recent study, the average vitamin K1 intake of a breastfed infant corresponded to 7-13% of the recommended dietary intake of 10 mcg/day.

The risk of Vitamin K deficient bleeding (VKDB) is enhanced by the following clinical situations, further emphasizing the importance of prophylaxis at birth:

- breast-fed infants where lactation takes several days to become established
- infants who may not be enterally fed for several days
- infants with intestinal malabsorption defects
- infants of mothers who are on anticonvulsant medications, specifically phenytoin.

VKDB is classified according to when it presents:

- **Early** VKDB: occurs within 24 hours of birth. Seen almost exclusively in newborns whose mothers took vitamin K inhibiting drugs during pregnancy.
- **Classic** VKDB: 24 hours to 7 days of age.
- **Late** VKDB: 2- 24 weeks of age.

VKDB in the newborn can manifest as bleeding from various sites such as, needle puncture sites, the circumcision site, the umbilical stump, the GI tract, and the brain. 30-60% of babies with late onset VKDB will have intracranial bleeding which can result in long term neurological sequelae and possibly death.

Without prophylaxis, the incidence of early and classical VKDB ranges from 0.25 – 1.7%. The incidence of late VKDB is estimated at 4.4-7.2 per 100,000 infants. Either oral or parenteral administration of vitamin K has been shown to prevent early-onset VKDB. However, parenteral administration of vitamin K is best for the prevention of late-

onset VKDB. Additionally, an oral form of Vitamin K for the prevention of VKDB has not been approved for use in the United States. Administration of neonatal vitamin K is not required by law in the state of Texas. However, if a parent refuses Vitamin K administration, a discussion should ensue with the provider about the role of IM vitamin K for the prevention of VKDB, and the potential devastating consequences of vitamin K refusal. Despite counseling, if a parent refuses vitamin K prophylaxis, the practitioner must provide detailed documentation in the permanent medical record. Additionally, if available at the institution, a refusal of medical treatment form should be signed by the parent and placed in the medical record.

Nails

Newborn fingernails are small and grow quickly. They should be trimmed as needed using an emery board or nail clippers made specifically for babies. Fingernails should be kept short and smooth to prevent scratching.

Non-Sterile Deliveries

When a non-sterile delivery occurs, always question whether the infant was placed at risk for infection. Each case must be considered individually. However, if the umbilical cord was not cut with sterile scissors or a sterile scalpel, prevention of neonatal tetanus may be a consideration, although the risk is quite low. Most mothers who have been immunized for tetanus have adequate levels of tetanus antibodies to protect their infants. When the mother's immunization status is unknown, or inadequate, and the umbilical cord was not cut in a sterile fashion, tetanus immune globulin, 250 IU, IM -- regardless of the age or weight should be given as soon as possible. If tetanus immune globulin is unavailable, IVIG is recommended.

Security

Before a newborn leaves Labor & Delivery, the parent(s) and the infant receive matching identification bracelets bearing mother's name and other identifying data. Hospital staff should always check these bracelets when an infant is taken from or returned to the mother's room. Only the parents and authorized hospital personnel, clearly identified by ID badges, should transport infants in the hospital. It is also standard of care to place an electronic monitor on the baby as an additional security measure. These monitors will cause an alarm to sound in the event the monitor (i.e., infant) approaches an exit.

Skin

A newborn's skin may be sensitive to chemicals in new clothing or detergent residues. All washable items should be laundered with mild detergents and double-rinsed before use. In general, newborn skin does not need any lotions, creams, oils, or powders. If skin is excessively dry or cracked, apply only skin care products made for infants.

Sleep Position

The AAP recommends that healthy infants be placed in a supine position for sleep. A supine position confers the lowest risk for sudden infant death syndrome (SIDS). The side position is not recommended. Soft surfaces, such as pillows, soft mattresses or sheepskin should not be placed under infants. The use of pacifiers at naptime and bedtime throughout the first year of life has been associated with a reduced risk of SIDS. Rarely will conditions such as gastroesophageal reflux and upper airway anomalies preclude the recommended supine position. Nighttime sleeping in car seats or baby swings is not recommended.

Social Issues

A Social Work consultation in the newborn nursery is recommended for the following situations:

- Maternal age 16 years or younger, or mother is multiparous and less than 18 years of age
- Maternal history of substance use disorder.
- Maternal history of mental illness
- Suspected abuse of the mother (either mental or physical) by a family member or significant other.
- Significant maternal postpartum complications necessitating discharge of baby without the mother.

Urination and Bowel Movements

Twenty-five percent (25%) of males and 7% of females will void at delivery, and 98% of all infants will urinate within the first 30 hours of life. Newborns may void as frequently as every 1 to 3 hours or as infrequently as 4 to 6 times a day. First voids occurring on the warmer at delivery need to be clearly documented in the baby's medical record. Any infant with suspicion of failure to void within the first 30 hours of life requires a thorough examination, with focus on palpable, enlarged kidneys or a distended bladder, as well as a careful neurologic examination of the lower extremities. It is important to also ensure that the baby is receiving adequate intake **(Ch 12.6-Feeding).** Diagnostic investigation with ultrasound, and urology consultation if abnormal exam findings are present, should be considered.

Meconium usually is passed within the first 48 hours of life. An infant who does not pass stool in the first 48 hours of life requires further evaluation. Over several days, the stool transitions to a yellow-green color and looser consistency. Bowel movement frequency varies. Many infants will stool after each feeding (gastrocolic reflex), others only once every several days. In general, formula-fed infants have at least one bowel movement a day; breast-fed infants usually have more. Change diapers as frequently as an infant wets or stools. Clean the area with mild soap and water. Keeping the area as clean and dry as possible prevents most irritations and diaper rash.

If redness occurs, change the diapers more frequently, expose the area to air to promote healing, and consider applying a protective barrier of ointment. Excoriation of the diaper area is common in the early newborn period and should be treated with simple barrier preparations such as zinc oxide (Desitin™, A&D Ointment™) or petroleum jelly (Vaseline™), in lieu of expensive preparations such as Aquaphor™ or those that contain cholestyramine.

If a red, raised, pinpoint rash develops, irritation persists, or the creases are involved, a secondary Candida infection may be present and should be treated with topical nystatin or antifungal azole.

Vaccines

As recommended by the AAP and the Advisory Committee on Immunization Practices of the CDC, all babies with a birth weight greater than or equal to 2 kg should receive the first Hepatitis B vaccine (HBV) by 24 hours of age. Infants with a birth weight < 2 kg should receive the first (HBV) at one month of age, or at hospital discharge, whichever occurs first. **(Ch 8.9-Hepatitis B).**

12.2 Cardiac Murmurs

One of the most common abnormalities noted in the physical exam of an otherwise asymptomatic neonate is a murmur. Appropriate management requires knowledge of the transitional circulation (**Sec 2-Cardiac Care**).

Normally, upon delivery and initiation of spontaneous respiration, pulmonary vascular resistance drops rapidly with increased pulmonary blood flow and a transient reversal of blood flow at the level of the atria and ductus arteriosus. Based on these changes, murmurs in the first 24-48 hours of life often reflect flow through the ductus arteriosus or turbulent flow in the branches of the pulmonary arteries.

While much of the focus of the cardiac examination is on the presence or absence of a murmur, auscultatory findings must be assessed in the context of the rest of the cardiac exam including:

- assessment of general well-being by inspection,
- respiratory rate and work of breathing,
- peripheral perfusion,
- absence or presence of central cyanosis,
- upper and lower extremity pulses, and
- inspection and palpation of the precordium.

Assessment

Murmurs are common in the neonatal period. The majority of these murmurs are physiologic and can be separated into several main types.

Ductus arteriosus murmur represents left-to-right blood flow through the ductus as the pulmonary vascular resistance falls and before the ductus closes. Often it is heard in the first day of life. The murmur can be continuous but most often is mid-systolic and crescendo. It is best heard at the cardiac base and over the left scapula. It often disappears by the second day of life as the ductus closes functionally. When a murmur consistent with a ductus arteriosus is heard, serial exams are indicated. If the murmur persists or the infant becomes symptomatic, consider a more complete workup.

Pulmonary branch stenosis murmur results from turbulent blood flow in the pulmonary artery branches secondary to:

- rapidly falling pulmonary vascular resistance
- difference in the diameters between the main pulmonary branch and the left and right pulmonary branches
- acute angle of the branches

The murmur of pulmonary branch stenosis is benign and is heard best over the cardiac base and lung fields with radiation to the axillae and back.

Pathological murmurs heard on the first day generally are related to obstructed ventricular outflow. They are heard best at the left or right upper sternal border and typically are grade 2 or 3 and systolic. Murmurs that are consistent with increased blood flow, such as those occurring with atrial septal defects, are rarely heard in the first week of life. Murmurs consistent with a ventricular septal defect often are not heard on initial exam and usually are first heard late on the first day or into the second or third day of life. Initially the murmur may be assessed as being unremarkable, resembling a benign flow murmur but, as the pulmonary vascular resistance drops, the murmur becomes more evident. The murmur of a ventricular septal defect is heard best over the mid to lower-left sternal border. The murmur is harsh and high-pitched and often obliterates the first heart sound.

Workup

Once a murmur is detected, the extent of the workup is based on several factors. In an asymptomatic infant with a heart murmur, the likelihood that the murmur indicates congenital heart disease has been reported to be less than 10%. Asymptomatic murmurs that do not require a workup usually are grade 1 or 2, do not radiate significantly, and are not heard over the ventricular outflow tracks.

Consider a workup for murmurs that are greater than or equal to grade 2 to 3 with extensive radiation, and any murmur heard best over the ventricular outflow tracks. The cardiac work-up consists of a chest X-ray to evaluate heart size, an ECG, four extremity blood pressures, and pre and post-ductal pulse oximetry readings in room air. An echocardiogram and consultation with a Cardiologist may be necessary; this should be discussed with the Newborn Attending or the Senior Resident.

12.3 Dental

Natal teeth are present at birth and neonatal teeth erupt from birth to 30 days after birth. The incidence of natal or neonatal teeth is 1:2000 live births, 15% have a family history of natal or neonatal teeth, and natal teeth are more common than neonatal teeth (4:1). In 95% of cases, both types of teeth correspond to normal primary dentition, while 5% are supernumerary. The teeth are more prevalent on the mandible than the maxilla (10:1). Although usually an isolated finding, natal teeth may be associated with some syndromes such as Ellis-van Creveld syndrome, Soto's syndrome, pachyonychia congenita, and Hallerman-Streiff syndrome. Treatment of natal teeth can include observation only, smoothing of the incisal edge to prevent discomfort during breast feeding, or extraction.

The decision to keep or extract a natal or neonatal tooth should be evaluated on a case-by-case basis. Factors to consider include:

- implantation and degree of mobility
- interference with breastfeeding
- risk of aspiration (especially in someone with specific inability to protect the airway)
- normal dentition vs. supernumerary - supernumerary teeth are typically extracted

Some evidence demonstrates the importance of keeping a tooth that is part of the normal dentition since premature loss of a primary tooth may cause a loss of space and collapse of the developing mandibular arch with consequent malocclusion in permanent dentition. Consider consultation with a pediatric dentist or the Oral and Maxillofacial surgery service if extraction is desired or the management approach is unclear.

12.4 Dermatology

Birthmarks

The majority of birthmarks noted in the newborn period are not of medical significance and warrant only observation.

Common benign birthmarks include:

- **Salmon patches** (a.k.a. macular stain, nevus simplex, "stork bite", "angel kiss") - are the most common vascular malformations, are of capillary origin, found on baby's forehead, eyelids, nose, upper lip or back of the neck and almost always fade by 18 months without need for intervention.
- **Congenital dermal melanocytosis (CDM)** - also known as Mongolian spots, are the most common form of cutaneous hyperpigmentation seen in neonates. They occur when some of the skin's pigment gets "trapped" in the deeper layers of skin during the infant's development. When the pigment does not reach the surface, it appears as a gray, greenish, blue, or black mark, most often in the sacral region. They are present in 96% of African American babies and 46% of Hispanic babies. They are less common in Caucasian babies. Mongolian spots are benign and typically fade by adulthood.
- **Infantile hemangiomas** - are the most common benign tumors of infancy, consist of proliferation of vascular endothelium, are not typically present at birth, and are characterized by phases of rapid proliferation followed by involution in greater than 80% of patients. Very few require active therapy (see following section).

Occasionally, certain skin findings require further investigation and/or Dermatology consult.

These include:

- **Café au lait spots** - may be a first sign of neurofibromatosis. These are often seen in healthy children, but six or more spots greater than 0.5 cm in diameter warrant further investigation or consult.
- **Nevus-Flammeus (Port-Wine Stain) -** typically a darker red and larger than the salmon patch, and it may be indistinguishable from early infantile hemangiomas. These do not fade and can be associated with Sturge-Weber syndrome, particularly if large and located in the distribution of the first two branches of the trigeminal nerve, or in the setting of macrocephaly or seizures.
- **Nevi, melanocytic** - benign proliferations of cutaneous melanocytes, present either at birth or within the first few weeks of life. The incidence of congenital melanocytic nevi (CMN) is approximately 1%. Newborns with large CMN (>9cm on the head or >6cm on the body) should be referred to dermatology for close follow-up due to the risk of malignant transformation associated with large lesions.
- **Infantile hemangiomas -** further investigation is necessary and treatment may be needed if the lesion is in a concerning location such as periorbital, the beard area, the midline back, more than 10 are present or if they are large, ulcerated or painful.
- **Depigmented lesions** - Multiple hypo pigmented (ash-leaf) macules should raise concern of tuberous sclerosis, particularly in the setting of seizures and/or heart murmur.
- **Nevi, sebaceous** - occur in 0.3% of newborns. Typically located on the scalp or face, these lesions are isolated smooth plaques that are hairless, round or linear, slightly raised, and range from pink to yellow, orange, or tan. Large lesions require investigation, particularly in the setting of abnormal neurological findings and/or seizures, and may become a cosmetic concern during adolescence secondary to the onset of verrucous hyperplasia. A variety of benign and malignant tumors may arise from within sebaceous nevi but this is uncommon.

Dimples

Skin dimples - Either simple depressions in the skin of no clinical significance or actual sinus tracts connecting to deeper structures. Dimples are often seen over bony prominences such as the knee joint. If found over long bones, consider the diagnosis of congenital hypophosphatasia or other bony disorders. Skin dimples located over the sacrum or lower back are often normal. Occasionally these dimples can reflect occult spinal dysraphism (OSD).

In general, a sacral or lower back dimple is benign if all of the following are noted:

- Solitary lesion
- Located within the gluteal cleft
- Located less than 2.5 cm above the anus
- Completely covered by skin

Certain findings associated with sacral or lower back dimples warrant further evaluation. **These findings include:**

- location more than 2.5 cm above the anus
- multiple dimples
- diameter greater than 5 mm
- Presence of cutaneous markers such as:
  - » Duplicated gluteal cleft
  - » Dermal sinuses (if discharge is present, immediate referral to neurosurgery is warranted due to risk of bacterial meningitis or intraspinal abscess.)
  - » Mass or lipoma
  - » Hypertrichosis
  - » Vascular lesions (i.e., hemangioma or telangiectasia)
  - » Dyschromic lesions (other than CDM)
  - » Aplasia cutis congenita
  - » Polypoid lesions (i.e., skin tags or tail-like appendages)

MRI is more reliable than ultrasound for the diagnosis of OSDs. However, because ossification of the vertebral arches does not occur before 3 months of age, ultrasound is a useful, non-invasive tool for evaluating sacral dimples in the newborn nursery. If the ultrasound is abnormal, an MRI of the spine should be performed.

Ear Tags and Pits

The incidence of pre-auricular skin tags and/or ear pits (PSEP) is estimated to be 0.3-5%. Often PSEPs are familial, they are twice more common in females than in males, and more common in blacks than whites. Infants with ear anomalies (as well as those with facial, head, or neck anomalies) have a higher risk for hearing impairment. Inclusion in the Universal Newborn Hearing Screening Program should detect hearing loss and OAE has been shown to be sufficient screening for infants with PSEPs. Babies with isolated PSEPs are not at increased risk for renal anomalies, however, isolated preauricular pits or tags accompanied by one or more of the following warrants a renal ultrasound:

- other malformations or dysmorphic features
- family history of deafness,
- maternal history of gestational diabetes.

In the absence of these findings, renal ultrasonography is not indicated.

Forceps Marks

Forceps marks may occur where instruments were applied and may be associated with nerve, soft tissue, or bony injury. Periorbital bruising may indicate an eye injury. Consult an ophthalmologist to evaluate for the presence of hyphema or vitreous hemorrhages. Ear injury may be associated with inner ear hemorrhage and fracture of the temporal bone requiring an ENT evaluation.

Lacerations

Lacerations may occur during cesarean sections and commonly affect the scalp, buttocks, and thighs. Superficial wounds can be treated with wound closure adhesive strips. Deeper wounds, especially if bleeding, should be sutured. Consider a Plastic Surgery consult if the laceration is located on the face. Keep the affected area clean to minimize risk of infection.

Nipples, Extra

Incidence of supernumerary nipples is 2 to 3 per 1000 live births. They are more common in darkly pigmented racial groups and occur along the milk line. The breast tissue may present as another fully developed nipple or as an oval, pigmented spot that is smaller than half the size of the normal nipple. There is no association with other anomalies.

Rashes, Benign

Erythema Toxicum (urticaria neonatorum) is the most common rash in term infants (40% to 50% of newborns) and is self-limiting and benign. It is not seen in premature infants and is rarely seen in postmature infants. It usually appears in the second or third day of life although it can be present at birth (18% to 20% of infants). It is seldom seen after 14 days of age. The etiology is unknown. Biopsy or a stain of the material in the lesions reveals eosinophils.

Pustular melanosis is a skin eruption consisting of vesicopustules and pigmented macules and has a reported incidence of 0.5% to 2% of newborn infants. The lesions usually are present at birth and are not associated with systemic symptoms or evidence of discomfort. The pigmented macules (freckles) persist for weeks to several months. It is a self-limiting, benign condition that requires no therapy and is more common in darkly pigmented infants.

Scalp Electrode Marks

Electrode marks result from direct monitoring of the fetal heart rate during labor. Applying an electrode to a fetal scalp or other presenting part may lead to lacerations, hematomas, and superficial abrasions. Usually only local treatment is required. If an abscess develops, evaluate for possible sepsis.

Subcutaneous Fat Necrosis

Subcutaneous fat necrosis is characterized by necrosis and crystallization of subcutaneous fat with an inflammatory and foreign-body–like giant cell reaction, which most often is found in the subcutaneous fat adjacent to a bony structure. This usually occurs during the first week of life and is described as a well-defined red or purple induration of variable size appearing on the skin. The nodules are usually not tender or warm, but they can be. Most frequently it is seen in large-for-gestational-age infants, especially those born via vaginal or traumatic delivery, and those with birth asphyxia. There is risk of hypercalcemia when extensive subcutaneous fat necrosis is present. Lesions usually self-resolve within 1-2 months but may persist longer if calcified.

12.5 Extracranial Swelling

Caput Succedaneum

Caput succedaneum is a vaguely demarcated area of edema and bruising of the presenting portion of the scalp due to increased pressure of the vaginal and uterine walls on the fetal head during labor. The soft tissue swelling extends across suture lines above the periosteum and directly under the skin, and may be associated with petechiae, purpura, and ecchymosis. Usually no specific treatment is indicated, and resolution occurs within several days.

Chignon

Chignon or artificial caput succedaneum is caused by interstitial fluid and micro hemorrhage that occur under a vacuum cup during vacuum assisted deliveries. Chignons are less pronounced with soft cups. The chignon should resolve in 12 to 18 hours.

Cephalohematoma

A cephalohematoma is a subperiosteal collection of blood usually affecting the parietal bones. The bleeding generally occurs during labor or delivery and is caused by the rupture of diploic blood vessels and the separation of periosteum from the bone. The occurrence rate is 1-2% of all deliveries regardless of the mode of delivery. They are more common in prolonged labors and instrument assisted deliveries.

Clinical Manifestations

A cephalohematoma is sharply demarcated by periosteal attachments to the surface of one cranial bone and will not cross suture lines. Cephalohematomas usually do not have overlying discoloration and they can have a delayed or gradual presentation due to slow subperiosteal bleeding. Generally, cephalohematomas are benign; however, some may be associated with complications such as skull fractures (rare), hyperbilirubinemia, hyperkalemia, infection, and anemia.

Management

Cephalohematomas typically require no intervention and spontaneously resorb by 2 weeks to 3 months of age.

Calcification may occur when the hematoma does not resolve spontaneously. Calcium deposits can cause a bony swelling that may persist for several months, less often years, and rarely even into adulthood. Incision or aspiration of the cephalohematoma is contraindicated since the clots will tamponade the bleeding.

Subgaleal Hemorrhage

Subgaleal hemorrhage (SGH) is an accumulation of blood in the space between the epicranial aponeurosis and the periosteum, caused by rupture of the emissary veins. This potential space extends from the orbital ridge to the nuchal ridge and laterally to the temporal facia. This potential space is so large that this type of extracranial bleeding may become massive and life-threatening. The occurrence of SGH is highest with vacuum extraction deliveries, but can also occur with spontaneous vaginal delivery, particularly in the setting of prolonged pushing. The incidence of SGH is estimated to be 59/10,000 for vacuum extraction deliveries and 4/10,000 for spontaneous vaginal deliveries. The risk of SGH increases with failed vacuum extraction, "rocking" motion of the vacuum cap on the newborn skull, and multiple pulls with the vacuum.

Clinical Manifestations

Subgaleal hemorrhage may present with rapidly progressing, diffuse cranial swelling, ill-defined borders, and firm, pitting, or fluctuant consistency possibly with fluid waves. SGH often displaces the ears anteriorly and causes periorbital swelling and ecchymosis. It can cause a "helmet-like" appearance and is often most prominent in the dependent areas. The anatomic limits of SGH include the frontal orbital margins, posterior nuchal ridge and lateral temporal fascia. Extracranial symptoms include signs of hypovolemia (pallor, tachycardia, shock) and CNS injury (lethargy, hypotonia, seizures). Intracranial bleeds and skull fractures are often associated with SGH. The potential for massive blood loss into this space (up to the entire neonatal blood volume) contributes to the high mortality rate of 11-15% associated with this lesion. **(Table 12–1)**

Evaluation and Management

Treatment of SGH begins with early recognition and is an important key to intact survival. When subgaleal hemorrhage is suspected, the infant must be closely monitored in the NICU, with frequent vital signs, serial head circumference measurements done hourly until stable, serial hematocrits, and close observation for signs of hypovolemia. A decrease in hematocrit is a late sign. The infant's head circumference will increase 1 cm with each 40 mL of blood deposited in the subgaleal space. Treatment includes volume resuscitation with normal saline, packed red blood cells, and fresh frozen plasma as appropriate for ongoing bleeding and coagulopathy correction. If SGH is suspected, an MRI or CT of the head, or head ultrasound (if done by an experienced provider), will be helpful in distinguishing SGH from other forms of extracranial swelling. A neurosurgical consultation should be obtained for infants who continue to worsen despite aggressive volume resuscitation. Long term neurologic follow up is important.

Table 12–1. Features of extracranial swelling

	Condition		
Feature	**Caput Succedaneum**	**Cephalohematoma**	**Subgaleal hemorrhage**
Location	crosses sutures	does NOT cross sutures	crosses sutures, most prominent in dependent areas
Findings	vaguely demarcated, "wet sponge" consistency	firm; distinct margins, "hard-boiled egg" consistency	diffuse, shifts to dependent area, "water-bed" consistency
Timing	noted at birth	hours to days after birth	at birth or hours later
Blood Volume	None to very little	10-40 mL	>50-40 mL

12.6 Feeding

Breastfeeding

Breastfeeding has long been recognized as the superior form of nutrition during the first year of life. The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for the first 6 months of life and encourages practitioners to "promote, protect, and support" the practice of breastfeeding. Formula fed infants have significantly more respiratory, middle ear, and gastrointestinal infections than breastfed infants. Additionally, formula fed babies are more likely to develop allergic and autoimmune disorders and have a higher incidence of Sudden Infant Death Syndrome (SIDS). Physicians should encourage all mothers to breastfeed unless medically contraindicated, and must be able to assist new mothers with common breast feeding issues.

Methods and Practices

A newborn should be put skin to skin with mother as soon after delivery as possible and allowed unlimited access to the breast. The AAP recommends the initiation of breastfeeding within the first hour after birth for both vaginal and cesarean deliveries. If the mother is unable to breastfeed within an hour after delivery, donor breastmilk may be available in some hospitals for baby's first feedings. Breastfeeding should occur **with baby hunger cues**, usually at a frequency of **8-12 times a day**, and lasting until the infant is satisfied, which is usually for a duration of at least 10 to 15 minutes on each breast. Breastfeeding is a supply-and-demand phenomenon; frequent and effective emptying of the breast is required for a plentiful milk supply. Water supplements should not be given to newborns. Introduction of a pacifier and other artificial nipples should be discouraged before breastfeeding is well established (~ first 4 weeks of life) as it may decrease breastfeeding success.

Assessment of Breastfeeding

Infant signs of effective breastfeeding include:

- Maintains deep latch on to breast.
- Long jaw movements observed
- Some swallowing heard/observed
- Minimal to no maternal discomfort

Assess all breastfed newborns for adequate hydration status in the first few days after delivery, especially if mother is nursing for the first time.

The following are guidelines for breastfeeding and output during the first few days:

- Birth-24 hours:
  - » Frequent Skin to Skin (STS)
  - » At least 8 breastfeeding attempts (volume will be ~2-7 ml/feed)
  - » 1 urine/1 or more stool
  - » ≥8-12 breastfeeds (volume will be ~10-20 ml/feed)
  - » 3 urine/3 or more stools.

Most babies have at least 1 wet diaper for each day of life up to day 6, at which time expect at least 6 wet diapers per day. The breastfed newborn usually has 1 stool with each feeding, however, stooling patterns are variable and should not be exclusively used as an indicator of effective breastfeeding. The stools of breastfed babies are typically yellow, seedy and have a loose consistency, while formula stools are more formed and occur less frequently. Mothers who are nursing for the first time may need additional reassurance that these stools are normal. Loose bright green stools in a breastfed infant may be an indication that the mother has an oversupply of milk and the infant is getting too much foremilk compared to hindmilk. In these situations, the mother may need lactation assistance in achieving a more appropriate balance of foremilk and hindmilk for the infant.

Ankyloglossia and Superior Lingual Frenulum

Ankyloglossia, commonly known as tongue-tie, is a congenital oral anomaly characterized by an anterior attachment of the lingual frenulum, or a short/tight lingual frenulum, that can restrict the mobility of the tongue. Reported prevalence of ankyloglossia ranges from 4 to 11% and tends to run in families. While diagnosis and management of tongue-tie remains controversial, the AAP Section on Breastfeeding states "Tongue-tie is a significant clinical entity which, when symptomatic, should be treated as early as possible." Assessing an infant with suspected ankyloglossia often requires collaboration between the nurse, lactation consultants and pediatrician. The use of a validated objective assessment tool such as the Hazelbaker Assessment Tool for Lingual Frenulum Function is recommended. Ankyloglossia in infants can be treated with frenotomy (clipping of the frenulum). A 2017 Cochrane review revealed that frenotomy reduced maternal nipple pain scores, however, a positive effect on infant breastfeeding quality was not consistently seen in the small number of studies included. The review also showed no serious complications in any of the studies reviewed.

Superior Labial Frenulum, commonly known as upper lip-tie, is a diagnosis of unknown significance. All newborns have some degree of superior labial frenula. Some experts feel that superior labial frenulum can interfere with breastfeeding by restricting the movement of the upper lip and interfering with proper latch. Classification systems for severity of superior labial frenulum exist but none show good intra- or inter-rater reliability. Currently, few studies of lip-tie and breastfeeding exist and there are no randomized controlled trials. Overall evidence is poor that breastfeeding outcomes are improved by release of upper lip-tie. Referral to a pediatric dentist or otolaryngologist is typically necessary to obtain a lip-tie release.

Supplementation: Healthy Term Newborns

A mother who plans to breastfeed should be encouraged to feed her baby on demand and avoid any formula supplementation. If medically indicated, babies can be supplemented with expressed breastmilk (EBM), pasteurized donor human milk or, if these are not available, standard infant formulas can be used. When supplementation is medically necessary, the volume given to the infant should be appropriate for his/her age in order to prevent overfeeding that can interfere with breastfeeding (**Supplementation Guidelines below).**

Indications for Supplementation: Infant Issues

- Asymptomatic hypoglycemia unresponsive to appropriate and frequent breastfeeding
- Significant dehydration (10% weight loss or greater with insufficient urine output, hypernatremia, lethargy, poor feeding) not improved with lactation support and intervention.
- Weight loss of greater than 7% associated with delayed lactogenesis II (DOL 5 or later).
- Continued meconium stools on DOL 5
- Poor milk transfer despite an adequate milk supply

Indications for Supplementation: Maternal Issues

- Sheehan syndrome (Postpartum hemorrhage followed by absence of lactogenesis)
- Primary glandular insufficiency
- Breast pathology/surgery resulting in poor milk production.

Supplementation Guidelines

Type: Colostrum/EBM and/or donor human milk is first choice, then formula.

Method: tube feeding at breast (such as Medela® Supplemental Nursing System (SNS) or Lact Aid Nursing Trainer) is first choice where available, then syringe, spoon, cup, or bottle. Method should be determined in consultation with mother. Note that bottle feeding is the most likely method to interfere with proper latch to the breast.

Amount per feed:

- Birth-24 hours: 2-5 mls
- 24-48 hours: 5-15 mls
- 48-72 hours: 15-30 mls

Supplementation, Vitamins and Iron

Exclusive breastfeeding for more than 6 months has been associated with increased risk of iron deficiency anemia at 9 months of age. Thus, the AAP recommends that exclusively breastfed term infants receive an iron supplementation of 1 mg/kg/day starting at 4 months of age and this supplementation should continue until appropriate iron-containing complimentary foods have been introduced. Breastfed term infants who are < 2500 gm at birth require a daily iron supplement beginning in the first week of life. The AAP also recommends a daily intake of vitamin D of 400 IU/day for all infants. Breastfeeding infants can achieve this with an over the counter infant vitamin D supplement (i.e., 1 ml/day of D-Vi-Sol®) beginning in the first few days of life. **(Sec 13-Nutrition).**

For a lactating mother on a normal diet, the need for vitamin supplementation is not well documented. Some vegetarian diets (especially vegan diets) are deficient in B12, and B12 deficiency has been documented in breastfed infants of some vegetarian mothers. Thus, continued intake of prenatal vitamins may be particularly helpful for lactating vegetarian women.

Weight Loss

Infant weight loss during the first several days after birth is physiologic. The AAP recommends prompt evaluation of newborns with **> 7%** weight loss with a careful feeding history, physical exam, and breast feeding assessment **(see Assessment of Breastfeeding above)**. Historically, weight loss of up to 10% has been considered within normal limits. Babies delivered by C-section tend to lose more weight than babies delivered vaginally. A large study of exclusively breastfed infants demonstrated 50th percentile for weight loss to be 7% for vaginally delivered infants, and 9% for infants delivered by C-section.

Infants should stop losing weight by DOL 5 and typically regain their birthweight by 10-14 days of age. Once feeding is established, newborns are expected to gain 20-30 gm/day. If intake seems sufficient and weight loss persists, consider evaluation for failure to thrive.

Working Mothers

Ideally, nursing mothers should continue to provide their infants with human milk after returning to work. An efficient, double electric breast pump can facilitate this (hand powered or battery powered pumps are less effective in maintaining a milk supply). Federal law (Section 7 of the Fair Labor Standards Act) requires an employer to provide both reasonable break time and a place, other than a bathroom, that is shielded from view and free from intrusion for an employee to express breastmilk for her nursing child for one year after the child's birth. If a mother does not desire to express breastmilk at work, she should be encouraged to continue nursing when she is with her infant and to supplement feedings with an iron-containing formula while separated from her infant. If good breastfeeding has been established, the mother's body will usually adjust to the new schedule.

Contraindications to Breastfeeding

(Sec. 13-Nutrition)

Very few contraindications to breastfeeding exist. These include:

- Infants with classic galactosemia
- Mothers who are positive for human T-cell lymphotropic virus type I or II
- Mothers with untreated brucellosis
- Maternal active, untreated tuberculosis (TB)(breastfeeding is allowed after a minimum of 2 weeks of treatment and documentation that the mother is no longer infectious)
- Active herpes simplex lesions on the breast
- HIV-positive mother (in the U.S.)
- Active maternal substance use disorder

Breastfeeding and Maternal Substance Use

Mothers with substance use disorders undergoing treatment and with a negative urine drug screen at delivery are highly encouraged to breastfeed.

Mothers with a valid prescription for an opiate or benzodiazepine and with a positive urine drug screen at delivery can breastfeed but should be informed of and be vigilant for potential side effects in the infant. If any side effects present in the infant (ex. excessive sleepiness in the infant), breastfeeding should cease.

Per the AAP, breastfeeding is contraindicated for mothers using amphetamines with or without a prescription (ex. Adderall).

Breastfeeding in other mothers with a positive urine drug screen at delivery is not immediately recommended. If a mother with a positive drug screen desires to breastfeed, she should be abstinent from any substance use, pump frequently to maintain a milk supply but discard the milk until the substances are no longer in her system (aka her urine drug screen is negative). Abstinence with subsequent initiation of breastfeeding should be encouraged and supported.

Cannabis (THC) may be harmful to infant's neurodevelopment. Mothers with a UDS positive for THC should be counseled on the impact to her infant's health and encouraged to abstain during breastfeeding. The decision of whether or not to use breastmilk with possible THC contamination should be made on a case by case basis between the baby's physician and mother.

CBD products often have THC amounts that can turn urine drug screens positive. Mothers should be encouraged to abstain from all CBD products while breastfeeding. Recent research has shown THC to be harmful to infant's neurodevelopment and the THC content in CBD products is usually not known.

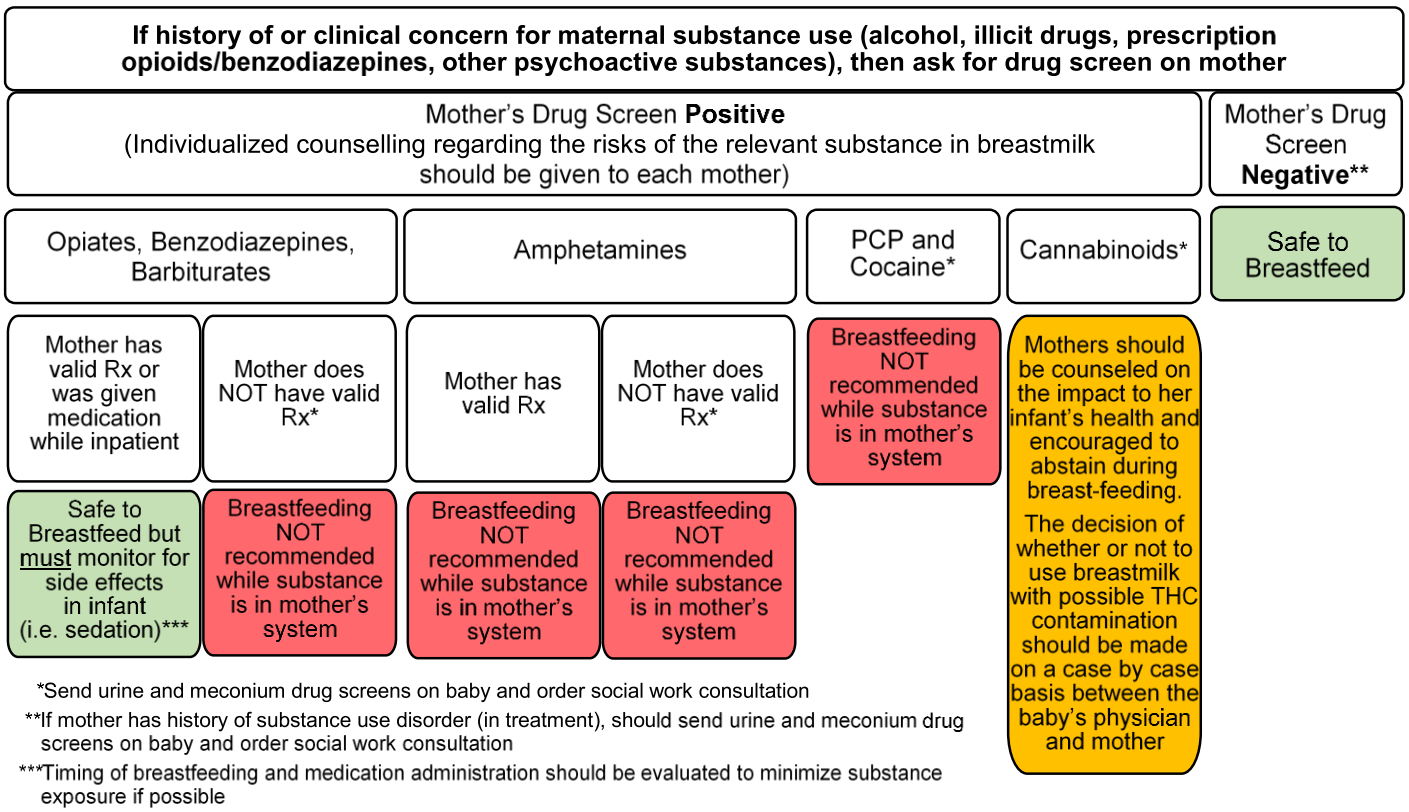
Maternal Medications

Most medications are thought to be compatible with breastfeeding, although few have actually been well studied. Additionally, breastfeeding is generally not recommended for mothers receiving medication from the following classes of drugs: amphetamines, chemotherapy agents, ergotamines, and statins. If mothers desire to breastfeed while taking a medication with some potential risk to the infant, it may be beneficial to consult with a pharmacist in order to determine the optimal timing of medication administration in relation to breastfeeding to decrease the transmission of the medication into breastmilk.

Useful resources for determining the safety of maternal medications while breastfeeding include:

- Drugs and Lactation Database (LactMed): an internet source with comprehensive information regarding the safety of maternal medications and breastfeeding. This website can be accessed at http://ncbi.nlm.nih.gov/books/NBK501922
- "Medications in Mothers" by Dr. Thomas Hale. Dr. Hale's website at http://www.infantrisk.com
- "Drugs in Pregnancy and Lactation" edited by Briggs and Freeman

Figure 12-1. Breastfeeding recommendations with substance use



Lactation Consultations

All BCM-affiliated hospitals have Lactation Consultants who can provide information about breastfeeding to parents and hospital staff. These consultants function to aid breastfeeding mothers, and are competent in the evaluation of the mother-baby breastfeeding dyad. All breastfeeding mothers should have trained RN support throughout their stay and be offered a lactation consult as needed during the postpartum/newborn hospital stay.

Contact Information for Lactation consultants:

- **Texas Children's Hospital** – 832-824-6120
- **Ben Taub Hospital, Breastfeeding Clinic -** 713-873-3350

Baby Friendly Hospitals

In 1991, World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) launched the Baby-Friendly Hospital Initiative to promote breastfeeding and discourage inappropriate marketing of breastmilk substitutes worldwide. BCM-affiliated hospitals, Ben Taub Hospital and Texas Children's Hospital, are both designated Baby Friendly Hospitals. This means that they have implemented the Ten Steps to Successful Breastfeeding and abide by the International Code of Marketing of Breastmilk Substitutes. The Ten Steps have been shown to increase breastfeeding initiation and duration.

The Ten Steps to Successful Breastfeeding are:

1. Have a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in the skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within one hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation, even if they are separated from their infants.
6. Give infants no food or drink other than breast-milk, unless medically indicated.
7. Practice rooming in – allow mothers and infants to remain together 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no pacifiers or artificial nipples to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or birth center.

Formula and Expressed Breast Milk

Direct breast feeding is the ideal and most physiologic method of infant feeding, but there are circumstances in which an infant may need to be bottle fed either with expressed breast milk (EBM) or formula.

Many of the immune benefits of breastfeeding will be delivered by bottle-feeding with EBM, depending upon how the EBM is collected, the storage temperature and the length of time it is stored. Therefore, expressed breast milk feeding is preferable to formula feeding. Risks exist with both expressed breast milk and formula feeding. These include contamination/infection risks, improper mixing of formula and overfeeding. Knowledge of proper storage and preparation are

essential to mitigating these risks.

Expressed Breastmilk Storage

EBM may be safely stored at different temperatures for a variety of time frames **(Table 12-2).** To thaw frozen EBM, place the frozen EBM in a refrigerator overnight or in a bowl of warm water. **Never** microwave breastmilk to warm it. After thawed, it must be used within 24 hours. Milk left in the feeding container after a feeding may be contaminated with oral flora and should be discarded after 1 hour.

Table 12–2. Expressed breastmilk storage

Temperature	Duration
Room temperature (up to 85ºF or 29ºC)	4 hours ideal (up to 8 hours under very clean conditions)
Insulated cooler bag with ice packs (59ºF or 15ºC)	24 hours
Refrigerator (39º F or 4º C)	4 days ideal (up to 8 days under very clean conditions)
Freezer compartment of refrigerator/freezer with separate door (0ºF or -18ºC)	3-6 months
Deep freezer (<-4ºF or <-20ºC)	6-12 months

Formula Preparations

In the newborn nursery, an iron-fortified, 19-20-calorie-per-ounce bovine milk-based formula is suitable for most term babies.

Mixed unused formula can last 2 hours at room temperature and up to 24 hours in the refrigerator. Milk left in the feeding container after a feeding may be contaminated with oral flora and should be discarded after 1 hour.

Several types of formula are available:

- **Ready-to-Feed** - No preparation is required and if unopened, can be left at room temperature until expired. This is the most convenient and sterile preparation, but also the most expensive.
- **Concentrate** - Mix equal parts of formula concentrate and water. Formula concentrate can be stored in a refrigerator for up to 48 hours if covered.
- **Powder** - Thoroughly mix 1 level scoop with 2 ounces of sterile water. Powder formula is lightweight and the least expensive. Unmixed powder may be stored in a bottle for several days without spoiling. Bacterial contamination of powdered formulas has been reported. However, in general, the use of powder infant formulas is safe for healthy full-term infants, although caution should be used, especially in the first month to ensure clean technique in preparing the formula

Bottle Feeding During the First Weeks

Bottle fed term newborns will often eat more than breastfed infants, especially in the first few days. They usually start by feeding approximately 0.5 ounce (15 ml) per feed and increase gradually. Infants usually will take 2 to 3 ounces every 3 to 4 hours during the first few weeks. By the end of the first month, they typically will take 4 ounces every 4 hours. Feeding on demand is best. Supplemental iron and vitamins are generally not needed for term infants receiving iron-fortified formula, unless the infant is SGA. **(Ch 13.3-Enteral Nutrition)**

12.7 Hospital Discharge

The AAP Committee on the Fetus and Newborn recommends that the hospital stay of the mother and her infant be long enough to identify early problems and to ensure adequate maternal recovery and readiness for discharge. An assessment of maternal and family preparedness and competency to provide newborn care at home is a condition for discharge. Every effort should be made to keep mothers and infants together in support of a simultaneous hospital discharge.

Minimum Criteria for Discharge

- Normal physical examination and uncomplicated perinatal course that has not identified any abnormalities requiring continued hospitalization.
- Stable vital signs for 12 hours before discharge, including thermal stability in open crib.
- Infant has completed 2 successful, consecutive feedings and has urinated adequately and passed stool spontaneously at least once.
- Successful latch, swallow, and satiety of the breast fed infant should be documented in the medical record by a caregiver knowledgeable in breastfeeding.
- The ability to coordinate sucking, swallowing and breathing should be documented for bottle fed infants.
- Infant has been adequately monitored for sepsis based on maternal risk factors and in accordance with current guidelines for management of neonates with suspected or proven early-onset sepsis.
- Maternal laboratory data has been obtained and reviewed as normal or negative.
- Infant laboratory data has been obtained and interpreted.
- Newborn metabolic, hearing, and CCHD screening has been performed.
- Clinical risk for subsequent hyperbilirubinemia has been assessed. Follow-up plans have been instituted as recommended in the AAP's clinical practice guidelines for the management of hyperbilirubinemia.
- No evidence of excessive bleeding from circumcision site for at least 2 hours.
- Appropriate education to mother has been provided regarding normal feeding and voiding patterns, general infant care and jaundice recognition.
- If not previously vaccinated, the infant's mother should receive the Tdap vaccine immediately after the infant is born. Other adult family members or caretakers who anticipate close contact with the infant should be encouraged to receive the Tdap vaccine.

- Family, environmental, and social risk factors (domestic violence, history of child abuse/neglect, homelessness, teen mother, history of substance abuse) have been assessed and addressed.
- Family members, or other support persons, familiar with newborn care are available to the mother and infant after discharge.
- A car safety seat that meets Federal Motor Vehicle Safety Standard 213 has been obtained and is available before hospital discharge.

Early Discharge

Infants discharged early, as defined by a postpartum length of stay less than 48 hours, must be at least 37 0/7 weeks old, have a normal physical examination, uncomplicated perinatal course and have outpatient follow-up within 48 hours of discharge; If this cannot be ensured, discharge should be deferred until a mechanism for follow-up is identified. A permanent medical home for the infant should also be identified prior to discharge. When considering an infant for early discharge, it is important to perform a careful, thorough evaluation to identify problems that could present after discharge. Potentially serious neonatal problems that may not present before 48 hours of life include:

- hyperbilirubinemia **(Ch 7.5-Management of Neonatal Jaundice),**
- gastrointestinal obstruction
- ductus-dependent congenital heart defects
- bacterial and viral sepsis including HSV
- inborn errors of metabolism.

It is imperative to instruct mothers about early recognition of danger signs (lethargy, poor feeding, respiratory distress, temperature instability, and seizures). A follow-up appointment should be scheduled and its importance emphasized to the infant's primary caregiver before the newborn is discharged early.

Infants of group B streptococcus-positive mothers are not eligible for early discharge with one exception. Newborns ≥ 37 weeks gestation, whose mothers received adequate intrapartum GBS prophylaxis, may be eligible for early discharge if continued close observation at home can be assured and early follow-up (within 24 hours) with the pediatrician has been arranged.

The timing of discharge should be the decision of the physicians caring for the mother and the newborn based on these guidelines. For infants born at Ben Taub, the Texas Health Steps Newborn Follow-Up Clinic is recommended for all infants discharged early.

12.8 Neuromusculoskeletal

Consequences of Labor and Delivery

Since many clinical findings (e.g., prolonged labor, macrosomia, dystocia, and cephalopelvic disproportion) are related to the malposition of an infant, such consequences of labor and delivery may be unavoidable despite superb obstetrical care.

Fractures

Clavicle - The clavicle is the most frequently fractured bone in newborns (0.2% to 16% of vaginal deliveries). Most often, the fracture is unilateral and greenstick type but may be displaced. Frequently, they are asymptomatic. Discoloration, swelling, localized crepitus, and absent ipsilateral Moro reflex may be observed. The great majority of clavicular fractures will present with minimal or no findings in the first few days of life. An x-ray can be obtained to document the fracture was present at birth. If pain is associated with the fracture, it can be splinted by pinning the infant's sleeve to the chest with the elbow flexed at 90 degrees for comfort. Pain usually subsides by 7 to 10 days when a callus forms at which time immobilization may be discontinued.

Humerus - The humerus is the second most common bone fractured. The fractures usually are in the diaphysis. Occasionally the fracture is complete with overriding of the fragments. A greenstick fracture may be overlooked until a callus is present. A complete fracture frequently presents with immobility of the affected arm and an absent ipsilateral Moro reflex. Treatment is immobilization in adduction for 2 to 4 weeks maintaining the arm in a hand-on-hip position with a triangular splint or Velpeau bandage. Healing is associated with callus formation and union of fragments occurring by 3 weeks. Outpatient follow-up with Orthopedic Surgery is recommended to ensure proper healing.

Femur - Femoral fractures are relatively uncommon. They occur in the middle third of the shaft and are transverse. Frequently there is an obvious deformity or swelling of the thigh associated with pain and immobility of the affected leg. Traction-suspension may be necessary for shaft fractures. The legs may be immobilized in a Spica cast or a simple splint for up to 3 to 4 weeks until adequate callus has formed and new bone growth started. Obtain Orthopedics consult.

Skull - Skull fractures are uncommon because at birth the skull bones are less mineralized and more compressible than other bones. Open sutures also allow alterations in the head's contour, easing passage through the birth canal. Skull fractures can be linear or depressed, and are easily diagnosed with plain radiographs of the skull. Linear fractures usually heal within several months and rarely will a leptomeningeal cyst develop. Depressed skull fractures with a visible indentation on the skull and are often associated with a forceps assisted delivery; in these instances, further imaging (CT scan) is recommended to assess for associated intracranial lesions. Neurosurgical consultation is necessary for depressed skull fractures greater than one centimeter in depth and/ or associated intracranial lesions, as these usually require surgical intervention.

Neurological

Brachial Plexus Palsies

The incidence of birth-related brachial plexus injury varies from 0.3 to 2 per 1000 live births. Brachial plexus injury is manifested by a transient or permanent paralysis involving the muscles of the upper extremity after trauma to the spinal roots of C-5 through T-1 during birth. Depending on the site of injury, the forms of brachial plexus palsy commonly seen are Erb palsy, Klumpke palsy, and facial nerve palsy.

Erb palsy - is the most common injury and presents with the affected upper extremity being limp, the shoulder adducted and internally rotated, the elbow extended, the forearm pronated, and wrist and fingers flexed (waiter's tip position) resulting from injury of C-5 and C-6 roots.

Klumpke palsy - is less common and presents with lower arm paralysis involving the intrinsic muscles of the hand and the long flexors of the wrist and fingers resulting from injury of C-8 and T-1 roots. Dependent edema, cyanosis, and atrophy of hand muscles may develop. Also, sensory impairment may occur along the ulnar side of the forearm and hand. Horner syndrome may be observed with associated injury to the cervical sympathetic fibers of the first thoracic root. Delayed pigmentation of the iris may be an associated finding. Rarely does paralysis affect the entire arm; but when it does, the whole arm is flaccid and motionless, all reflexes are absent, and sensory loss is from the shoulder to the fingers.

Most infants with a birth-related brachial plexus injury (90% to 95%) require only physical therapy. The primary goal of treatment is prevention of contractures while awaiting recovery of the brachial plexus. Partial immobilization and appropriate positioning are helpful in the first 2 weeks because of painful traumatic neuritis. Referral to OT/PT while the baby is hospitalized is encouraged. Outpatient follow-up of babies with brachial plexus injuries who are born at Ben Taub can be done at Shriner's Hospital. A referral form will need to be completed before the appointment. Babies born at TCH will require outpatient referral to a pediatric orthopedist who specializes in this type of injury.

Facial nerve palsy - results from compression of the peripheral portion of the nerve by forceps or by prolonged pressure on the nerve by the maternal sacral promontory, a fetal tumor, or an abnormal fetal position. Central nerve paralysis from contralateral CNS injury involves the lower half or two-thirds of the face. Peripheral paralysis is unilateral; the forehead is smooth on the affected side and the eye is persistently open. With both forms of paralysis, the mouth is drawn to the normal side when crying and the nasolabial fold is obliterated on the affected side. Differential diagnoses include Möbius syndrome and absence of the depressor anguli muscle of the mouth (aka asymmetric crying facies). Most facial palsies secondary to compression of the nerve resolve spontaneously within several days and most require no specific therapy except for the application of artificial tears to the eye when necessary to prevent corneal injury.

Phrenic Nerve Injury

Isolated phrenic nerve injury is rare. Diaphragmatic paralysis often is observed along with an ipsilateral brachial nerve injury. Chest radiograph shows elevation of the diaphragm on the affected side. Fluoroscopy reveals elevation of the affected side and descent of the normal side on inspiration. Mediastinal shift to the normal side is noted on inspiration. Electrical stimulation of the phrenic nerve may be helpful in cases in which the palsy is secondary to surgery. The infant may present with signs of respiratory distress and may require mechanical ventilation. Most infants recover spontaneously.

Developmental Dysplasia of the Hips

Examination to identify developmental dysplasia of the hips (DDH) is the most common musculoskeletal evaluation in the neonatal period. DDH is an evolving process and is not always detectable at birth. Hip dysplasia may occur in utero, during the perinatal period, or during infancy and childhood. All newborns should be examined for hip dislocation, and this examination should be part of all routine health evaluations up to 2 years of age, when a mature gait is established. Additionally, careful hip examination should be performed for babies with musculoskeletal anomalies related to tight intrauterine "packaging," such as congenital torticollis and metatarsus adductus, The etiology of DDH is unknown, but appears to involve physiologic factors (i.e. ligamentous laxity) and mechanical factors (i.e. intrauterine positioning). **(Table 12-3)**

Risk Factors for DDH include:

- Firstborns: due to the confines of the primigravid uterus.
- Breech positioning at > 34 WGA: DDH is associated in as many as 23% of breech presentations, even after external cephalic version (ECV). The left hip is involved more often than the right.
- Female gender (more than 6 times higher than males).
- Positive family history
- Diminished intrauterine space: i.e., LGA, multiple gestation, fibroids.
- Tight lower extremity swaddling

Assessment and Management

Diagnostic clues to DDH include:

- asymmetrical number/placement of thigh skin folds
- lack of spontaneous movement in lower extremities
- uneven knee levels (Galeazzi sign)
- discrepancy in leg length
- limitation of hip abduction (generally not present in infants < 3 months of age)
- positive Barlow test (a "clunking" sensation when the femur – at a 90-degree angle to the examining surface – is dislocated posteriorly when the hip is gently adducted; no downward pressure should be applied
- **most important**: positive Ortolani test (a "clunking" sensation when the physician abducts the thigh to the table from the midline while lifting up on the greater trochanter with the finger).

If the newborn has a positive Ortolani test, or limited or asymmetric abduction, obtain a Pediatric Orthopedic consultation. Repeated hip exams should be limited for babies with suspected DDH. For infants with a positive Barlow maneuver, serial exams by the PCP or Orthopedic Surgery should be performed to ensure hip stability.

In the Ben Taub nurseries, Orthopedic Surgery should be consulted for babies with a positive Ortolani or Barlow test, and outpatient follow-up at Shriner's Hospital or Texas Children's Hospital should be arranged. At TCH, the Orthopedic Surgery service should be consulted for babies with suspected DDH, with outpatient follow-up arranged per the consulting physician.

Infants with risk factors (male or female breech > 34 WGA, family history of DDH, or history of clinically unstable hip) who have a normal exam during the newborn hospitalization should be referred for outpatient hip ultrasound at 6 weeks of age.

Table 12-3. Risk for developmental dysplasia of the hip

Gender	Risk Factor	Rate/1000	Risk for DDH
Male	None	4.1	low
	Family history	9.4	low
	Breech	26	medium
Female	None	19	medium
	Family history	44	high
	Breech	120	high

Jitteriness

Jitteriness in the newborn is a frequent finding and often is confused with neonatal seizures. Many potential etiologies exist, including metabolic disturbances, hypoxic-ischemic encephalopathy, drug withdrawal, hypoglycemia and hypocalcemia. A distinguishing feature is that jitteriness tends to be stimulus-sensitive, becoming most prominent after startle, and its activity can cease by holding the baby's arm, neither of which is true for seizures. These movements are not accompanied by EEG changes and require no specific treatment. Jitteriness from drug withdrawal often presents with tremors, whereas clonic activity is most prominent in seizures. Reversing transient metabolic disturbances can reduce the jitteriness.

Positional Deformities

Postural, or positional, deformities include asymmetries of the head, face, chest, and extremities. They are often associated with conditions related to intrauterine crowding such as, primigravid uterus, multiple gestation, LGA infants, etc. Most correct spontaneously. The most common positional deformities involve the feet.

Positional Deformations of the Lower Extremities

Metatarsus adductus is the most common congenital foot deformity in which the forefoot is adducted while the hind foot remains in neutral position. It is due to intrauterine positioning and a small percentage of these infants have congenital hip dysplasia, thus warranting a careful examination of the hips. Treatment is conservative as 90% + will resolve without intervention.

Calcaneovalgus feet is a common newborn positional deformity in which the hind foot is in extreme dorsiflexion while the forefoot is abducted. Treatment is usually conservative and the condition typically resolves in the first 6 months of life.

Talipes Equinovarus (Clubfoot) is a complex condition that involves both the foot and lower extremity. It is characterized by the foot being excessively plantar flexed, with the forefoot swung medially and the sole facing inward. Club feet can be can be classified as follows:

- **Congenital clubfoot** is the most common type. It is usually an isolated anomaly without a well-delineated etiology. Current management is based upon manipulation that includes casting and bracing (referred to as the Ponseti method).
- **Syndromic clubfoot** is associated with intrinsic etiologies of club feet including connective tissue, genetic or neuromuscular disorders, or syndromes, i.e. spina bifida, myotonic dystrophy, trisomy 18.
- **Positional clubfoot** is due to intrauterine crowding or breech position. It is not a true club foot. It is a normal foot that has been held in a deformed position in utero. The positional clubfoot easily corrects to a normal position with manipulation. It usually self-resolved by 4-12 months of age.

Polydactyly

Polydactyly is the most common hand anomaly noted in the newborn period; reported incidence is 1:300 live births for blacks and 1:3000 for whites. The inheritance pattern may be autosomal recessive or autosomal dominant. It can be an isolated malformation or part of a syndrome.

The most commonly seen defect in the nursery is postaxial (ulnar) polydactyly. Often, the extra digit is pedunculated and without bone. Ligation by tying off the extra digit with suture carries the risk of infection and undesirable cosmetic outcome. Thus, consultation with Pediatric Surgery is recommended for removal. If bone is present in the extra digit, outpatient follow-up with pediatric surgery, plastic surgery or orthopedics should be arranged when the baby is older, as the procedure is more complicated when bone is involved.

Syndactyly

Syndactyly (isolated syndactyly) is reported in 1:3000 live births and may be either a sporadic finding or an autosomal dominant trait. Syndactyly of the second and third toe is the most commonly reported location of the anomaly (noted to affect more males than females). The second most frequent type is isolated syndactyly of the middle and ring fingers. When present in the hand, surgery usually is performed to improve function. If noted on the feet, surgery is indicated if the toes are angular.

12.9 Newborn Falls

Newborn falls in the hospital are uncommon and typically occur in the setting of co-sleeping, or when a breast feeding baby slips out of the arms of a sleepy mother. Newborn drops are also reported in the literature, occurring when a weak or sleepy caregiver attempts to stand-up while holding the newborn. Upon admission, many of our Baylor-affiliated nurseries provide education regarding the risks of newborn falls and require the mother to sign an agreement that she will not co-sleep with her baby, and that she will call for assistance when she feels too tired to care for her newborn independently. Most newborn falls and drops occur during nighttime and early morning hours and are unwitnessed by healthcare providers.

Guidelines for management of a newborn who has fallen or been dropped are as follows:

- Immediate examination by a physician or advance practice provider.

- Imaging with non-contrast head CT. (Head CT is the preferred diagnostic test because intracranial hemorrhage may be present in the absence of external trauma and/or skull fracture).
- Consider extended monitoring in the NICU based on physical exam findings and head CT results.

12.10 Newborn Screening

State Newborn Screening, Dried Blood Spot Screening

Texas Department of State Health Services (DSHS) requires newborn blood spot screening for multiple genetic disorders and congenital conditions for which early intervention is expected to decrease morbidity and mortality of Texas newborns. Texas currently screens for more than 50 disorders, including core conditions as well as secondary conditions. Secondary conditions are discovered during the testing for core conditions. These conditions are considered to be clinically significant and may lack a clear natural history or medical therapy. The disorders screened in Texas include: cystic fibrosis, congenital hypothyroidism, galactosemia, hemoglobinopathies, congenital adrenal hyperplasia, biotinidase deficiency, severe combined immune deficiency (SCID), and inborn errors of metabolism (amino acid disorders, organic acid disorders, and disorders of fatty acid oxidation). Spinal muscular atrophy (SMA) was added to the Texas NBS on June 1, 2021. Regardless of feeding status or prematurity, specimens are collected on all newborns at 24 to 48 hours of age. A second newborn screen is repeated at one to two weeks of age. Blood transfusions can cause invalid results, therefore, the first screen should be collected prior to the first intervention, including babies on ECMO or babies requiring emergency blood transfusions. Transfused newborns must be retested six to eight weeks following transfusion. **(Ch 6.2-Genetic Testing)**

Abnormal blood spot screens

Ben Taub General Hospital (BTGH)

Abnormal newborn screen results are received through the Newborn Screening Program Office of Carolyn Fairchild. For infants still on the inpatient service, the primary medical team is notified. For discharged patients, primary follow-up is coordinated through DSHS with assistance through Carolyn Fairchild's office when needed.

Texas Children's Hospital (TCH)

Abnormal results of infants admitted to BCM Neonatology are routed to the Newborn and Infant Screening Service (NBISS) (832-824-1093).

Hearing Screening

The prevalence of newborn hearing loss is approximately 1 to 2 per 1000 live births, with an incidence of 1-3 per 1000 in the normal newborn nursery population and 20 to 40 per 1000 in the NICU population. Only 50% of newborns with significant congenital hearing loss can be detected by high-risk factors. Newborn hearing screening using a physiologic assessment tool is required by law for all babies born in Texas. The rate of failed newborn hearing screens should be less than 5%.

Well Babies

Newborns admitted to the normal newborn nursery (mother-baby unit) are screened with an otoacoustic emissions (OAE). If the OAE is failed/referred, further screening is attempted with an automated auditory brainstem response (AABR). Newborns who unilaterally or bilaterally refer the screening AABR require a urine CMV PCR (or culture), and an outpatient Audiology appointment for a diagnostic auditory brainstem response (diagnostic ABR). The newborn's follow-up pediatrician should be informed of the pending CMV results, as well as the need for outpatient diagnostic ABR.

NICU Babies

High risk NICU infants, including those admitted to the NICU for > 5 days, should be screened with an AABR instead of an OAE. Hearing screens (AABR) should occur when criteria is met. **(Table 12-4)**

If a NICU infant Fails/Refers the hearing screen **(AABR)** (unilaterally or bilaterally) an "Audiology Diagnostic Evaluation" order needs to be placed, in addition to an order for urine CMV PCR or culture. On the date the diagnostic auditory brainstem response **(Diagnostic ABR)** is scheduled, the infant should be moved to a private room and given nasal versed (0.2mg/kg) thirty minutes prior to the procedure for sedation. A repeat dose of versed can be given during the test if needed.

If hearing loss is detected with diagnostic ABR, ENT is consulted to assess for possible treatment options. If treatment is performed by ENT, an order for repeat "Audiology Diagnostic Evaluation" is placed prior to discharge

The goal is to screen by one month of age. Diagnosis of hearing loss should occur before 3 months of age, with intervention by 6 months of age.

Infants readmitted to the hospital within the first month of life should be re-screened when there are conditions associated with potential hearing loss such as:

- Hyperbilirubinemia requiring exchange transfusion.
- Culture + sepsis/meningitis

Table 12-4. Hearing screen (AABR) criteria in NICU level 2, 3, or 4

Eligible Infants	Non-Eligible Infants Include
• > 34 weeks • In open crib, isolette, or warmer • On NCPAP • On LFNC or HFNC • Mechanically ventilated (Endotracheal or Trach)	• < 34 weeks CGA • On HFOV • On Continuous EEG • On Vasoactive drips

Critical Congenital Heart Disease (CCHD) Screening

Congenital heart defects are the most common birth defect, with an incidence of 9/1000 births in the United States. Some of these defects are critical, requiring early intervention and management to save the life of the baby. In fact, Critical Congenital Heart Disease (CCHD) is the leading cause of death in infants less than 1 year of age. In the United States, 4800 infants (2/1000 live births) are born annually with

CCHD. Early diagnosis and timely intervention of CCHD can significantly reduce morbidity and mortality and lead to better outcomes.

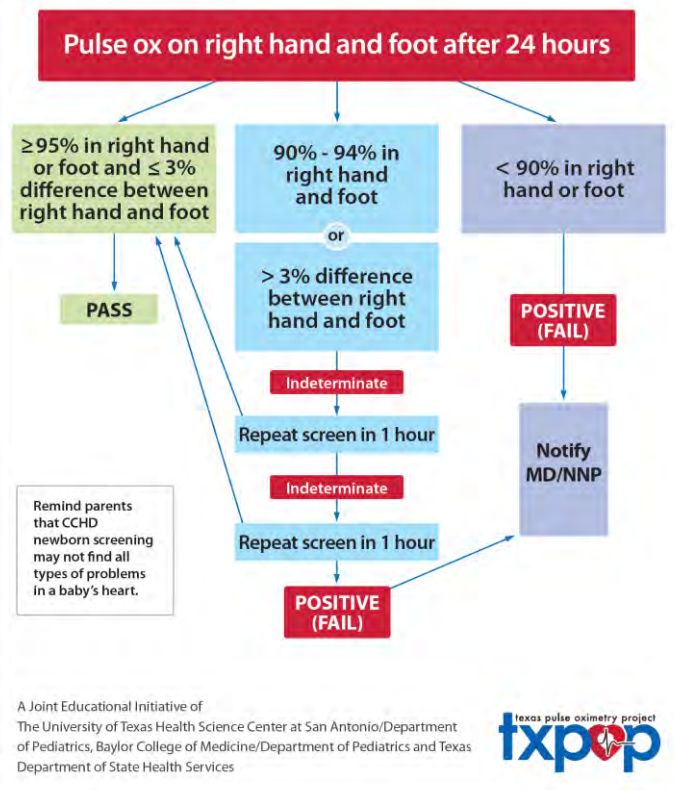
Newborn screening with pulse oximetry has been shown to be useful for the detection of seven primary targets of CCHD. These seven defects represent 17–31% of all congenital heart defects.

These defects are:

- Hypoplastic Left Heart Syndrome
- Pulmonary Atresia (with intact atrial septum)
- Tetralogy of Fallot
- Total Anomalous Pulmonary Venous Return
- Transposition of the Great Arteries
- Tricuspid Atresia
- Truncus arteriosus

Texas law requires all newborns to be screened for CCHD. Screening should occur after 24 hours of age, but before hospital discharge. Screening is done by obtaining and comparing pre and post ductal oxygen saturations via pulse oximetry **(Fig 12–2**). Other heart defects can be as severe as the primary targets of CCHD screening. Unfortunately, pulse oximetry screening does not detect these as consistently as the seven CCHD disorders. Infants with a positive screen (fail) require prompt attention for further evaluation. Texas state law also requires reporting of all infants with confirmed CCHD. The form for reporting confirmed cases of CCHD can be found on the Texas Department of State Health Services website.

Figure 12.2. Newborn screening algorithm for critical congenital heart disease (CCHD)



Bilirubin Screening

Screening for hyperbilirubinemia via collection of a serum total and direct (or conjugated) bilirubin occurs in all Baylor-affiliated nurseries, typically at 24-48 hours of age (to coincide with collection of the blood spot screen). An elevated direct (or conjugated) bilirubin level on initial screening has been shown to be a marker for biliary atresia. For management of elevated total bilirubin levels **refer to Ch 7.5-Management of Neonatal Jaundice**; for management of elevated direct (or conjugated) bilirubin refer to **Ch 5.3-Cholestasis.**

Risk Based Screening: Glucose Screening

Babies at risk for hypoglycemia include those who are LGA, SGA, preterm (GA < 37 weeks), and infants of diabetic mothers (IDM). Babies who are in one or more of these categories should have an initial glucose screen at 30 mins to 2 hours of life, and at regular intervals during the first 12 to 24 hours of life to ensure euglycemia. 40% oral glucose gel is available in some Baylor-affiliated newborn nurseries for the initial treatment of hypoglycemia. Glucose gel is administered in conjunction with oral feeds (breast, EBM/DBM, formula). Refer to **Ch 3.4-3.6-Endocrinology** for management of babies with persistent hypoglycemia despite administration of oral glucose gel and oral feeds.

12.11 Urology

Single Umbilical Artery

This anomaly occurs in 0.7% to 1% of singletons and in 3% to 7% of multiple births. The incidence is low in black infants and higher in neonates with aneuploidy or other congenital malformations. Among infants with a single umbilical artery (SUA), the prevalence of cardiac and renal anomalies is significantly higher than the general population (7% and 5% respectively). These infants are also 2 times more likely to have intrauterine growth restriction. The finding of other associated anomalies is not specific for any one organ system. Further investigation of an infant with SUA is recommended only when another major anomaly is suspected. Infants with an isolated SUA generally have a good prognosis with similar outcomes to unaffected infants.

Urinary Tract Dilation (UTD) (Antenatal Hydronephrosis)

Introduction

Advances in ultrasonography make possible an earlier and more accurate prenatal diagnosis of urinary tract abnormalities. Prenatal diagnosis of fetal urinary tract dilation (also termed antenatal hydronephrosis) occurs in 1-2% of all pregnancies.

UTD can be caused by a variety of conditions, such as (in order of prevalence):

- Transient dilation of the collecting system
- Ureteropelvic Junction obstruction (UPJ)
- Vesicoureteral reflux
- Ureterovesicular Junction obstruction (UVJ)
- Multicystic dysplastic kidney disease
- Posterior urethral valves
- Other anatomic abnormalities i.e. ureterocele, duplication, cysts etc.

Often, the cause of UTD cannot be diagnosed prior to birth, thus postnatal imaging is necessary to determine the etiology of UTD and guide further management.

Risk factors for Postnatal Uropathy:

UTD associated with the following ultrasonographic findings confers an increased risk of urinary tract pathology:

- Abnormal anterior-posterior renal pelvis diameter (APRPD) measurement. Knowledge of this measurement is necessary to direct the postnatal work-up of fetal UTD. **(Table 12–5)**
- Calyceal dilation
- Abnormal parenchymal thickness
- Abnormal parenchymal appearance
- Ureteral dilation
- Abnormal bladder appearance
- Unexplained oligohydramnios.

Postnatal Management

All infants with prenatal risk factors for urinary tract pathology must have postnatal evaluation of the urinary tract specifically, infants with antenatal hydronephrosis detected by third trimester ultrasound require postnatal evaluation. Postnatal evaluation is not needed for infants in whom antenatal hydronephrosis was seen on an earlier ultrasound, but has resolved by third trimester (or the most recent) prenatal ultrasound. Appropriate postnatal evaluation of UTD includes two ultrasound evaluations. Even if the first ultrasound is interpreted as normal, a second ultrasound needs to be obtained. Because the neonate has relatively low urine output in the first few days of life, there is a tendency to underestimate the severity of hydronephrosis when the postnatal ultrasound is done prior to 48 hours of age. Thus, it is recommended that the first ultrasound be done at >48 hours after birth, but before 2-4 weeks of age. The second ultrasound is performed at 1-6 months. Postnatal ultrasound prior to 48 hours of age is considered in the following scenarios:

- Antenatal ultrasound findings concerning for obstructive urinary tract pathology (i.e. fetal hydronephrosis or other findings suggestive of bladder outlet or urethral obstruction)
- If appropriate outpatient follow-up cannot be ensured. Consultation with pediatric urology may be helpful to guide outpatient follow-up.

Table 12-5. Normal APRPD Values

Age	< 28 weeks	≥28 weeks	Postnatal
APRPD	< 4 mm	< 7 mm	< 10 mm

Urinary Tract Prophylaxis

The use of amoxicillin prophylaxis to prevent urinary tract infections is controversial. To date, there have been no prospective randomized trials to evaluate the efficacy of prophylactic antibiotics in children with UTD. Amoxicillin prophylaxis (10 mg/kg once daily) for babies with a history of UTD is approached on an individualized basis.

Circumcision

Indications

The AAP states that, although health benefits are not great enough to recommend routine circumcision for all male newborns, the evaluation of current evidence indicates that the health benefits of newborn male circumcision outweigh the risks.

Additionally, the procedure's benefits justify access to this procedure for families who choose it. Specific benefits identified include prevention of urinary tract infections, penile cancer, and transmission of some sexually transmitted infections, including HIV. Male circumcision performed during the newborn period has considerably lower complication rates than when performed later in life.

The decision to circumcise an infant should be one of personal choice for parents. It is important that parents discuss the risks and benefits of circumcision with their physician before delivery. If a decision for circumcision is made, the AAP recommends that procedural analgesia (local anesthesia) be provided; BCM-affiliated providers prefer either the subcutaneous ring block technique or dorsal penile nerve block using 1% lidocaine without epinephrine. 24% sucrose solution is provided to the infant orally during the procedure. **(Ch 11.8-Pain Assessment and Management).**

Contraindications

Circumcision is contraindicated for:

- medically unstable infants
- infants with genital anomalies (i.e. hypospadias)
- Infants with a family history of bleeding disorders, (i.e. Von Willebrand, hemophilia): these infants should have appropriate screening laboratory tests before the procedure.
- Parental refusal of Vitamin K (in some units, including TCH and Ben Taub)
- Consider delaying circumcision in boys with bilateral cryptorchidism.

For premature newborns, the recommendation is to delay circumcision until the baby is close to hospital discharge. Circumcision is not contraindicated in infants with a history of urinary tract dilation.

Referral to a Pediatric Surgeon or Pediatric Urologist should be considered when:

- an infant is 44 weeks or greater corrected gestational age,

or

- an infant's weight is more than 10 pounds,

or

- a size 1.6 Gomco is required, or any combination of these circumstances exist.

Post-Procedure Care

Closely observe infants for excessive bleeding for at least 1 to 2 hours post-circumcision. Parents should examine the area every 8 hours for the first 24 hours post-circumcision. Liberally apply petroleum jelly for at least 3 to 5 days to circumcisions done with a Gomco or Mogan clamp. Circumcisions done with a Plastibel clamp require routine hygiene only. Parents should report any erythema, edema, or foul odor of the penis. A white-yellowish exudate may develop on the penis; this is normal and is not an indication of infection. Infants usually void urine within 8 hours after circumcision. Discharge home should not be delayed while awaiting urine output in the recently circumcised newborn.

Outpatient Circumcision

Newborns for whom circumcision cannot be performed prior to discharge can be referred to the Texas Children's Division of Urology Newborn Circumcision Clinic. Newborns must be under 10 pounds and less than 30 days of age. An outpatient referral can be placed in EPIC, or parents can call 832-822-2778 to schedule this appointment. TCH pediatric surgery also performs outpatient circumcision; parents can call 832-822-3135 to schedule an appointment.

Uncircumcised Infants

Parents should keep their baby's penis clean with soap and water, as would be done for the rest of the diaper area. They should be counseled that the foreskin will adhere to the glans for several months to years and, therefore, should not be forcibly retracted. When the foreskin is easily retractable, it should be retracted during each bath so the glans can be cleaned. After cleaning, the foreskin should be reduced over the glans.

Cryptorchidism (Undescended Testes)

Undescended testes represent the most common genital anomaly in male infants. The incidence is 1:125 male infants but is much higher in premature infants and those with a positive family history. Cryptorchidism may be unilateral (75% to 90%) or bilateral (10% to 25%), with the right testis more commonly involved than the left.

Descent of the testes occurs during the last 3 months of gestation and is under hormonal control. A cryptorchid testis may be anywhere along the line of testicular descent, most commonly in the inguinal canal.

A cryptorchid testis may be confused with a retractile testis, an otherwise normal testis with an active cremasteric reflex that retracts the testis into the groin. This testis can be "milked" into the scrotum. Potential implications of cryptorchidism include malignancy, infertility, testicular torsion, and inguinal hernia.

Treatment

Initial management of cryptorchidism is to confirm the condition, which is best done with serial physical examinations. When cryptorchidism is bilateral, ultrasonography can be useful for locating testes in the abdomen and confirming the newborn is male. In many boys, the testis will descend in the first few months of life thus, management after discharge includes monthly follow-up. However, testicular descent is extremely unlikely after 6 months of age. Ideally, surgical correction should be carried out by 1 year of age.

Hernias

Inguinal hernias are common in neonates but rarely are present at birth. They are most common in males and premature infants, and they present a risk of testicular entrapment and strangulation. Gentle reduction during all physical exams is recommended as is referral to Pediatric Surgery before or after discharge.

Hydroceles

Hydroceles arise from an abnormal collection of fluid in the tunica vaginalis that has failed to invaginate after descent of the testis. They are clinically recognized as scrotal masses that transilluminate. At birth, up to 15% to 20% of male infants may have some degree of hydrocele. Complete spontaneous resolution can be expected within a few weeks to months.

Hypospadias

Hypospadias is defined as the urethra opening onto the ventral surface of the penis (as opposed to the tip of the penis) and is reported to occur in 3 to 8 per 1000 live births. Hypospadias is the second most common genital abnormality in male newborns. It occurs less frequently in blacks (0.4%) than in whites (0.6%). Approximately 87% of cases are glanular or coronal hypospadias, 10% are penile, and 3% are scrotal or perineal. Other anomalies that may be seen with hypospadias include meatal stenosis, hydrocele, cryptorchidism (8% to 10% of cases), and inguinal hernia (8% of cases).

Assessment and Management

Mild hypospadias (glanular to penile) without associated genital abnormalities or dysmorphic features is usually an isolated anomaly and requires no further work-up. Conversely, severe hypospadias (scrotal to perineal), is more likely to be accompanied by an endocrinopathy, disorder of sexual differentiation (DSD), and/or chromosomal abnormality.

Evaluation and management should include:

- history of possible maternal progestin or estrogen exposure,
- family history of hypospadias, endocrine or intersex disorders,
- careful genital examination to assess for accompanying anomalies (urethral meatus, chordee, scrotal folds),
- ultrasound assessment for absence of gonads and/or presence of a uterus if a DSD is suspected, particularly when hypospadias is accompanied by cryptorchidism. **(Sec 3-Endocrinology)**
- evaluation for gross abnormalities of the kidneys (if the hypospadias is severe),
- measurement of stretched penile length.

Further diagnostic studies should be done depending on the risk for endocrine or intersex disorders, and appropriate consultative services should be involved (Urology, Endocrinology, etc.) Ideally, surgical repair of hypospadias is done late in the first year of life.

Testicular Torsion

Testicular torsion occurs most in newborns with cryptorchidism particularly in the neonatal period, infancy and, occasionally, in utero. It can present clinically as a scrotal mass with reddish to bluish discoloration of the scrotal skin. Usually, the patient is otherwise well. Torsion of the unpalpable cryptorchid testis is difficult to identify early because pain and irritability may be intermittent, and some neonates have an abdominal mass. Torsion can lead to irreversible damage of the testis within 6 hours of the occurrence. Testicular salvage is almost unheard of because the torsion often occurs prenatally during testicular descent. Testicular torsion is considered a urologic emergency; call for a Urology consult as soon as the diagnosis is suspected.

Suggested Reading

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5. Shaw, BA and Segal, LS. American Academy of Pediatrics, Clinical Report: Evaluation and Referral for Developmental Dysplasia of the Hip in Infants. *Pediatrics.* 2016; Dec 138(6).
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8. Loyal J, et,al. Newborn Falls in a Large Tertiary Academic Center Over 13 Years. *Hosp Pediatr*. 2018 Aug;8(9):509-514.
9. Weston PJ, Harris DL, Battin M, Brown J, Hegarty JE, Harding JE. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD011027. DOI:10.1002/14651858.CD011027.pub2.

Section 13: Nutrition

Editors: Amy Hair and Muralidhar Premkumar

13.1 Initiation and Intravenous Fluids

In this chapter, high-risk neonates are defined as all term and preterm infants admitted to the NICU or Level 2 nurseries. Differentiation is made between high-risk, extremely or very low birth weight infants, and healthy preterm infants.

Human milk is the preferred nutrition for infants. A healthy infant should be put to the breast within one hour of delivery. Support mothers who intend to breastfeed or provide milk for their infants. **(Ch 13.3-Enteral Nutrition and Ch 13.5-Oral Feeding)**

Initial Orders after Delivery

Initiate intravenous fluid (IVF) 10% dextrose to provide an initial glucose infusion rate (GIR) of 5 to 7 mg glucose/kg/minute. Some ELBW infants may only tolerate 3.5-4.5 mg glucose/kg/minute in the first day of life.

- In all infants, initiate 10% dextrose at 80 mL/kg/day.

Neonatal Starter Solutions and Early PN

(Tables 13-1 to 13-5)

Providing amino acids and lipids as soon as possible will reverse a negative nitrogen balance and improve glucose homeostasis. Early nutrition is especially effective in infants < 1500 grams. Infuse parenteral nutrition (PN) at an appropriate volume based on body weight and clinical condition. Refer to **Table 13-4** for recommended nutrient composition.

Standard starter solution contains only glucose, amino acids, calcium, and water. No changes can be made to this solution. PN should be ordered to include phosphorus within the first 24 hours of life. Vitamins and trace minerals are automatically added by pharmacy.**(Table 13–6b)**

- Begin PN upon admission for infants < 1500 grams, for infants with major congenital heart disease (any requiring a prostaglandin infusion or vasopressors), and for infants with congenital bowel abnormalities such as gastroschisis or omphalocele. Consider PN for preterm infants (≥ 1500 grams and/or 29 weeks) that may require 5 to 10 days to achieve advancement of enteral nutrition to 120 mL/kg/day.
- Use standard starter solutions when the pharmacy is unavailable for PN compounding (1 pm to 10 am). Starter solutions will provide 3% amino acids.
- Limit standard starter solutions to a maximum of 100 mL/kg/day. Provide any additional fluid required as a piggyback IVFs.
  - » Infants ≤ 1000 grams, initiate 10% dextrose containing starter solution at 80 mL/kg/day or 5% dextrose containing starter solution at 100 mL/kg/day.
- At 24 hours of age or whenever the first daytime ability to write PN (which can be within hours of birth), transition to early (custom) PN. Sodium chloride and potassium chloride are generally not indicated.
- Initiate calcium and phosphorus once PN can be written. In infants < 1000 g birthweight (BW), limit calcium gluconate to 1.0 mmol/100 mL at 100 mL/kg/day or 1.0 – 1.2 mmol/kg/day in the first 72 hours of life, as tolerated.

Table 13–1. Parenteral nutrient (PN) goals

		Initiation Nutrient Needs*	Goals for Growth
Energy	kcal/kg	42 - 57	90–100
Protein	g/kg	2 - 3	3.5-4 (preterm)[a] 2–3 (term)
Fat	g/kg	0.5 - 2[b]	3
Glucose	mg/kg minute	5-7	11–12
Calcium	mmol/kg	1.0-1.2[c]	1.5–2[d]
Phosphorus	mmol/kg	1.0-1.2	1.5–2[d,e,]
Potassium	mEq/kg	0[f]	2–4[g]
Sodium	mEq/kg	0[f]	2–4[h]

* Early fluid and nutrient needs and tolerance will vary by gestational age, birth weight and clinical condition.

[a] Infants with GI diseases, surgery, other protein-losing state, or long- term PN may require 4 g/kg/day of protein.

[b] 5 mL/kg of 20% IL = 1 g fat/kg

[c] Standard starter and peripheral PN provides 1.2 mmol/100mL calcium gluconate and central PN provides 1.75 mmol/100ml. There is 40 mg of elemental calcium per mmol of calcium gluconate.

[d] Provide standard calcium and phosphorus in a 1:1 molar ratio. Phosphorus should be added to PN within 24 hours of life.

[e] Peripheral PN provides 1.2 mmol/100mL potassium phosphate and central PN provides 1.75 mmol/100mL. There is 31 mg of phosphorus per mmol of potassium phosphate.

[f] Sodium or potassium will be provided as a salt with phosphorus.

[g] There is 1.4 mEq of potassium per mmol of potassium phosphate.

[h] There is 1.3 mEq of sodium per mmol of sodium phosphate.

Table 13-2. Parenteral nutrition (PN) calculations

GIR (mg/kg /min)	% Dextrose (g/100mL) × Volume (mL/kg/day) ÷1.44 (1.44 = 1440 min/day ÷ 1000 mg/g glucose)
Dextrose	**3.4 kcal/g**
Protein	**4 kcal/g**
Fat (IL 20%)	**2 kcal/mL (1 g fat/5 mL)**

Table 13-3. Conversion factors for minerals

Element	mmol/dL	mEq/dL	mg/dL
Calcium	1	2	40
Phosphorus	1	–	31
Sodium	1	1	23
Potassium	1	1	39
Chloride	1	1	35
Magnesium	1	2	24

- Add phosphorus (either as potassium phosphate or sodium phosphate) in a 1:1 mmol ratio to calcium as early as can be provided.
- Magnesium (Mg) should not be omitted from PN unless serum Mg level is > 3.9 mg/dL. Monitor serum Mg level and when < 3.0 mg/dL, resume Mg in PN.
- Initiate lipid injectable emulsion (ILE) when PN is started or within the first 24 hours after birth. The inclusion of protein and fat with glucose aids with glucose control. **(Table 13-5)**

Table 13-4. Early neonatal solutions (0 to 24 hours of age)

	Standard Starter[1]	Early PN[2]	Amount/100 mL
Dextrose	5% or 10%	5-10%	5 to 10 g/100 mL
Amino acids	3%	3%	3 g/100 mL
NaCl	0	0	
K_2HPO_4	0	1.0 mmol	
Ca gluconate	1.2 mmol	1.0 mmol	equivalent to 516 – 430 mg/100 mL
Magnesium sulfate	0	0.5 mEq	
KCl	0	0	
Heparin	1 unit/mL	1 unit/mL	

[1] Standard Starter: When PN room is closed (1 pm to 10:00 am) contains no cysteine, phosphorous, trace minerals, or vitamins. No changes.

[2] Early PN should be ordered with GIR of 5-7 mg glucose/kg/min, amino acids at 2.4-3 g/kg, calcium and phosphorus at 1 mmol each per 100 mL. Sodium or potassium will be added with the phosphorus addition. No additional sodium, potassium or chloride is generally indicated. Vitamins and trace minerals will be added by pharmacy. Nutrition modifications can be ordered as needed.

13.2 Parenteral Nutrition (PN)

PN refers to intravenous nutrition (including glucose, amino acids, lipids, vitamins, and minerals) to provide a total nutrition source for an infant.

PN Goals (Tables 13–1, 13–5)

- Begin with the standard solution as specified in **Table 13–6a** and advance volume as tolerated to a maximum of 130 mL/kg/day, which will meet most nutrient requirements. In critically ill infants who require substantial volume for medications or who need frequent adjustment of electrolytes, consider concentrating PN constituents into a smaller volume as medically feasible. When providing greater than 130 mL/kg/day to meet fluid needs, adjust nutrients to meet goals and prevent toxicity.

Carbohydrate

- Provides the main energy source for an infant.
- Limit dextrose to 12.5% when administered through a peripheral line.
- Generally, initiate at a GIR of 5 to 7 mg glucose/kg/minute. Some ELBW infants may only tolerate 3.5-4.5 mg glucose/kg/min in the first day of life.
- Generally, advance by 1-2 mg glucose/kg/min if blood glucose <130-150 mg/dL.
- Advance dextrose to a goal GIR of 11-12 mg glucose/kg/minute.
- If glucose level is persistently >280-300 mg/dL, reduce GIR to 3.5 mg glucose/kg/minute prior to initiating insulin.

Amino Acids

- All infant PN solutions routinely use the amino acid solution TrophAmine®, which promotes plasma amino acid concentrations similar to the breastfed infant. Premasol® may also be used.

Table 13-5. Lipid Injectable Emulsion (ILE) initiation and advancement rates by birthweight

Birthweight		Initiation	Advancement[3]	Triglyceride Monitoring
≤ 750 grams		0.1 mL/hr x 12 hours[1,2]	2.5-5 mL/kg/day (0.5-1 gram/kg/day)	• 12 hours after initiation of therapy (or with morning labs)[4] • With every advancement
751-1000 grams		5 mL/kg/day (1 gram/kg/day)	5 mL/kg/day (1 gram/kg/day)	• With every advancement
> 1000 grams	SGA, IUGR, Postnatal Steroids, and/or Sepsis	5 mL/kg/day (1 gram/kg/day)	5 mL/kg/day) (1 gram/kg/day)	• With every advancement
	AGA	10 mL/kg/day (2 grams/kg/day)	5 mL/kg/day) (1 gram/kg/day)	• Once at goal of 15 mL/kg/day (3 grams/kg/day)

[1] Initiate ILE at the earliest time of 16:00 within the first 24 hours after birth.

[2] This is the minimum rate that can be run with the available syringe pumps. If a rate of 0.1 mL/hr is not tolerated after several attempts, discuss the use of special lower volume syringes that can be run at < 0.1 mL/hr with the NICU clinical pharmacy specialists.

[3] Advance as tolerated if triglyceride (TG) level is < 250 mg/dL.

[4] If TG level is > 250 mg/dL, stop the infusion and repeat TG level in 12-24 hours or sooner as clinically indicated. Infants with persistent TG values of 200-400 mg/dL should receive IL at 0.5 g/kg/day. If IL cannot be advanced beyond 0.5 g/kg/day within three days or if TG values remain above 400 mg/dL, please consult Nutrition Team.

- Current recommendations are 3.5 - 4 g protein/kg/day (preterm infants) and 2-3 g protein/kg/day (term infants). Infants with poor growth, gastrointestinal disease, surgery, or other protein- losing states may require up to 4 g protein/kg/day.
    - Initiate protein at 2-3 g protein/kg/day and advance to goal as soon as possible.
    - The amino acid cysteine is added at 30-40 mg/g amino acids, which improves Ca and P solubility.

Lipid Injectable Emulsion (ILE)

ILE provides essential fatty acids and is a calorie-dense energy source. Intralipid® (IL) is the standard ILE used. It is described below.

- 20% IL (50% linoleic acid), 2 kcal/mL
- Linoleic acid, an essential fatty acid, must be provided at 3% or greater of total kilocalories to meet the essential fatty acid requirement. IL® at 0.5 to 1 g fat (2.5 to 5 mL) per kilogram per day will provide minimum requirements.
- Use a continuous infusion at a constant rate. Initiate and advance per protocol. **(Ch 13.1-Neonatal Starter Solutions and Early PN and Table 13-5)**
- Advance as tolerated to a goal of 3 g fat/kg/day (15 mL/kg/day IL).

Some infants may persistently have TG values of 200-400 mg/dL. IL can be provided at 0.5 g/kg/day daily despite these values. If IL cannot be advanced beyond 0.5 g/kg/day (2.5 mL/kg/day) within three days or if TG values are above 400 mg/dL, please consult the Nutrition Team.

Discontinuation of lipid limiting strategy OR lipid minimization strategy for prevention of Intestinal Failure Associated Liver Disease (IFALD) - Lipid limiting or minimization is a strategy whereby IL is limited to prevent IFALD. This strategy has been shown to be suboptimal in prevention of IFALD. Hence, the practice of restricting IL to 1 g/kg/day when conjugated bilirubin (CB) reaches 1.5 mg/dL or greater is being discontinued. In infants with ongoing need for PNand rising conjugated bilirubin levels consider the use of SMOFlipid® for prevention of IFALD based on recommendations in **Ch 5.4-Lipid Injectable Emulsions**. Lipid limiting with SMOFlipid® is associated with essential fatty acid deficiency and is strongly discouraged (strong recommendation; very low-quality evidence). In situations where limiting ILE might be warranted (e.g. hypertriglyceridemia, fluid restriction, CDH either preoperative state or on ECMO with high conjugated bilirubin, cholestasis within 14 days after birth) please consult the Nutrition Team to institute safe ways of limiting ILE. Any lipid limiting should only be done in consultation with the Nutrition Team. **(Ch 5.3-Cholestasis)**

Vitamins and Minerals

- Intravenous vitamins are provided as a standard dose based on weight. Recommended intakes are listed in **Table 13–6b**.
- Limit peripheral calcium (Ca) and phosphorous (P) to 1.2 mmol /100 mL.
- Calcium, phosphorous, and cysteine amounts are ordered in accordance with guidelines and within safety limits on solubility curves. The solubility curves are provided in the PN order. Do not remove P from PN for more than 48 hours without also adjusting Ca and following serum ionized calcium.

Table 13–6a. Components of standard central parenteral nutrition (PN) for premature

Component	per 100 mL	Comments	Intakes at 130 mL/kg/day[1]
Glucose	12.5%		16 g/kg/day
Amino acids	2.8%	TrophAmine	3.6 g/kg/day
NaCl	2.6 mEq	= 2.6 mmol Na	3.4 mEq/kg/day
KH_2PO_4-- K_2HPO_4	1.75 mmol P	= 54 mg P	2.3 mmol/kg/day; 71 mg/kg/day
		= 2.5 mEq K+	3.2 mEq/kg/day
Calcium gluconate	1.75 mmol Ca	= 70 mg Ca	2.3 mmol/kg; 91 mg/kg/day
$MgSO_4$	0.5 mEq Mg	= 6 mg Mg	7.8 mg/kg/day
KCl	0.2 mEq	K from KCl	0.26 mEq/kg/day
ILE		1 to 3 g/kg/day	3 g/kg/day; 15 mL/kg/day
Cysteine	30-40 mg/g amino acids;	always add proportional to amino acids	
Heparin	1 unit/mL		

[1] Use intakes to calculate parenteral nutrient concentrations during fluid restriction. When providing greater than 130 mL/kg to meet fluid needs, adjust nutrients to meet goals and prevent toxicity.

Table 13-6b. AAP (2019) recommendations for vitamins

Vitamins	Preterm (per kg)	Term (per day)
Vitamin A (IU)[1]	700-1500	2300
Vitamin D (IU)[2]	40-160	400
Vitamin E (IU)[3]	2.8-3.5	7
Vitamin K (mcg)	10	200
Vitamin C (mg)	15-25	80
Thiamin B_1 (mg)	0.2-0.35	1.2
Riboflavin B_2 (mg)	0.15 -0.2	1.4
Pyridoxine B_6 (mcg)	150-200	1000
Niacin (mg)	4-6.8	17
Pantothenic acid (mg)	1-2	5
Biotin (mcg)	5-8	20
Folate (mcg)	56	140
Vitamin B_{12} (mcg)	0.3	1

Conversions: [1] Vitamin A (3.33 IU=1 mcg), [2] Vitamin D (40 IU=1 mg), [3]Vitamin E(1 IU=1mg)

- Sodium phosphate can replace potassium phosphate in the same molar concentrations when potassium intake needs to be limited or potassium phosphate is not available.
- Give standard calcium and phosphorous in most cases in a 1:1 mmol ratio. For infants < 1000 g BW, follow ionized calcium levels and serum phosphorus daily as the amount of calcium and phosphorus in PN is advanced in the first 3 days of life or until levels are stable. If ionized calcium is > 1.45 mmol/L, check serum phosphorous as infant may have a low phosphorus. Ca and P ratio may need to be unbalanced in the PN with elevated ionized calcium levels **(Ch. 9.4-Hypocalcemia or Hypocalcemic Seizures and Ch. 9.5-Hypercalcemia or Hyperphosphatemia)**

Trace Elements

The pharmacy adds trace elements as a standard dose based on infant weight and product availability. Recommended intakes are listed in **Table 13–6c.**

In infants with significant secretory losses of zinc (Zn) (e.g., those with gastrointestinal diseases or surgery), increase the Zn concentration by 400 mcg/kg/day for preterm infants and by 100 to 250 mcg/kg/day for term infants.

Alterations in trace element provision:

In Cholestasis - Since copper and manganese are excreted in the bile, in cholestasis, they may accumulate in the liver and cause worsening hepatic dysfunction. In the presence of cholestasis (conjugated bilirubin ≥2 mg/dL) it is recommended to reduce trace minerals in the PN. Growing infants, however, have a requirement for copper and will ultimately develop copper deficiency in the absence of adequate copper supplementation. Copper and zinc levels should be monitored every 4 weeks in infants while on PN. In the presence of cholestasis without either jejunostomy or ileostomy, trace minerals should be provided 3 times per week (Monday, Wednesday and Friday), and parenteral zinc and copper should be provided at maintenance levels daily. In the presence of cholestasis with either jejunostomy or ileostomy, apart from the above supplementation, extra zinc should be provided to compensate for gastrointestinal losses. Lab monitoring of copper and zinc levels may indicate the need for further adjustments to supplementation. In some circumstances such biochemical monitoring may not be feasible. In those instances, copper and zinc should be supplemented despite cholestasis, but levels should be monitored when medically feasible.

Table 13-6c. AAP (2019) recommendations for trace elements

Trace Elements (mcg/kg/day)	Preterm	Term
Zinc	400[1]	250[2]
Copper	20-40	20
Iodine	1	1
Manganese	1	1
Selenium	1.5-4.5	2
Chromium	0.05-0.3	0.2

[1] Preterm infants require 400 mcg/kg/day of zinc. Provide supplementation as indicated.

[2] Term infants require 250 mcg/kg/day of zinc initially; when >3 months of age, 50 mcg/kg/day is recommended. Adjust PN accordingly.

In renal failure - Because of accumulation of selenium and chromium, reduce frequency of administration.

In infants with cholestasis or renal failure, continue zinc daily per guidelines. **(Table 13-6c)**

Carnitine

Carnitine is a nitrogen-containing compound required for the transfer of fatty acids into the mitochondria. Human milk contains 3 to 5 mg/ dL of carnitine. Add L-carnitine (10 mg/kg/day) if the infant is expected to be on PN exclusively for longer than 14 days.

Volume Restricted PN (Severe Lung Disease or Total Body Cooling)

Infants with severe cardiopulmonary disease or those requiring total body cooling should be provided at least 2 g/kg/day of protein with an attempt to provide 2.5-3 g/kg/day as soon as feasible. The use of volume to provide protein is of greater importance in this setting than providing more than 1 g/kg/day of ILE or high concentrations of calcium and phosphorus.

It is important to maintain both total blood phosphorous and magnesium within physiological ranges. Blood levels should be monitored daily during cooling with adjustment of PN as indicated. Recommended goal PN composition for ECMO and Total Body Cooling are provided in **Table 13–7a and Table 13-7b**.

Table 13-7a. Volume restricted goal PN for ECMO 70mL/kg + 15 mL/kg fat (3 grams/kg)[1]

Nutrient	Order/100mL	Amount/kg	Goal Intake/kg
Dextrose	22%	15.4 g (10.7 mg/kg/day/min)	16 g (11-12 mg/kg/day/min)
Protein	5%	3.5 g	2-3 (term) 3.5-4 (preterm)
Calcium	1.75 mmol	1.2 mmol	1.5-2 mmol
Phosphorous	1.75 mmol	1.2 mmol	1.5-2 mmol
Magnesium	0.5 mEq	0.4 mEq	
		96 kcal (PN + IL)	90-100 kcals

[1]Order electrolytes as needed. Order vitamins and trace minerals.

Table 13-7b. Volume restricted PN for Total Body Cooling 40 mL/kg + 5 mL/kg fat (1 gram/kg)[1]

Nutrient	Order/ 100mL	Amount/kg	Goal Intake/kg
Dextrose	25%	10 g (6.9 mg/kg/day/min)	16 g (11-12 mg/kg/day/min)
Protein	5%	2 g	2-3 (term) 3.5-4 (preterm)
Calcium	1.2 mmol	0.5 mmol	1.5-2 mmol
Phosphorous	1.2 mmol	0.5 mmol	1.5-2 mmol
Magnesium	1 mEq	0.4 mEq	
		52 kcal (PN + IL)	90-100 kcals

[1]Order electrolytes as needed. Order vitamins and trace minerals.

Managing Slow Growth in PN-Dependent Infants

- Treat abnormalities that are unrelated to nutrition that might affect growth, such as metabolic acidosis, hyponatremia, increased work of breathing, cold stress, anemia, use of steroids, and infection.
- Assure that intake is within recommended levels. Adjust PN as appropriate.
- Generally, the unbalanced addition of carbohydrate is not recommended to increase total caloric intake.

Stop Parenteral Nutrition

- Stop IL when feeds are greater than or equal to 80 mL/kg/day.
- Stop PN when feeds are greater than or equal to 100 mL/kg/day except in infants with intestinal failure.

13.3 Enteral Nutrition

- Infants, especially VLBW/LBW infants, should start feeds as soon as possible (within 6 to 12 hours of birth) if medically stable (see below). For ELBW infants, consider starting feeds on the first day of life if medically feasible.
- Infants < 1250 g should start on trophic feeds at 15-20 mL/kg/day. Trophic feeds should generally not count towards the total fluid volume.
- Verbal assent should be obtained and documented in the electronic medical record at admission for feeding donor human milk (DHM) whenever it is used. Initial orders for feedings in these infants should specify that DHM is the secondary feeding choice after maternal expressed breast milk (EBM). Formula should not be listed as a backup feeding for infants ≤1800 grams or ≤ 34 weeks' postmenstrual age (PMA). The use of DHM may be considered for all infants but infant formula is also an appropriate backup for infants > 1800 g BW or > 34 weeks PMA.
- Initiation of enteral feedings and advancement rates should be individualized based on a patient's weight, age, and medical stability. Low dose vasopressors, including dopamine (usually 5 mcg/kg/day/minute or less), are compatible with initial trophic feeds. Umbilical catheters do not preclude trophic feeding. Trophic feeds are typically continued for 3 days for infants 751-1250 g and may continue for 3-5 days for infants ≤ 750 grams BW. Trophic feedings may be prolonged if the infant requires high dose pressor support. Trophic feedings can be provided during indomethacin or ibuprofen therapy. Twenty four hours after the last dose of medication, feedings can be advanced.
- Feedings should be given as bolus feedings every 3 hours. Consider bolus feeds every 3 hours given on a pump over 30 minutes if feeding intolerance occurs. Due to fat loss in tubing, it is preferred not to give continuous feeds unless there is severe feeding intolerance. **(Tables 13–8a, 13-8b,13-8c, 13-8d, 13-8e, 13-8f, 13-8g, and 13-8h**)

Providing Oral Care with Mother's Own Colostrum/Breast Milk

Purpose

Colostrum is rich in cytokines, growth factors and immune cells that provide bacteriostatic, bactericidal, antiviral, anti-inflammatory and immunomodulatory protection against infection. Closer in composition to amniotic fluid than mature breast milk, colostrum is the optimal transition for the infant's immature gastrointestinal tract. Studies have found that providing oral care with expressed colostrum or breast milk is safe and may impart protection from these factors in an infant that may not be ready to feed.

Procedure

Oral care using colostrum or expressed breast milk should initiate within 4 hours of birth or as soon as milk is available. Infants should receive oral care regardless of gestation, weight, NPO status, or medical stability at care times only, in accordance with unit policy. Contraindications to oral care with colostrum align with medical contraindications to breastfeeding, such as maternal HIV or TB infection.

Feeding and Nutrition Goals

Human milk is recommended for infants **(exceptions in Human Milk section of this chapter**). Unless feeding intolerance necessitates a slower pace, follow the schedules in **Tables 13–8a, to 13-8h and Figure 13–1**. Volumes are approximate. Nutrient components of human milk & fortified human milk are listed in **Table 13-12a**.

When infant formula is used, formula selection should be selected based on the infant's gestation, BW and/or medical condition **(Tables 13-9, 13–10 and 13-12b).**

The volume of full feedings that enables a good growth rate (15-20 g/kg/day if less than 2000 grams and 20 to 30 grams per day if greater than or equal to 2000 grams) usually is:

- Infants less than 34 weeks' postmenstrual age (PMA),
  - » 160 mL/kg/day of fortified human milk (24-26 kcal/oz).
  - » 150 mL/kg/day of high protein preterm formula (24 kcal/oz).
  - » 160-170 mL/kg/day of premature transitional formula (22 kcal/oz).
- Infants 34 weeks or greater PMA,
  - » 180 to 200 mL/kg/day of unfortified human milk or term formula (20 kcal/oz).
  - » Cue-based feeding with a minimum of 150 mL/kg/day may be used.
- **Energy intakes** of 110 to 130 kcal/kg/day will meet the needs for term and premature infants.
- **Protein intakes** of 3.5 to 4.5 g/kg/day will meet the needs for premature infants. Protein intakes of 1.5 g/kg/day will meet the needs of healthy term infants. Illness or surgery increases protein needs to 2-3 g/kg/day for the term infant.

Human Milk

Human milk is the first choice for feeding, and the nutrient content of human milk is the basis for infant nutrition guidelines. Thus, the caloric distribution and nutrient content of infant formulas are based on that of human milk. Known contraindications to use of human milk are galactosemia, maternal HIV-positive status, current maternal substance abuse, maternal chemotherapy, and miliary TB. Most medications are compatible with breastfeeding. Contact the Texas Children's Hospital Lactation Department with any questions regarding specific medications.

CMV and Breastfeeding/Breastmilk

- In general, mother's own milk **should be** used for infant feedings regardless of the CMV status of mom or baby. For infants infected with CMV congenitally or postnatally, the benefits of human milk from their mothers likely outweighs any risk of additional CMV exposure.
- Mother's own milk **should not be** used when mother is CMV IgG or IgM antibody positive or unknown status AND infant has a diagnosis of SCID or low TRECs on newborn screen and is undergoing immunological evaluation. For further questions about this evaluation, please page the Allergy/Immunology service.
- Mother may direct breastfeed or provide expressed breastmilk. Mother's own milk may be frozen for future use if baby isn't feeding.
- Testing of mother's own milk for CMV is not recommended.

Human milk in COVID-19 positive mothers

Due to lack of evidence to the contrary, the AAP supports direct breastfeeding of infants born to COVID-19 positive mothers. The following should be considered:

- Mothers should perform hand hygiene before breastfeeding and wear a mask during breastfeeding.
- If an infected mother chooses not to nurse her newborn, she may express breastmilk after appropriate hand hygiene. This may be fed to the infant by the mother or other uninfected caregivers. Mothers should perform hand hygiene before bottle feeding and wear a mask during feeding
- Mothers of NICU infants may express breast milk for their infants during any time that their infection status prohibits their presence in the NICU. Centers should make arrangements to receive this milk from mothers until they are able to enter the NICU.

Breastfeeding and Maternal Substance Use:

Abstinence and substance use disorder treatment, with subsequent initiation of breastfeeding should be encouraged and supported.

Cannabis (tetrahydrocannabinol or THC)

- Recent research has shown Cannabis (THC) to be harmful to infant's neurodevelopment. Mothers with a UDS positive for THC should be counseled on the impact to her infant's health and encouraged to abstain during breastfeeding. The decision of whether or not to use breastmilk with possible THC contamination should be made on a case by case basis between the baby's physician and mother.
- Cannabidiol (CBD) products often have THC amounts that can turn urine drug screens positive. Mothers should be encouraged to abstain from all CBD products while breastfeeding.

Circumstances generally compatible with breastfeeding:

- Mothers with substance use disorders undergoing treatment and with a negative urine drug screen at delivery are highly encouraged to breastfeed.
- Mothers with a valid prescription for an opiate or benzodiazepine and with a positive urine drug screen at delivery can breastfeed but should be informed of and be vigilant for potential side effects in the infant. If any side effects present in the infant (e.g., excessive sleepiness in the infant), breastfeeding and provision of expressed maternal EBM should cease.

Circumstances contraindicated with breastfeeding:

- Per the AAP, breastfeeding is contraindicated for mothers using amphetamines with or without a prescription (ex. Adderall).
- Breastfeeding with a maternal positive urine drug screen for opiates, benzodiazepines, PCP or cocaine at delivery (without a valid prescription) is not immediately recommended. If a mother with a positive drug screen desires to breastfeed, she should be abstinent from any substance use, pump frequently to maintain a milk supply, and be instructed to discard the milk until the substances are no longer in her system (i.e., her urine drug screen is negative).

Table 13-8a Suggested feeding schedules [1,2]

BW (g)	Initiation Rate (mL/kg/day)	When to Advance	Advancement Rate (mL/kg/day)
≤750	15-20	Maintain for 3 - 5 days	10-20
751-1250	15-20	Maintain for 3 days	10-20
1251-1500	20	If feeds tolerated, may advance after 24-48 hours	20-30
1501-2000	20	If feeds tolerated, may advance after 24-48 hours	30-40
2001-2500	25-30	Advance daily	30-40
Stable> 2500	50 mL/kg/day or ad-lib with minimum. Cardiac babies: 20 mL/kg/day	Cardiac babies may need 20 mL/kg/day for a longer period of time.	30-40

[1] Individual initiation and advancement rates based on patient's weight, age and clinical status.

[2] Feedings for infants < 1500 grams are usually best given by gravity, or in the setting of feeding intolerance, on a pump over 30-60 minutes.

Table 13-8b. BW ≤ 750 g feeding guidelines using Prolacta® fortifier

Day of Life	Kcal/oz EBM[1] or Donor EBM	Feeding Volume (mL/kg/day)	PN (mL/kg/day)	Lipids (mL/kg/day)	Total Fluid[2] (mL/kg/day)
1	20	15-20[3]	80-100[4]	2.5[5]	130
2	20	15-20[3]	80-100	2.5-5	140
3	20	15-20[3]	80-100	5-10	140
4	20	15-20[3]	100	10-15	140
5	20	15-20[3]	110	15	150
6	20	40	95	15	150
7	26 (add Prolact + 6)[6]	60	75	15	150
8	26 (Prolact + 6)	80	50-70	15 or Off Lipids	150
9	26 (Prolact + 6)	100	50	0	150
10	26 (Prolact + 6)	120	Off PN	0	120
11	26 (Prolact + 6)	140	0	0	140
12	26 (Prolact + 6)	150-160	0	0	150-160
13	26 (Prolact + 6)[7]	150-160	0	0	150-160

[1] EBM = expressed breast milk

[2] Anticipated total fluids include PN, lipids, TKO's, medications and flushes. Volume available for PN may differ depending on volume of meds, flushes, etc.

[3] Recommend begin enteral feeds within the first day of life if medically stable (i.e. not intubated or requiring pressors except low dose dopamine). Trophic feeds generally do not count towards total fluid. **Table 9-2b in Ch. 9.1-Fluid and Electrolyte Therapy**

[4] Standard starter used when PN room closed (1PM – 10AM).

[5] For infants ≤750 gram birth weight, initiate lipids at 2.5 mL/kg/day. See IL initiation protocol.

[6] Add Prolact +6 to EBM at 60 mL/kg.

[7] Add poly-vi-sol and fer-in-sol at 2- 3 mg/kg/day after parenteral nutrition is discontinued for infants consuming EBM + Prolacta. The infant should be at least 14 days of age for iron supplementation.

Table 13-8c. BW ≤ 750 g feeding guidelines using bovine human milk fortifier (HMF)

Day of Life	Kcal/oz EBM[1] or Donor EBM	Feeding Volume (mL/kg/day)	PN (mL/kg/day)	Lipids (mL/kg/day)	Total Fluid[2] (mL/kg/day)
1	20	15-20[3]	80-100[4]	2.5[5]	130
2	20	15-20[3]	80-100	2.5-5	140
3	20	15-20[3]	80-100	5-10	140
4	20	15-20[3]	100	10-15	140
5	20	15-20[3]	110	15	150
6	20	40	95	15	150
7	20	60	75	15	150
8	20	80	50-70	15 or Off Lipids	150
9	24 (add Similac HMF)[6]	80	50-70	15 or Off Lipids	150
10	24 (Similac HMF)	100	50	0	150
11	24 (Similac HMF)	120	Off PN	0	120
12	24 (Similac HMF)	140	0	0	140
13	24 (Similac HMF)[7]	150-160	0	0	150-160

[1] EBM = expressed breast milk

[2] Anticipated total fluids include PN, lipids, TKO's, medications and flushes. Volume available for PN may differ depending on volume of meds, flushes, etc.

[3] Recommend begin enteral feeds within the first day of life if medically stable (i.e. not intubated or requiring pressors except low dose dopamine). Trophic feeds generally do not count towards total fluid. **Table 9-2b in Ch. 9.1-Fluid and Electrolyte Therapy**

[4] Standard starter used when PN room closed (1PM – 10AM).

[5] For infants ≤750 gram birth weight, initiate lipids at 2.5 mL/kg/day. See IL initiation protocol.

[6] If Prolacta is unavailable use Similac HMF Hydrolyzed Protein Concentrated Liquid. After 1 day of 80 mL/kg of enteral feeds, fortify EBM with 4 packets of Similac HMF Hydrolyzed Protein Concentrated Liquid to reach 24 kcal/oz

[7] Add fer-in-sol at 2-3 mg/kg/day and 200 IU per day vitamin D after parenteral nutrition is discontinued for infants consuming EBM + Similac HMF. The infant should be at least 14 days of age for iron supplementation.

Table 13-8d. BW 751-1250g feeding guidelines Prolacta® fortifier					
Day of Life	**Kcal/oz EBM[1] or Donor EBM**	**Feeding Volume (mL/kg/day)**	**PN (mL/kg/day)**	**Lipids (mL/kg/day)**	**Total Fluid[2] (mL/kg/day)**
1	20	15-20[3]	80-100[4]	5-10[5]	80-110
2	20	15-20[3]	80-100	5-10	120-130
3	20	15-20[3]	80-100	10-15	120-130
4	20	40	80	15	120-135
5	26 (add Prolact + 6)[6]	60	70	15	150
6	26 (Prolact + 6)	80	50-70	15 or Off Lipids	150
7	26 (Prolact + 6)	100	50	0	150
8	26 (Prolact + 6)	120	Off PN	0	120
9	26 (Prolact + 6)	140	0	0	140
10	26 (Prolact + 6)	150-160	0	0	150-160
11	26 (Prolact + 6)[7]	150-160	0	0	150-160

[1] EBM = expressed breast milk

[2] Anticipated total fluids include PN, lipids, TKO's, medications and flushes. Volume available for PN may differ depending on volume of meds, flushes, etc.

[3] Recommend begin enteral feeds within 6-12 hours after birth if medically stable for VLBW/LBW infants. For ELBW infants, initiate on the first day if medically stable (i.e. not intubated or requiring pressors except low dose dopamine).Trophic feeds generally do not count towards total fluid. **Table 9-2b in Ch 9.1-Fluid and Electrolyte Therapy**

[4] Standard starter used when PN room closed (1PM – 10AM).

[5] For infants 751 -1000 grams birth weight, initiate lipids at 5 mL/kg/day. See IL initiation protocol.

[6] Add Prolact +6 to EBM at 60 mL/kg.

[7] Add poly-vi-sol and fer-in-sol at 2- 3 mg/kg/day after parenteral nutrition is discontinued for infants consuming EBM + Prolacta. The infant should be at least 14 days of age for iron supplementation.

Table 13-8e. BW 751-1250g feeding guidelines using bovine human milk fortifier (HMF)					
Day of Life	**Kcal/oz EBM[1] or Donor EBM**	**Feeding Volume (mL/kg/day)**	**PN (mL/kg/day)**	**Lipids (mL/kg/day)**	**Total Fluid[2] (mL/kg/day)**
1	20	15-20[3]	80-100[4]	5-10[5]	80-110
2	20	15-20[3]	80-100	5-10	120-130
3	20	15-20[3]	80-100	10-15	120-130
4	20	40	80	15	120-135
5	20	60	70	15	150
6	20	80	50-70	15 or Off Lipids	150
7	24 (add Similac HMF)[6]	80	50-70	15 or Off Lipids	150
8	24 (Similac HMF)	100	50	0	150
9	24 (Similac HMF)	120	Off PN	0	120
10	24 (Similac HMF)	140	0	0	140
11	24 (Similac HMF)[7]	150-160	0	0	150-160

[1] EBM = expressed breast milk

[2] Anticipated total fluids include PN, lipids, TKO's, medications and flushes. Volume available for PN may differ depending on volume of meds, flushes, etc.

[3] Recommend begin enteral feeds within 6-12 hours after birth if medically stable for VLBW/LBW infants. For ELBW infants, initiate on the first day if medically stable (i.e. not intubated or requiring pressors except low dose dopamine).Trophic feeds generally do not count towards total fluid. **Table 9-2b in Ch 9.1-Fluid and Electrolyte Therapy**

[4] Standard starter used when PN room closed (1PM – 10AM).

[5] For infants 751 -1000 grams birth weight, initiate lipids at 5 mL/kg/day. See IL initiation protocol.

[6] If Prolacta is unavailable use Similac HMF Hydrolyzed Protein Concentrated Liquid. After 1 day of 80 mL/kg of enteral feeds, fortify EBM with 4 packets of Similac HMF Hydrolyzed Protein Concentrated Liquid to reach 24 kcal/oz

[7] Add fer-in-sol at 2-3 mg/kg/day and 200 IU per day vitamin D after parenteral nutrition is discontinued for infants consuming EBM + Similac HMF. The infant should be at least 14 days of age for iron supplementation.

Table 13-8f. BW 1251-1500 g feeding guidelines

Day of Life	Kcal/oz EBM[1] or Donor EBM	Feeding Volume (mL/kg/day)	PN (mL/kg/day)	Lipids (mL/kg/day)	Total Fluid[2] (mL/kg/day)
1[3]	20	20	70[4]	5-10	80
2	20	50	50	10-15	100-120
3	20	80	20	15	100-120
4	24 (add Similac HMF)[5]	80	20	Off Lipids	100-120
5	24 (Similac HMF)	110	off PN	0	150
6	24 (Similac HMF)	140	0	0	150
7	24 (Similac HMF)[6]	150-160	0	0	150-160

[1] EBM = expressed breast milk

[2] Anticipated total fluids include PN, lipids, TKO's, medications and flushes. Volume available for PN may differ depending on volume of meds, flushes, etc.

[3] Recommend begin enteral feeds within 6-12 hours after birth if medically stable (i.e. not intubated or requiring pressors except low dose dopamine). Trophic feeds generally do not count towards total fluid. **Table 9-2b in Ch 9.1-Fluid and Electrolyte Therapy**

[4] Standard starter used when PN room closed (1PM – 10AM).

[5] After 1 day of 80 mL/kg of enteral feeds, fortify EBM with 4 packets of Similac HMF Hydrolyzed Protein Concentrated Liquid to reach 24 kcal/oz.

[6] Provide iron supplementation at 2-3 mg/kg/day. For infants <1500 g birthweight, also provide 200 IU per day of vitamin D.

Table 13-8g. BW 1501-2000 g feeding guidelines

Day of Life	Kcal/oz EBM/Donor EBM[1] or premature formula	Feeding Volume (mL/kg/day)	IVF (mL/kg/day)	Total Fluids[2] (mL/kg/day)
1	20-24[3]	20	60	65-80
2	20-24	50	50	100
3	20-24	80	20	100
4	24 (Similac HMF)[4,5]	80	20	110
5	24	110	Off IVF	110
6	24	130	0	130
7	24	150	0	150

[1] EBM = expressed breast milk

[2] Individualize initiation and advancement rates and total fluids based on patient's weight, age and clinical status. **Table 9-2b in Ch 9.1-Fluid and Electrolyte Therapy.**

[3] Initiate feedings with EBM/donor EBM 20 kcal/oz or Similac Special Care 24 kcal/oz High Protein or Enfamil Premature 24 kcal/oz High Protein.

[4] After 1 day of ≥ 80 mL/kg of enteral feeds, EBM feeds are fortified with 4 packets of Similac HMF Hydrolyzed Protein Concentrated Liquid to reach 24 kcal/oz for infants birth weight <2000 g or < 34 weeks PMA. The infant should be at least 14 days of age for iron supplementation.

[5] Provide iron supplementation at 2 mg/kg/day for infants 1500 to 2500 g birthweight.

Table 13-8h. BW >2000 g feeding guidelines[5]

Day of Life	Kcal/oz EBM/Donor EBM[1] or formula[2]	Feeding Volume (mL/kg/day)	IVF (mL/kg/day)	Total Fluids (mL/kg/day)
0-1	20	ad lib to 30	0-40	65-80 (exclusive po: 30-40 minimum)
2	20	ad lib to 60	0-40	100 (exclusive po: 30-40 minimum)
3	20	ad lib to 90	0	100 (exclusive po: 30-40 minimum)
4	20	ad lib to 120	0	150 (exclusive po: >50 minimum
≥ 5	20	ad lib to 150	0	150[3, 4]

[1] EBM = expressed breast milk

[2] Initiate feedings with human milk. Term formula (20 kcal/oz) can be used if EBM is not available. Transitional formula may be provided as initial feedings for infants whose birth weight is 1800 to 2200 g.

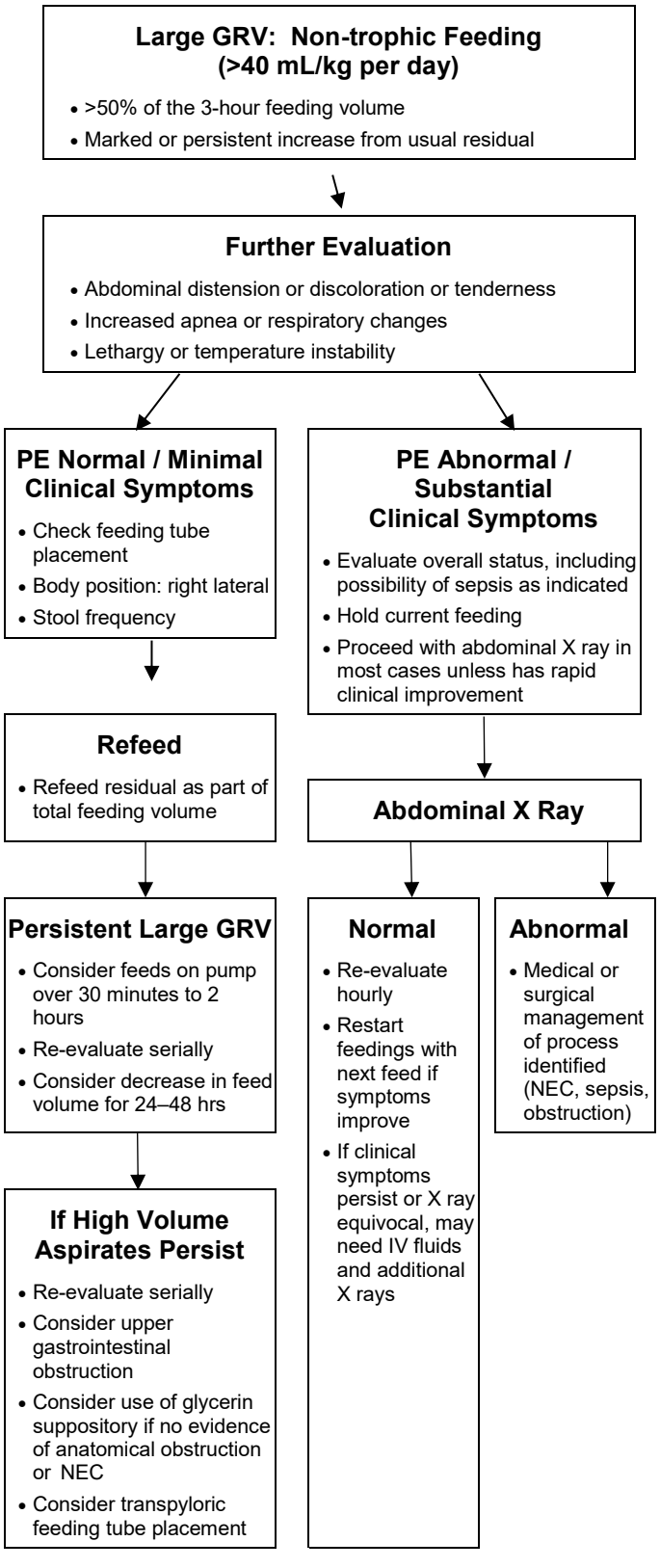
[3] Should be on full volume goal after day of life 5. Infants may need 180-200 ml/kg/day of unfortified human milk or term formula.

[4] The infant should be at least 14 days of age for iron supplementation. **See vitamin Table 13-13** for recommendations.

[5] **Tables 9-2a and 9-2b in Ch 9.1-Fluid and Electrolyte Therapy.**

Figure 13-1. Feeding tolerance algorithm

There is no strong evidence for the evaluation of residuals in most VLBW infants. Current practice is to check gastric residual volume **(GRV)** every 3 hours for infants receiving >40 mL/kg of feedings or if infant appears ill. Evaluate if residuals exceed 50% of the feeding volume or the infant has other symptoms of feeding intolerance.



TCH Donor Human Milk Protocol

Parental assent must be obtained and documented in the electronic medical record prior to giving any DHM product.

All infants (≤ 1800 g or ≤ 34 weeks' PMA), are eligible for DHM.

Other potential indications for DHM (>1800 g or >34 weeks' PMA):

- History of NEC - Recommend using for all with Stage 2 or above.
- Major congenital heart disease.
- Significant feeding intolerance, especially in infants with abdominal wall defects.
- Family request. It is important to respect the family's choices and in every case where a mother requests "no formula" this should be honored unless there is a special medical indication to use an infant formula.

Table 13-9. Milk selection[1]

Milk	Indication
Human milk*	Milk initiation for all infants and single milk source for infants > 2000 g or > 34 weeks[1] PMA[2]
Human milk + Prolacta [3,4,5]	Birth weight ≤ 1250 g
Human milk + bovine milk based fortifier [4,5,6]	Birth weight 1251 - 2000 g or < 34 weeks PMA
Premature infant formula with iron[4]	Birth weight < 2000 g or < 34 weeks PMA
Term formula with iron[7]	Birth weight > 2000 g or > 34 wks PMA and able to consume at least 180 mL/kg/day
Premature transitional formula	Premature infants post discharge with birth weight <1800 g[7]

PMA= post-menstrual age

* Consider donor human milk supplementation of mother's milk for infants ≤1800 g or ≤34 weeks

[1] **Table 13-11** for special use formulas.

[2] See section in this chapter on **Human Milk** for contraindications to human milk usage

[3] Add Prolact +6 at 60 mL/kg EBM.

[4] To avoid nutrient overload, fortified human milk or premature infant formula should not be fed ad lib.

[5] For infants ≤1250 BW, if Prolacta fortifier is not available, infants should receive mother's own milk or donor milk fortified with Similac HMF Hydrolyzed Protein Concentrated Liquid.

[6] Add bovine human milk fortifier when infant has tolerated at least 80 mL/kg/day unfortified milk or if unfortified human milk has been used at > 50 mL/kg/day for 5 to 7 days. Add 4 packets/vials of HMF per 100 mL milk, thereafter.

[7] May be provided as initial feedings for healthy infant whose birth weight is 1800 to 2200 g. Data regarding nutrient needs for this weight group are limited.

Prolacta® (Donor Human Milk Fortifier) Indications:

- BW ≤ 1250 grams.
- Intolerance to bovine milk-based HMF.
- Other possible uses (individualized decision, discuss with Nutrition Team).

Prolacta® Cream (Donor Human Milk Cream Supplement):

- Premature infants receiving a diet of mother's milk or donor human milk fortified with Prolacta® at full feeds are eligible for Prolacta® Cream if weight gain is suboptimal for 3-5 days.
- Prolacta® Cream will be added to the 24 hour batch of feeds at a standard amount to provide an additional 2 kcal/oz.
- If concerns about poor growth or caloric content of mother's own milk, consider analysis of milk with assistance of the Nutrition Team. Analysis sample will be from a 24 hour feeding aliquot.
- Optimize protein intake, with Prolacta® fortifier prior to initiation of Prolacta® Cream. **(Table 13-10).**

In general, it is our practice to transition off DHM, donor human milk fortifier and donor milk cream at 34 weeks PMA as the peak incidence of NEC occurs at 31-33 weeks PMA in premature infants.

Transitioning from DHM to formula (assuming no mother's milk available) may be done as follows (assuming formula is tolerated):

- Day 1, add 1 formula feeding
- Day 2, add 2 formula feedings
- Day 3, add 4 formula feedings
- Day 4, all formula feedings

In order to facilitate back-transfer of VLBW infants closer to home, once all elements of transfer are in place, certain low-risk VLBW infants may be eligible to be transitioned off donor human milk fortifier (Prolacta®) before 34 weeks PMA. Please consult the TCH Neonatal Nutrition Team. Infants receiving DHM or donor human milk fortifier should transition to formula at least one week prior to discharge.

- For infants ≤ 1250 g BW, if Prolacta® fortifier is not available, infants should receive mother's own milk or DHM fortified with Similac® HMF Hydrolyzed Protein Concentrated Liquid.
- Generally, enteral nutrition milk volume and concentration are not increased concurrently when using bovine fortifier.
- Advance the volume of fortified human milk until weight gain is satisfactory.
- Satisfactory weight gain is 15-20 g/kg/day when < 2 kg.
- Consider stopping fortification of human milk or premature formula at about 34 weeks PMA in preparation for discharge, if growth and bone indices are appropriate and if patient is not being fluid restricted.

Table 13-10. Suggested Prolacta® concentrations when using Prolacta® cream according to feeding volume.

Total EN volume (mL/kg/day)	Prolacta® Fortifier	Protein (g/kg/day)	Prolacta Cream
160	Prolact +6	3.8	2 kcal/oz
150	Prolact +6	3.6	2 kcal/oz
150	Prolact +8	4.4	2 kcal/oz
140	Prolact +8	4.1	2 kcal/oz
130	Prolact +8	3.8	2 kcal/oz
130	Prolact +10	4.5	2 kcal/oz

Vitamin and Mineral Supplementation

- Infants on EBM + Prolacta should receive 1 ml/day of poly-vi-sol and 2-3 mg/kg/day of iron
- Infants < 1500g on EBM + Similac HMF should receive 200 IU of Vitamin D /day (cholecalciferol) and 2-3 mg/kg/day of iron.
- Infants should be at least 14 days of age for iron supplementation.
- **Table 13–13** provides guidelines.

Infants 34 or More Weeks' Gestation or 2000 Grams or Greater Birth Weight

- Breastfeeding or expressed breast milk (EBM) is encouraged. If infant is not breastfeeding, use term or premature transitional infant formula with iron. **(Table 13–11)**
- Milk volumes in the first 4 days of life are generally low in full term infants. Most infants will not need more than 30-40 ml/kg/day total daily volume in the first 48 hours of age or more than 50 ml/kg/day in the third and fourth days of life. Feeding orders should reflect this.
- For initiation and advancement rates, **Table 13–8a, Table 13-8g and Table 13-8h.**
- Infants who are unable to feed orally require oro or naso-gastric feedings.
- Generally, infants 34 or more weeks' gestation or 2000 grams or more birth weight receiving full oral feedings at an adequate volume do not need fortification of human milk, premature formula, or premature transitional formula.
- Premature transitional formula may be provided as initial feedings for healthy infants whose birth weight is 1800 to 2200 grams. Data regarding nutrient needs for this weight group are limited.
- Weight gain of 20-30 grams/day is desired after initial weight loss during the first 3 to 7 days of life for infants who weigh greater than or equal to 2 kg. Infants less than 2 kg should gain 15-20 g/kg/day after initial weight loss.

Table 13-11. Indications for human milk and infant formula usage in high-risk neonates

		Nutrient Source		
Milk/Formula	**Indication for Use**	**Carbohydrate**	**Protein**	**Fat**
Low Birth Weight Infants				
Donor human milk fortifier (pasteurized)	supplement to breast milk for infants ≤ 1250 g birthweight fortified with minerals and electrolytes	lactose, glucose oligosaccharides	concentrated human milk protein	human milk fat
Donor human milk cream fortifier (pasteurized)	caloric fortifier	none	none	human milk cream
Human milk fortifier bovine milk-based	supplement to breast milk for premature infants	maltodextrin, modified corn starch	casein hydrolysate	MCT oil, soy oil, coconut oil, DHA, ARA
Premature formulas 20, 24 (high and regular protein) or 30 kcal/oz with iron	premature infants	corn syrup solids or maltodextrin, and lactose	nonfat milk, whey protein concentrate	40–50% MCT oil, soy, high oleic sunflower, and/or coconut oils, DHA, ARA
Premature transitional formulas 22 kcal/oz with iron	discharge formula for infants with birth weight <1800-2200 g, on limited volume intake or history of osteopenia or poor growth	Maltodextrin or corn syrup solids and lactose	nonfat milk and whey protein concentrate, and/or whey	20–25% MCT oil, soy oil, coconut oil, and/or high oleic sunflower or safflower oil, DHA, ARA
Special Use				
Alfamino® Infant	cow's milk protein allergy, multiple food allergies, eosinophilic GI disorders, malabsorptive conditions, short bowel syndrome	corn syrup solids, potato starch, maltodextrin	100% free amino acids	43% MCT oil, soy bean, high oleic sunflower, and high 2-palmitic vegetable oils, DHA, ARA
Alimentum®	sensitivity to intact protein (cow's milk), protein maldigestion, severe food allergies, or fat malabsorption	sucrose, modified tapioca starch or corn maltodextrin	casein hydrolysate with added amino acids	33% MCT oil, high-oleic safflower or safflower, soy oils, DHA, ARA
Elecare® (for infants)	intolerance to intact protein (cow's milk) or hydrolyzed protein, protein maldigestion, malabsorption, severe food allergies, short bowel syndrome, eosinophilic GI disorders, or GI tract-impairment	corn syrup solids	100% free amino acids	33% MCT oil, high oleic safflower, soy oils, DHA, ARA
Enfaport®	chylothorax, LCHAD deficiency, available as 30 kcal/oz, can be prepared at 20 kcal/oz for infants	corn syrup solids	nonfat milk, whey protein concentrate	83% MCT oil, soy oil, DHA, ARA
Gerber Extensive HA® (contains probiotics)	extensively hydrolyzed whey protein, for cow's milk protein allergy or intolerance	corn maltodextrin, potato starch, corn syrup solids	enzymatically hydrolyzed whey protein isolate	49% MCT oil, soy, high oleic sunflower, high 2-palmitic vegetable oils, DHA, ARA
Neocate Infant DHA/ARA®	cow milk allergy, multiple food allergies, related GI and allergic conditions	corn syrup solids	100% synthetic amino acids	33% MCT oil, high-oleic sunflower, sunflower, canola oils, DHA, ARA
Nutramigen® (Liquids)	intact protein allergy (cow and soy milks)	corn syrup solids, modified corn starch	casein hydrolysate with added amino acids	palm olein, soy, coconut, high, oleic sunflower oils, DHA, ARA
Puramino®	severe cow's milk protein allergy (not effectively managed by an extensively hydrolyzed formula), multiple food protein allergies, protein maldigestion, malabsorption, short bowel syndrome, and eosinophilic esophagitis	corn syrup solids, modified tapioca starch	100% free amino acids	33% MCT oil, high-oleic sunflower, soy oils, DHA, ARA
Pregestimil®	fat malabsorption, sensitivity to intact proteins	corn syrup solids, modified corn starch	casein hydrolysate with added amino acids	55% MCT oil, soy, high-oleic sunflower and/or safflower oils and/or corn oil, DHA, ARA
Similac® PM 60/40, low iron	low mineral formula for infants with hypocalcemia or hypercalcemia due to hyperphosphatemia or renal disease	lactose	whey protein concentrate, sodium caseinate	high-oleic safflower, soy, coconut oils
Gerber® Good Start® Gentle and GentlePro (powder formula contains probiotics)	normal nutrition for term infants, low mineral formula for infants with hypocalcemia or renal disease	lactose, corn maltodextrin, lactose	whey protein concentrate (from cow's milk, enzymatically hydrolyzed, reduced in minerals) and/or nonfat dry milk	palm olein, soy, coconut, high oleic safflower or sunflower oils, DHA, ARA
Standard Term Formula/Milk				
Human milk, 20 kcal/oz	recommended for all infants; fortification needed for premature infants	lactose, glucose, oligosaccharides	whey, casein	human milk fat
Term formulas with iron, 19/20 kcal/oz	normal nutrition for term infants (when breast milk not available)	lactose and/or corn maltodextrin, and/or oligosaccharides, and/or polydextrose	nonfat milk, whey protein concentrate or whey protein concentrate (from cow's milk, enzymatically hydrolyzed, reduced in minerals)	vegetable oil (palm olein and/or coconut, soy, high oleic sunflower and/or high oleic safflower oils), DHA, ARA
Soy formulas with iron, 19/20 kcal/oz**	galactosemia, hereditary lactase deficiency (rare), vegetarian diet, not indicated for use in preterm infants	corn syrup and/or corn syrup solids or corn maltodextrin and/or cornstarch, and/or sucrose, and/or oligosaccharides	soy protein isolate or enzymatically hydrolyzed soy protein isolate	vegetable oil (soy, coconut and/or palm olein oil, high oleic safflower and/or high oleic sunflower oils), DHA, ARA

* Premature infants receiving milk or formulas not designed for premature infants may be at risk for osteopenia. Serum calcium, phosphorous and alkaline phosphatase activity should be monitored, and calcium, phosphorus and vitamin D supplementation may be indicated.

**Soy formulas are not recommended for premature infants due to the development of osteopenia and poor growth. Osteopenia is due to the lower formula mineral content and the presence of soy phytates that bind phosphorus and make it unavailable for absorption.

Vitamin and Mineral Supplementation

- Full-term, breastfed infants should receive a vitamin D supplement of 400 IU per day (use D-Vi-Sol®, 1 mL per day).
- Supplemental iron and vitamins are not needed for term infants receiving iron-fortified formula. The AAP recommends using only iron-fortified formulas
- Healthy term, breastfed infants do not need iron supplementation until 4 months of age, at which time they should be initiated at 1 mg/kg/day. Early iron supplementation should be considered for infants who have had significant blood loss in the neonatal period or thereafter. Earlier iron supplementation is required for infants < 2500 grams birthweight at 2 mg/kg/day.

When to Use Human Milk Enriched with Formula or Concentrated Formula

Generally, infants born at 34 weeks' gestation or at 2000 grams or greater will progress easily to full oral feeding on the diets discussed above. Additional nutrition support is indicated for those infants who:

- Have slow growth (less than 20 grams/day for infants greater than or equal to 2 kg or less than 15 grams/kg/day for infants less than 2 kg),
- Manifest abnormal biochemical indices (low serum phosphorus, high alkaline phosphatase activity, or low BUN),
- Need a restricted milk volume (less than 150 mL/kg/day), or have diagnoses such as BPD or CHD that require nutrient dense milk or formula.

For infants fed human milk, consider breastfeeding plus a few feedings of formula. Formula powder may be added to expressed human milk to equal 24, 27, or 30 kcal/oz milk. Recognize potential risk of powdered formula use if this is chosen.

For term infants fed formula, use term liquid concentrate formula when available and prepare to desired caloric density greater than 20 kcal/oz.

For preterm infants fed formula, use ready-to-feed preterm 30 kcal/oz formula and mix with high protein preterm 24 kcal/oz formula to achieve greater than 24 kcal/oz formula. Continue these diets until abnormalities resolve or fluid restriction is liberalized.

Table 13-12a. Nutritional components of human milk and fortified human milk

	Energy		Protein		Fat		Carbohydrate		Calcium mg/dL	Phosphorus mg/dL	Sodium mEq/dL	Potassium mEq/dL	Chloride mEq/dL	Zinc mg/dL	Iron mg/dL	Vitamin A IU/dL	Vitamin D IU/dL	Potential Renal Solute Load mOsm/dL	Osmolality mOsm/Kg/H_2O
	kcal/oz	kcal/dL	g/dL	%kcals	g/dL	% kcals	g/dL	% kcals											
Human milk[1]	20	68	0.9	5	3.5	46	8.0	47	23	13	0.8	1.2	1.2	0.2	0.06	160	1.0	8.8	295[2]
EBM + Prolact+4 = 24[3]	24	83	1.9	9	4.7	51	8.2	40	113	63	2.2	2.2	1.6	0.8	0.1	166	3	19.1	NA[4]
EBM + Prolact+6 = 26[3]	26	91	2.4	11	5.6	55	8.3	37	119	66	2.3	2.3	1.7	0.8	0	158	3	22.3	NA[4]
EBM + Prolact+8 = 28[3]	28	99	2.9	12	5.8	53	8.4	34	124	65	2.4	2.3	1.8	0.9	0	167	5	25.4	NA[4]
EBM + Prolact+10 = 30[3]	30	106	3.5	13	6.4	54	8.5	32	123	66	2.5	2.4	1.8	0.9	0	157	4	28.4	NA[4]
EBM + Prolact+8 (1:1 ratio) = 30[3]	30	106	3.5	13	6.4	54	8.5	32	150	78	2.8	2.6	1.9	1.1	0	169	5	29.5	NA[4]
Liquid Similac FEBM 22[5]	22	75	1.7	9	3.6	43	8.6	46	76	43	1.1	2.0	1.8	0.8	0.3	503	65	16.3	375
Liquid Similac FEBM 24[5]	24	80	2.4	12	3.6	41	9.2	46	119	68	1.4	2.7	2.3	1.2	0.4	790	118	22.4	450
Liquid Similac FEBM 26[5]	26	86	3.2	15	3.7	38	9.8	45	167	95	1.6	3.4	2.9	1.7	0.6	1105	176	29.3	NA[4]
Similac FEBM[5] + NeoSure = 27	27	90	2.7	12	4.2	42	10.2	45	129	74	1.5	3.0	2.5	1.3	0.6	817	123	25	NA[4]
Similac FEBM[5] + EnfaCare = 27[6]	27	90	2.7	12	4.2	42	10.2	45	131	74	1.5	2.9	2.5	1.3	0.6	829	124	24.9	NA[4]
Similac FEBM[5] + NeoSure = 30	30	100	3	12	4.8	43	11.2	45	139	79	1.6	3.4	2.7	1.4	0.8	844	130	27.5	NA[4]
Similac FEBM[5] + EnfaCare = 30[6]	30	99	3	12	4.7	42	11.2	45	142	80	1.6	3.2	2.7	1.4	0.8	866	130	27.2	NA[4]

[1] Adapted from American Academy of Pediatrics Committee on Nutrition: Pediatric Nutrition Handbook, 8th ed. 2019

[2] Adapted from Handbook of milk composition. Reproduced with permission of Elsevier Science & Technology from Handbook of milk composition by Jensen, Robert G ©2021 via Copyright Clearance Center.

[3] Values obtained from mature human milk (AAP) and Prolacta.com

[4] NA = not available

[5] FEBM = expressed breast milk with Similac Human Milk Fortifier Hydrolyzed Protein Concentrated Liquid

[6] Enfamil NeuroPro Enfacare

Table 13-12b. Nutritional components of commercial formulas[1]

	Energy		Protein		Fat		Carbohydrate												
	kcal/oz	kcal/dL	g/dL	%kcals	g/dL	% kcals	g/dL	% kcals	Calcium mg/dL	Phosphorus mg/dL	Sodium mEq/dL	Potassium mEq/dL	Chloride mEq/dL	Zinc mg/dL	Iron mg/dL	Vitamin A IU/dL	Vitamin D IU/dL	Potential Renal Solute Load mOsm/ dL	Osmolality mOsm/Kg/ H2O
Enfamil NeuroPro Infant 20[5]	20	68	1.4	8	3.6	48	7.6	44	53	29	0.8	1.9	1.2	0.7	1.2	200	47	12.5	300
Good Start Gentle 20[5]	20	68	1.5	9	3.4	46	7.9	46	45	26	0.8	1.9	1.3	0.5	1.0	203	41	13.3	255
Similac Pro-Advance 20	20	68	1.4	8	3.8	49	7.1	44	53	28	0.7	1.8	1.2	0.5	1.2	203	41	12.6	310
Enfamil 24	24	81	1.7	8.5	4.3	48	9.1	43.5	63	35	1.0	2.3	1.5	0.8	1.5	240	61	15.4	370
Similac with Iron 24	24	81	1.7	8	4.4	49	9.1	45	63	34	0.8	2.2	1.5	0.6	1.5	243	61	15.2	380
Enfamil Premature 20	20	68	2.2	13	3.4	44	7.3	43	112	61	2.0	1.7	2.1	1.0	1.2	910	200	20.0	260
Similac Special Care 20	20	68	2.0	12	3.7	47	7.0	41	122	68	1.3	2.2	1.6	1.0	1.2	845	101	18.8	235
Enfamil Premature 24 HP[2]	24	81	2.9	14	4.1	44	8.5	42	134	73	2.5	2.1	2.4	1.2	1.5	1100	240	26.0	300
Enfamil Premature 24	24	81	2.7	13	4.1	44	8.8	43	134	73	2.5	2.1	2.4	1.2	1.5	1100	240	25.0	320
Similac Special Care 24 HP[2]	24	81	2.7	13	4.4	47	8.1	40	146	81	1.5	2.7	1.9	1.2	1.5	1014	122	24.0	280
Similac Special Care 24	24	81	2.4	12	4.4	47	8.4	41	146	81	1.5	2.7	1.9	1.2	1.5	1014	122	22.6	280
Enfamil Premature 27 HP[2]	27	90	3.1	14	4.6	45	9.7	43	151	82	2.7	2.3	2.7	1.4	1.7	1229	271	28.1	NA[3]
Similac Special Care 27 HP[2]	27	91	2.9	13	5.6	55	8	35	164	92	1.8	3	2.1	1.4	1.6	1141	137	26.1	305
Enfamil Premature 30	30	100	3.3	13	5.1	44	10.9	43	167	91	3.1	2.5	3.1	1.5	1.8	1370	300	30.0	320
Similac Special Care 30	30	101	3.0	12	6.7	57	7.8	31	183	101	1.9	3.4	2.3	1.5	1.8	1268	152	28.2	325
Enfamil EnfaCare 22[4]	22	75	2.1	11	3.9	47	7.7	42	89	49	1.2	2.0	1.7	0.7	1.3	330	56	18.4	230
Similac NeoSure 22	22	74	2.1	11	4.1	50	7.5	40	78	46	1	2.7	1.6	0.9	1.3	260	52	18.7	250
Enfamil EnfaCare 24[4]	24	81	2.3	11	4.4	49	8.4	42	97	53	1.3	2.2	1.8	0.8	1.5	370	61	19.8	NA[3]
Similac NeoSure 24	24	80	2.2	11	4.4	50	8.1	40	84	50	1.1	2.9	1.7	1.0	1.4	280	56	20.2	NA[3]
Enfamil EnfaCare 27[4]	27	89	2.5	11	4.8	49	9.3	42	107	59	1.4	2.4	2	0.9	1.6	410	68	22.0	NA[3]
Similac NeoSure 27	27	90	2.5	11	5.0	50	9.1	40	95	56	1.3	3.2	1.9	1.1	1.6	316	63	22.7	NA[3]
Enfamil EnfaCare 30[4]	30	100	2.8	11	5.4	49	10.4	42	120	66	1.6	2.7	2.2	1.0	1.8	460	76	24.6	NA[3]
Similac NeoSure 30	30	101	2.8	11	5.6	50	10.2	40	106	63	1.4	3.6	2.1	1.2	1.8	354	71	25.5	NA[3]
Nutramigen 20 (Liquids)	20	68	1.9	11	3.6	48	7.0	41	64	35	1.4	1.9	1.7	0.7	1.2	200	41	16.9	320
Pregestimil 20	20	68	1.9	11	3.8	49	6.9	40	64	35	1.4	1.9	1.7	0.7	1.2	240	34	16.9	290
Pregestimil 24	24	81	2.3	11	4.5	49	8.3	40	76	42	1.6	2.3	2.0	0.8	1.5	280	41	20.0	340
Similac Alimentum 20[5]	20	68	1.9	11	3.7	48	6.9	41	71	51	1.3	2.0	1.5	0.5	1.2	203	41	17.1	370
Elecare Infant 20	20	68	2.1	15	3.3	42	7.2	43	78	57	1.4	2.6	1.1	0.8	1.2	185	41	18.7	350
Neocate Infant 20	20	68	1.9	11	3.4	46	7.3	43	79	56	1.2	1.9	1.5	0.8	1.0	190	49	16.8	340
PurAmino 20	20	68	1.9	11	3.6	47	7.2	42	79	44	1.4	1.9	1.7	0.7	1.2	200	41	17.2	350
Alfamino Infant 20	20	68	1.9	11	3.4	45	7.4	44	80	53	1.1	1.8	1.6	1.1	1.2	214	38	16.9	330
Similac PM 60/40 20	20	68	1.5	9	3.8	50	6.9	41	38	19	0.7	1.4	1.1	0.5	0.5	203	41	12.4	280
Enfaport 20	20	68	2.4	14	3.7	46	6.8	40	64	35	0.9	2.0	1.7	0.7	1.2	240	34	19.4	NA[3]

[1]All formulas are with iron [2]HP = High Protein [3]NA = not available [4]Enfamil NeuroPro Enfacare [5]RTF= Ready to Feed

Statement about use of powdered formulas – Powdered infant formulas are not commercially sterile and *Cronobacter spp* contamination has been. When infant formula is fed to immuno-compromised infants, including preterm infants, ready-to-feed formulas or liquid formula concentrate mixed with sterile water are preferred. Powdered formula is indicated when there is no available alternative that meets the infant's nutritional needs.

Tube-feeding Method

A variety of methods are available for tube feeding, and the approach used should be individualized for each patient:

- Intermittent bolus feeding mimics the feed-fast pattern and may be associated with less feeding intolerance. This can be done as a true bolus, or in the case of feeding intolerance, given over 30 minutes to 1 hour by pump.
- Continuous infusion is beneficial for infants with intestinal failure or gastrointestinal dysmotility. It may also be tried for infants < 1000 g BW who do not tolerate feeds, although resumption of feeds over 30 minutes to 1 hour as soon as possible is preferable in these cases.

Transpyloric continuous infusion may be needed in infants with severe gastroesophageal reflux, marked delays in gastric emptying, or both.

Other Considerations

Low lactose products and soy-based infant formulas should generally be avoided in this population. There are no data to support a benefit to their use as optimal nutrition in any group of infants. Infants with evidence of severe reflux or colic type symptoms should be evaluated by our nutrition team before switching formulas. We do not recommend the use of products such as simethicone drops.

Statement about the use of commercial thickening agents
The Neonatology Section recommends that no infant be provided any commercial thickening agent designed to be added to infant formula or human milk in any of our Level 2, 3 or 4 NICUs. Consideration of the use of such agents should only be done in the context of an IRB-approved research protocol.

Infants with Chylothorax

Chylothorax, the most common cause of pleural effusion in the newborn, is most often either idiopathic or caused by injury to the thoracic duct.

It also can be caused by:

- congenital malformation of the thoracic duct
- congenital fistulae
- pulmonary lymphangiectasia
- venous obstruction
- obstruction of the lymphatic channels

In general, conservative antenatal management is recommended since many resolve spontaneously. Postnatally, chylothorax usually presents as respiratory distress with diminished breath sounds and pleural effusion on chest radiograph. Pleural tap demonstrates lymphocytosis and elevated triglycerides. Recurrent symptomatic pleural effusions may be treated with thoracentesis. If repeated taps are necessary, a chest tube should be considered. Because chylous fluid is produced at an increased rate when the child is being fed enterally, it is important for the infant to be challenged with enteral feedings before removing a chest tube.

Long-chain fatty acids increase chyle flow and worsen the chylothorax. A diet with medium-chain fatty acids as the main source of fat will reduce chyle production. Total parenteral nutrition often is successful in decreasing chyle production and may be preferable in the initial management of chylothorax. Somatostatin is reported to help in decreasing the duration of chylothorax. Patients should be given 2 to 4 weeks of non-operative therapy before surgical therapy is considered. Resolution of chylothorax is reported in up to 80% of cases treated with MCT, PN, and chest tube drainage. Use of ILE is not contraindicated and should be provided.

For infants with chylothorax, a diet low in long chain fatty acids (LCFAs) minimizes the accumulation of chylous effusions in the pleural cavity. A diet regimen in which the fat source is primarily medium chain triglycerides (MCTs) with a minimal amount of LCFAs to prevent essential fatty acid deficiency (EFAD) is recommended. As human milk is high in LCFAs, it is recommended that infants receiving maternal human milk have the milk skimmed to produce lower fat milk.

Since skimmed human milk is lower in calories, essential fatty acids, and fat-soluble vitamins, it requires fortification of these nutrients. It is recommended that skimmed human milk be fortified with Enfaport® to equal 20 kcal/oz. Enfaport® can also be used if fortification above 20 kcal/oz is needed (i.e. due to fluid restriction). Multi-vitamin and iron supplementation is also recommended to meet vitamin and iron needs. Education on preparation of skimmed human milk mixed with formula will need to be provided to parents prior to discharge.

If an infant is discharged home on a diet regimen with skimmed human milk, it is necessary for the caregiver(s) to bring the maternal expressed breast milk (EBM) to the Milk Bank once to twice a week (depending on the supply of EBM) to have the milk skimmed for home use. This must be coordinated prior to discharge. Contact the nutrition team with any questions.

Infants with Intestinal Failure and Rehabilitation

General guidelines for feeding infants with intestinal failure and rehabilitation are located in **Ch 5.2-Intestinal Failure and Intestinal Rehabilitation.**

Infants with Probiotic Indications

For recommendations and policy on probiotic use, refer to **Ch. 5.7-Probiotics.**

Infants with Transfusion and Risk of Necrotizing Enterocolitis

Evidence relating to the risk of NEC associated with transfusion (TANEC) is limited, primarily retrospective, and conflicting. The evidence is based on infants who received non-human milk containing enteral nutrition.

There are few data to base a definitive approach in our nurseries. Data from recent meta-analyses and randomized trials suggest that transfusions alone may not cause NEC, but rather the severity of anemia that may potentially lead to an increased risk of NEC. Given the available literature suggesting TANEC is

associated with severe anemia, for infants < 1500g BW, we recommend following the Baylor College of Medicine's Hematology section guidelines for transfusion parameters.

Holding feedings routinely for PRBC transfusion is not recommended. However in the event of severe anemia or concern for feeding intolerance, holding one feed around the time of transfusion may be considered. **(Ch 7.3-Transfusion of Blood Products.)**

Managing Slow Growth in Enterally-Fed Infants

Intervention may be considered for weekly weight gain of less than 15 grams per/kg/day in infants less than 2000 grams or of less than 20 grams/day in infants greater than or equal to 2000 grams. Progress with the following steps sequentially. Allow 3 to 4 days between changes to the nutrition plan to allot sufficient time to evaluate the effects of any nutritional change(s). (**Ch 13.4-Nutrition Assessment)**

Managing Slow Growth in Human-Milk–Fed Premature Infants

Consider the following sequentially as listed:

- Evaluate for evidence of feeding intolerance such as abnormal stools, persistent gastric residuals, or excessive reflux (emesis).
- Treat clinical conditions unrelated to nutrition that might affect growth such as acidosis, hyponatremia, increased work of breathing, cold stress, anemia, use of steroids, and infections including UTI.
- Ensure human milk fortifier has been added to human milk as Prolact+6® or as bovine milk-based fortifier 4 pkts per 100 mL.

Table 13–13. Enteral vitamin and mineral supplementation

Premature infants receiving	Adjusted by Weight or Condition	Vitamin/Iron Supplementation per day (suggested)	Iron Goals (mg/kg /day)[9,10]	Vitamin D Goals (IU/day)
Fortified breast milk (Prolacta)	< 2.5 kg	2-3 mg/kg Fe 1 mL MV[1]	2-3	400
Fortified breast milk (Prolacta)	If osteopenia or elevated alkaline phosphatase activity > 800	2-3 mg/kg Fe 1 mL MV[1] 1 mL D-Visol (400 IU)	2-3	800
Fortified breast milk (Similac HMF Hydrolyzed Protein Concentrated Liquid)[2, 10]		2-3 mg/kg Fe 0.5 mL D-Visol (200 IU)[11]	2-3	200-400
Preterm formula		None	2-3	200-400
Fortified breast milk (Similac HMF Hydrolyzed Protein Concentrated Liquid)[2]	If osteopenia or elevated alkaline phosphatase activity > 800	2-3 mg/kg Fe 1-1.5 mL D-Visol (400-600 IU)[11]	2-3	800
Preterm formula	If osteopenia or elevated alkaline phosphatase activity > 800	1 mL D-Visol	2-3	800
Non-fortified human milk [3]	< 2.5 kg[4]	2 mg/kg Fe 1 mL MV[1]	2-3	400
Non-fortified human milk[3]	> 2.5 kg	1 mL MV with Fe[5]	2-3	400
Transitional formula	< 5 kg	0.5 mL MV with or without Fe[5,6]	2-3	400
Transitional formula	> 5 kg or > 6 months	None	2	400
Term formula	< 3 kg	0.5 mL MV with Fe[5]	2-3	400
Term infants receiving	**Adjusted by Weight or condition**	**Vitamin/Iron Supplementation per day**	**Iron Goals (mg/kg/day)**	**Vitamin D Goals (IU/ day)**
Human milk	LOS < 1 week, > 2.5 kg	1 ml D- Visol	1 (at 4 months)[7]	400
Human milk	LOS > 1 week, SGA < 2.5 kg, or multiple blood draws	1 ml MV with Fe[5]	2	400
Term formula	> 2.5kg	None	1	400[8]

1 MV = Poly-Vi-Sol

2 Fortified breast milk (Similac HMF Hydrolyzed Protein Concentrated Liquid)

3 This includes infants receiving unfortified human milk, supplemented with 2-3 feeds of formula.

4 At discharge and 2.5 kg or greater, infants can be discharged with 1 MV with Fe .

5 Poly-Vi-Sol with iron

6 Infant will receive 2 mg of iron/kg at 150 mL/kg of transitional formula. Goal is 2 to 3 mg iron/kg.

7 Or iron containing complementary foods at 6 months

8 May take several weeks to achieve

9 Initiate iron supplementation when full feeds are tolerated and infant is at least 14 days of life

10 Provide iron supplementation at 2-3 mg/kg/day for infants < 1500 g birthweight and at 2 mg/kg/day for infants 1500 to 2500 g birthweight

11 Infants <1500g on EBM + Similac HMF should receive 200 IU of Vitamin D/day (cholecalciferol) in addition to iron. Infants < 1500g with osteopenia on EBM + Similac HMF should receive 400-600 IU of Vitamin D/day (cholecalciferol) in addition to iron.

- Provide bolus tube feeding when tolerated because continuous infusions increase loss of fat.
- Advance the volume as medically feasible. Increase volume of fortified expressed breast milk (FEBM) to 150 mL/kg/day then advance stepwise as tolerated to about 160 mL/kg/day.
- If at goal feeding volume when using Prolacta®, ensure protein intake is meeting estimated needs and then add Prolacta® Cream at 2 kcal/oz.
- If not growing after initiating Prolacta® Cream, request nutrient analysis by milk bank of mother's own milk to determine fat and protein content and consider increase to Prolacta® Cream 4 kcal/oz.
- Advance to Prolact+8® (28 kcal/oz) or Prolact +10® (30 kcal/ oz) if needed. Use Prolact +8® (prepared at a 1:1 ratio to equal +10 (30 kcal/oz.) when Prolact +10 is not available.
- Provide 1-4 feedings/day of 30 kcal/oz premature formula alternated between fortified expressed breast milk (FEBM) feedings.
- Consider the use of hind milk if the milk bank confirms sufficient milk supply. Speak with a lactation consultant.
- Consult with nutrition team to consider advancing bovine milk-based fortifier to 26 kcal/oz.
- Consider adding premature transitional formula powder to the FEBM to increase the nutrient density to greater than 24 kcal/oz. Recognize potential risk of powdered formula use if this is chosen.

Managing Slow Growth in Formula-Fed Premature Infants

- Evaluate for evidence of feeding intolerance such as abnormal stools, persistent gastric residuals, or excessive reflux (emesis).
- Ensure that correct formula (iron-fortified premature formula 24 kcal/oz) is given.
- Advance volume to 150-160 mL/kg/day.
- When fluid volumes are restricted, use ready-to-feed preterm 30 kcal/oz formula. Preterm 30 kcal/oz formula may be mixed with preterm 24 kcal/oz formula to achieve a caloric density greater than 24 kcal/oz.

Table 13–14. Growth rate guidelines

Age	Weight	Length (cm/week)	FOC (cm/week)
Newborn Infants (Premature and Term)			
< 2 kg	15 to 20 g/kg/day	0.8 to 1.1	0.8 to 1.0
≥ 2 kg	20 to 30 g/day		
Older Infants (> 4 months corrected gestational age)			
4 to 8 months	10 to 16 g/day	0.37 to 0.47	0.16 to 0.20
8 to 12 months	6 to 11 g/day	0.28 to 0.37	0.08 to 0.11

- If poor growth persists and all other methods are exhausted, then consider using single modulars. Discuss with the registered dietitian for your team.

13.4 Nutrition Assessment

Growth

Monitor growth (weight, length, and head circumference) as a sign of adequate nutrient intake. The goal of nutrition support in high-risk neonates is to mimic the intrauterine growth rate. Body weight, weekly length, and weekly head circumference are plotted electronically on the appropriate growth charts. Compute weight gain rates over the previous week.

An electronic app is available for the Fenton growth charts at http://www.ucalgary.ca/fenton. In this electronic app, tools are available to calculate percentiles and z-scores to compare neonatal growth. **(Table 13-14, Figs 13-4a and 13-4b)**

Biochemical Monitoring

- Serum albumin is not useful in routine screening of nutritional status and it should not be ordered except in extraordinary situations. Its half-life approximates 21 days. Albumin levels may be affected by infection, liver disease, shifts in body fluid status, rapid growth, and prematurity.
- Serum prealbumin has a shorter half-life of 2 to 3 days. Levels followed over time might rarely be helpful to assess nutritional status. Prealbumin also may be affected by liver disease, infection, rapid growth, and prematurity. It may occasionally be helpful in our older infants with complex disorders affecting growth. Discuss with nutrition team before ordering.
- Serum alkaline phosphatase is an indicator of bone mineralization problems, rapid bone growth, and biliary dysfunction. To determine the cause of the elevated serum alkaline phosphatase, it is helpful to measure serum P, Ca, and conjugated bilirubin. Low serum alkaline phosphatase is a marker of zinc deficiency but is not sensitive. Serum Zn is needed if this is being considered.

Parenteral Nutrition

Blood glucose concentration should be monitored in all infants receiving intravenous dextrose infusions. For most infants, daily monitoring is recommended until blood glucose concentration is stable. For ELBW, stressed or septic infants (or those receiving insulin infusion) more frequent monitoring is necessary usually every 6 to 12 hours. Infants on insulin may require hourly blood glucose checks.

For all infants on PN, obtain ionized calcium every 24 hours for first 3 days of life and as calcium and phosphorus are advanced or until levels are stable. If ionized calcium is >1.45 mmol/L, check serum phosphorus. Refer to **Ch 9.4-Hypocalcemia and Hypocalcemic Seizures, and Ch 9.5-Hypercalcemia or Hyperphosphatemia**. For infants on ILE, refer to **Table 13-5 and Table 13-15** for TG monitoring guidelines.

Obtain conjugated bilirubin measurement in the first 24 hours of life. When infants are on PN, monitor electrolytes,

BUN, creatinine, glucose, conjugated bilirubin, and triglycerides weekly. Monitor ALT, AST, GGT, Alk phos, Ca, phos, and Hct every two weeks or as clinically indicated.(**Table 5-3 and Table 13-15).**

Enteral Nutrition

Infants with birth weight less than 1500 g. Obtain serum phosphorus and alkaline phosphatase activity around day of life 35.

Alkaline phosphatase > 600 IU/L and phosphorus < 4.5 mg/dL

- If clinical suspicion of osteopenia (incidental findings on unrelated radiograph, fractures, PN for > 3-4 weeks, alkaline phosphatase > 800 IU/L) check alkaline phosphatase and phosphorus weekly until alkaline phosphatase< 600 IU/L and phosphorus > 4.5 mg/dL
- If no clinical suspicion of osteopenia check levels every 2 weeks, twice until stable.
- Despite biochemical results, premature infants continue to remain at risk for osteopenia and rickets for a period of time and may require further investigation when additional risk factors are present. Risk factors may include birth gestational age < 27 weeks, ELBW, prolonged parenteral nutrition, intolerance to fortified human milk, prolonged diuretic use, history of NEC, and history of ostomy.

Alkaline phosphatase < 600 IU/L and phosphorus > 4.5 mg/dL and no clinical suspicion of osteopenia

- No need for routine monitoring of alkaline phosphatase or phosphorus
- Hemoglobin/Hematocrit should be monitored as clinically indicated and before discharge

Infants > 1500 g birthweight. There is no indication for any routine nutritional lab monitoring except for a hemoglobin/hematocrit before discharge. Infants who are fluid restricted or have a prolonged course to full feeds should have phosphorous, alkaline phosphatase activity and hemoglobin/hematocrit monitored as clinically indicated.

Infants receiving Prolacta® should have serum phosphorus monitored 3 to 5 days after PN is discontinued. Consider checking additionally 1 week later if initial value is > 8 mg/dL. Serum phosphorus >10 mg/ dL may require holding Prolacta® from every other feed or all feeds for 1-2 days. Obtain an ionized calcium and creatinine when serum phosphorus >10 mg/dL. Oral calcium supplementation is generally not recommended in this setting. Discuss with nutrition team if Prolacta® is removed for more than 48 hours.

Table 13-15. Suggested lab table

Initial	Conjugated bilirubin	• All infants screened during the first 24 hours of life.
	Ionized Calcium Glucose	• Obtain at 24 hours of age for at risk infants admitted to the NICU including infant of diabetic mother, SGA, IUGR, and premature infants.
PN[2]	Glucose	• Blood glucose concentrations should be monitored in all infants receiving glucose infusions until stable » For ELBW, stressed, septic, or infants receiving insulin infusions may need to monitor BG q 6-12 hrs[1] » Infants on insulin infusions may require hourly blood glucose checks »Monitor BG daily or more often until stable.
	Ionized Calcium, Phosphorus	• Obtain ionized calcium every 24 hrs for first 3 days of life, as calcium and phosphorus are advanced or until levels are stable[1] • If I Cal >1.45 mmol/L check serum phosphorus.
	Triglycerides (TG)	Initiation • **BW ≤ 750**. Obtain TG at 12 hours after initiation of IL and with every advancement. Stop IL if TG is >250mg/dL. Advance as tolerated if TG is <250 mg/dL. • **BW 751-1000g**. Monitor TG with every advancement. • **BW ≥ 1000g, SGA, IUGR, received postnatal steroids, or believed to be septic.** Monitor TG with every advancement. [3] • Monitoring TG is generally not needed with every advancement in infants not listed above.[3]
	Electrolytes, BUN, Creatinine, Glucose, TG	• Monitor weekly or as clinically indicated
	Conjugated bilirubin	• Monitor weekly or as clinically indicated after 14 days of PN
	ALT, AST, GGT, Alkaline phosphatase, Calcium, Phosphorus, Hct	• Monitor every 2 weeks or as clinically indicated after 14 days of PN
	Zinc, Copper, Se	• Every 4 weeks while on PN as medically feasible
Enteral	Alkaline Phosphatase, Phosphorus	**BW ≤1500g.** (Check at 35 days of age) Alk phos > 600 IU/L and phos < 4.5 mg/dL • If clinical suspicion of osteopenia (incidental findings on unrelated radiograph, fractures, PN for > 3-4 weeks, alkaline phosphatase > 800 IU/L) check alkaline phosphatase and phosphorus weekly until alkaline phosphatase < 600 IU/L and phosphorus > 4.5 mg/dL • If no clinical suspicion of osteopenia, check every 2 weeks times 2 until stable. Alk phos < 600 IU/L and phos > 4.5 mg/dL and no clinical suspicion of osteopenia • No need to check alkaline phosphatase or phosphorus **BW >1500g.** No need for routine nutritional monitoring. Monitor as clinically indicated.
	Hct	• BW <1500g. As needed & prior to discharge • BW >1500g. Monitor as clinically indicated.
Prolacta	Phosphorus	• Obtain 3-5 days after PN discontinued, & consider checking again 1 week later if phosphorus is > 8 mg/dL. • Serum phosphorus >10 mg/dL may require holding Prolacta from all feeds for 1-2 days or providing with every other feed. • Obtain ionized calcium and creatinine when phosphorus is >10mg/dL

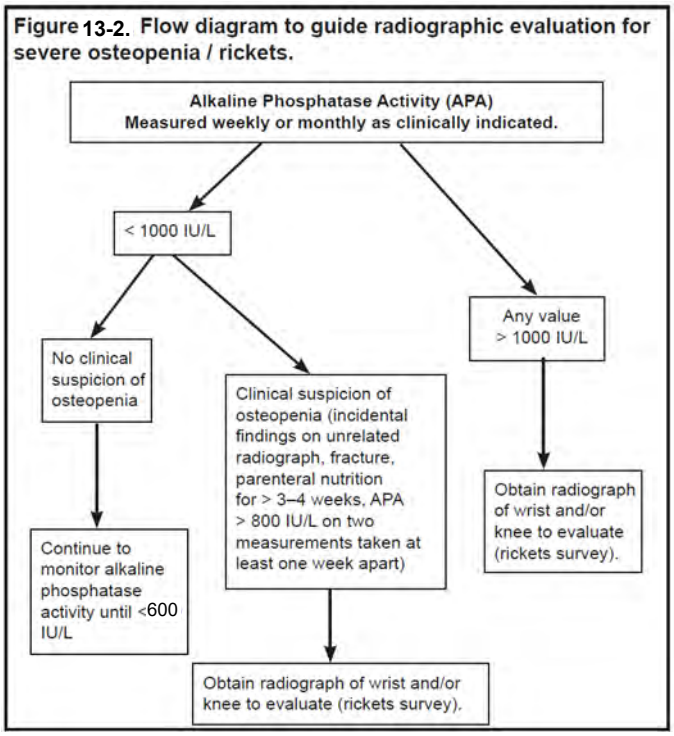
[1] See suggested labs for infants ≤28 weeks GA or ≤ 1000g at birth.
[2] See Labs to monitor for infants requiring intestinal rehabilitation in **Table 5-3.**
[3] Infants with persistent TG values of 200-400 mg/dL should receive IL at 0.5 g/kg/day. If IL cannot be advanced beyond 0.5 g/kg/day (2.5mL/kg/day) within three days, or if TG values are above 400 mg/dL, please consult Nutrition Team for safer ways to restrict IL.

Table 13-16. Suggested labs to obtain for infants ≤ 28 weeks GA or ≤ 1000g BW in the first week of life		
Frequency	**≤ 24 6/7 weeks or ≤ 750g**	**25-28 weeks or 751-1000g**
At delivery room	BG, then q 1 hr times 2 until stable. 30 mins after if bolus if given	BG, then 1 hr after fluids initiated
Every 12 hrs for 1st 48 hrs	Electrolytes/BG, Triglycerides (at 12 hrs of initiation)	
Every 24 hrs for 1st 3 days	Chem 10, TG, and ionized calcium	Chem 10, TG, and ionized calcium
At 24 hours	Obtain Bili Panel	Obtain Bili Panel
With every advancement of IL	Triglycerides	Triglycerides

Osteopenia Risk

Flow Diagram to guide radiographic evaluation for severe osteopenia **Fig 13-2.**

Figure 13-2. Flow diagram to guide radiographic evaluation for severe osteopenia / rickets.



13.5 Guidelines for Oral Feeding

The majority of hospitalized neonates will have difficulty feeding orally by breast or bottle. This may be due to any of the following conditions:

- Inadequate oral feeding skills resulting from inadequate sucking and/or swallowing and/or coordination with respiration
- Clinical instability
- Congenital anomalies
- Neurological issues
- Prematurity
- Poor endurance and/or unstable state of alertness
- Inappropriate feeding approach
- **Table 13-17 Risk approach for assessing oral feedings**

Preparing for Oral Feeding (Breast or Bottle)

- Encourage breastfeeding first whenever possible.
- Assure parental involvement and appropriate education regarding developmental progression of oral feeding skills. Safe oral feeding and infant's limited skills should be emphasized.
- Prepare infants for breastfeeding; initiate and encourage frequent skin-to-skin holding if infant is clinically stable.
- Request lactation support consults to initiate breastfeeding as early as possible. **(Ch13.5-Guidelines for Oral Feeding -Breastfeeding Low Birth Weight Infants)**
- Initiate nonnutritive oral-motor stimulation (pacifier) during tube feedings as early as possible (e.g., stable, intubated).

Promoting a Positive Oral Feeding Experience

- Facilitate appropriate feeding skills (e.g., coordination of suck-swallow-breathe).
- Prevent oral feeding problems (e.g., oxygen desaturation, apnea, bradycardia, aspiration) to achieve safe feeding.
- Prevent oral feeding aversion.

Table 13-17. Risk approach for assessing oral feedings				
Ask	**Observe-Determine**	**Assess**	**Classify**	**Treat-Manage**
PMA	• vital signs • abnormal physical exam	• <32 wks GA • Severely ill • Very immature • Clinically/ unstable	High risk	• NPO • OG/NG • GT
Medical/ surgical problems	• clinical stability • feeding readiness • feeding intolerance	• 32-34 wks GA • Clinically unstable	Moderate risk	• Tube feeding • Nonnutritive sucking • Cue based feeding • Consider feeding specialist consult
		• ≥ 35 wks GA • Medically stable	Low risk	• PO/tube feeding • Breastfeeding • Ad libitum

To meet these goals:

- Offer a pacifier for nonnutritive sucking practice as early as possible (e.g., when intubated, during tube feeding).
- Provide appropriate feeding approach, i.e., allow infants to feed at their own pace. It is inappropriate to rush them to finish a feeding. Some infants need more time to develop appropriate sucking patterns, to coordinate suck-swallow-breathe, for catch-up breathing, and/or rest more frequently.
- Feed orally (PO) only as tolerated to minimize oral feeding aversion.
  - » Do not force infants to finish a bottle feeding; if necessary, gavage remainder by NG tube.
  - » It is more important to develop good feeding skills than to complete a feeding.
  - » Monitor feeding performance closely and document consistently.

Starting Oral Feeding

- At 32 to 34 weeks postmenstrual age (PMA), if clinically stable
  - » May provide during nasal CPAP if medically stable.
- Starting oral feedings at 30 weeks PMA may not result in earlier attainment of full oral feedings or discharge, but is safe for infants who are not severely tachypneic or receiving positive pressure.
- When feeding readiness cues are present (e.g., sucking on pacifier, waking or fussing near feeding times, maintaining a drowsy-to quiet alert/active state)

Oral feeding of infants, both at the breast and by bottle should be guided by the infant's readiness to feed and evidence that the infant will be responsive to oral feeding. This approach, called "cue-based" feeding, should underlie oral nutrition, especially in preterm infants.

Oral Feeding Difficulties

- Clinical signs: oxygen desaturation, apnea, bradycardia, coughing, choking, poor skin color (e.g., mottling, dusky, blue), aspiration, increased work of breathing, distress signs (e.g., panic look, pulling away, fingers splay, arching), poor tone.
- Risk factors for overt and silent aspiration: long-term intubation, severe hypotonia, neurological issues (e.g., craniofacial paralysis, tracheotomy, ventilation-dependency).
- Lactation consultants are available for initiation and progression of breastfeeding.
- At TCH occupational therapist are available for non-nutritive oral stimulation, bedside swallow assessments, transition to spoon feeding, and co-consult with speech pathologist for craniofacial disorders. Occupational Therapist can be consulted to assess bottle feeds if a patient is not advancing on oral feeds or is having difficulty with bottle feeds.
- Speech pathologists will evaluate for clinical signs of dysphagia or swallowing issues (e.g., aspiration), swallow function study, and co-consult with occupational therapists for craniofacial disorders with suckling as tolerated.
- The use of swallow function studies to evaluate feeding disorders should be carefully considered by the medical team due to the radiation exposure of this test and limited evidence of clinical correlation of findings.

Breastfeeding Low Birth Weight Infants

It is critical for the medical team to support a mother's decision to provide breast milk and breastfeed her premature infant. Lactation support professionals are available to assist mothers with milk expression and breastfeeding.

Activities promoting breastfeeding include:

- Early skin-to-skin contact between infant and mother augmented with suckling as tolerated.
- Encouraging frequent breast stimulation (every 3 hours or 7 to 8 times per day) in the first few weeks after birth to promote an adequate milk supply.
- Introducing the breast before the bottle.
- Educating mothers on appropriate diet and potential effects of her medication(s). Provide initial and ongoing
- Lactation consultant support as needed. A visual map is provided to mothers to show the various stages of providing their breast milk to their infant during the NICU hospitalization. **(Fig 13-3)**

Initiation and Progression

- Consultation with the mother prior to oral feeding initiation to determine her feeding goals (i.e., exclusive breastfeeding, breast and bottle) will allow for an integrated plan.
- Once an infant shows signs of interest in latching on and is clinically stable, initiate nutritive breastfeeding:
  - » Consider lactation consultation for initial breast feeding to determine efficacy and to assess infant's feeding ability.
- If indicated, measure milk intake during early breastfeeding by test weighing procedures.
  - » Test weighing measures are performed by weighing the clothed infant under exactly the same conditions before and after breastfeeding on an electronic scale.
  - » Pre- and post-weights (1 gram of weight change = 1 mL of milk intake) provide an objective measure of milk transfer. This will be indicative of the infant's feeding ability and need for supplemental milk feedings provided by gavage or bottle feeds after breastfeeding attempts. It is usually best to limit this evaluation to once or twice a day, but it can be particularly helpful in the initial phases of transitioning a preterm infant towards breastfeeding.
  - » Consider delaying initiation of bottle feedings until the infant achieves two successful breastfeeds a day for mothers who wish to achieve exclusive breastfeeding.

13.6 Discharge Nutrition Preparation

- Change diet to the home regimen at least 3 to 4 days before discharge to allow ample time for evaluation of intake, tolerance, and growth.
- Instruct parents on milk supplementation, formula preparation, and vitamin/mineral supplementation as indicated.

Breastfeeding Success at Home

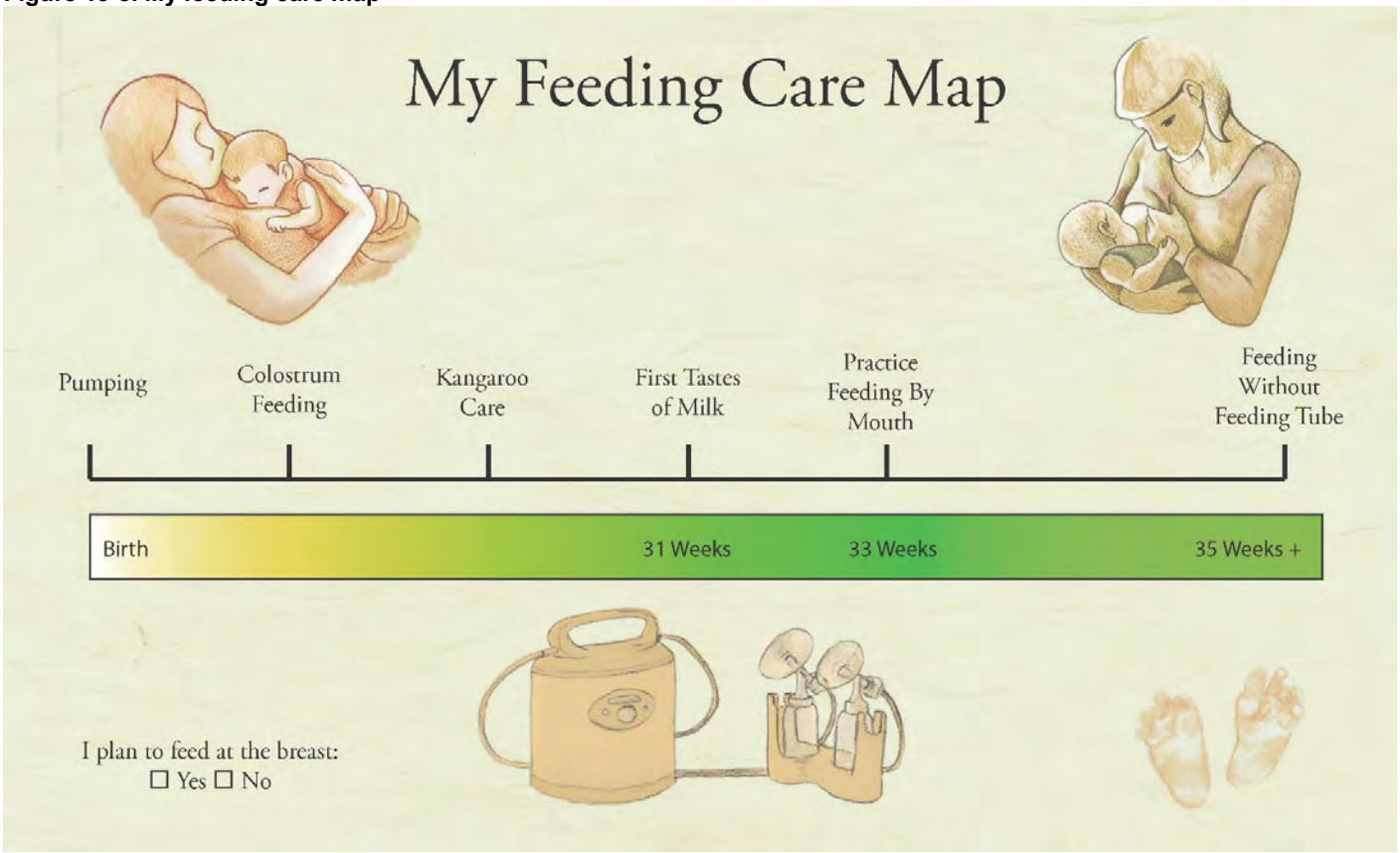
- Breastfeeding progression prior to discharge will depend upon the mother's availability and her infant's feeding ability.
- Consultation with the lactation consultant will provide individualized feeding strategies to assist in progression of breastfeeding.
- Pre-discharge education and planning is key to breastfeeding success.
- Factors to consider for an individualized discharge nutrition plan include:
  - » Infant's nutrient and growth needs
  - » Infant's oral feeding ability
  - » Need to continue breast pumping to protect milk supply.

Consideration of the above factors will ensure an optimal nutrition plan to meet the infant's needs, while supporting mother's breastfeeding plan.

Infants on Fortified Breast Milk

- Discontinue bovine milk-based fortifier (HMF) for infants greater than 2000 grams and greater than 34 weeks' gestation and use unfortified human milk (breastfeeding or expressed breast milk) ad lib.
- HMF is not recommended after discharge.
- Infants who are less than or equal to 1800 grams at birth:
  - » If infant is to be discharged on unfortified human milk, suggest minimum of 2 feedings per day (some infants may need up to 4 feedings per day depending on growth) with premature transitional formula and the remainder as breastfeeding. Premature transitional formula (22 kcal/oz) is available as a liquid ready-to-feed.
  - » If infant is receiving mother's expressed breast milk and not breastfeeding, can consider adding premature transitional formula powder (Enfamil® EnfaCare® or Similac® NeoSure®) to expressed breast milk to make 24 to 30 kcal/oz milk. This regimen is less favored due to the risk of powdered infant formulas. Suggest delaying introduction of powder formula until infant is ~48 weeks PMA.

Figure 13-3. My feeding care map



(Carmichael-Swanner, Hurst, Hair, July 2016)

» In special cases (such as intolerance to cow's milk protein or refusal to use any infant formula), a former very low birth weight (VLBW) infant, being at risk for nutritional insufficiency including both growth-failure and metabolic bone disease, may benefit from direct dosing with minerals including calcium and phosphorus. Discuss with nutrition team. In addition to providing multivitamins and iron, it is recommended that infants be evaluated 2 to 4 weeks after discharge. This evaluation should include weight, length, head circumference, serum phosphorus, and alkaline phosphatase activity.

Infants on Premature or Premature Transitional Formula

Transition to premature transitional formula (Enfamil® EnfaCare® 22 kcals/oz or Similac® NeoSure® 22 kcals/oz)for infants of birth weight less than 2000 grams or infants with a poor growth history, fluid restriction, or abnormal laboratory indices.

Encourage parents to use ready-to-feed only (until ~48 weeks PMA).

Premature infants may receive transitional formula up to 6 to 9 months corrected age. Infants may demonstrate catch-up growth quickly after discharge and can be changed to a standard term formula at 48-52 weeks post-menstrual age if weight and length (for corrected gestational age), and weight-for-length are all at least at the 25% percentile for age.

Continuously monitor nutritional status including intakes, growth, and biochemical indices as indicated.

On WIC prescription: *Order Ready-to-Feed ONLY for 3 months. OK to give powder after 3 months***.** Check 6 months for requested length of issuance of formula.

Vitamins and Iron

Table 13–13.

Introduction of Solid Food to Older Premature Infant

The purpose of introducing solid foods is to meet the patients' developmental milestones, not nutritional needs which are met through milk or formula intake.

Parents should be involved in this important milestone in their infant's life. Please make every attempt to have a parent present for the baby's first solid food feeding.

Consider an Occupational Therapy consult to assess developmental appropriateness and to assist with solid food introduction along with caregivers and parents.

The AAP recommends that solid foods be introduced at 6 months of age.

For the premature population, this is 6 months corrected gestational age.

Signs of Readiness for Solid Foods

- Medically stable and does not have an endotracheal tube,
- Functional swallow and not at risk for aspiration,
- Able to sit with support; 60 to 90 degrees, and
- Good head and neck control or can achieve good positioning.

Solid Food Guidelines

- Introduce single-ingredient baby foods one at a time and continue 3 to 5 days before introducing an additional new food.
- For infants with history of intestinal failure, consider non-starchy vegetables (i.e. green beans) as a first food.

Suggested Reading

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Figure 13-4a. Fenton growth chart-girls

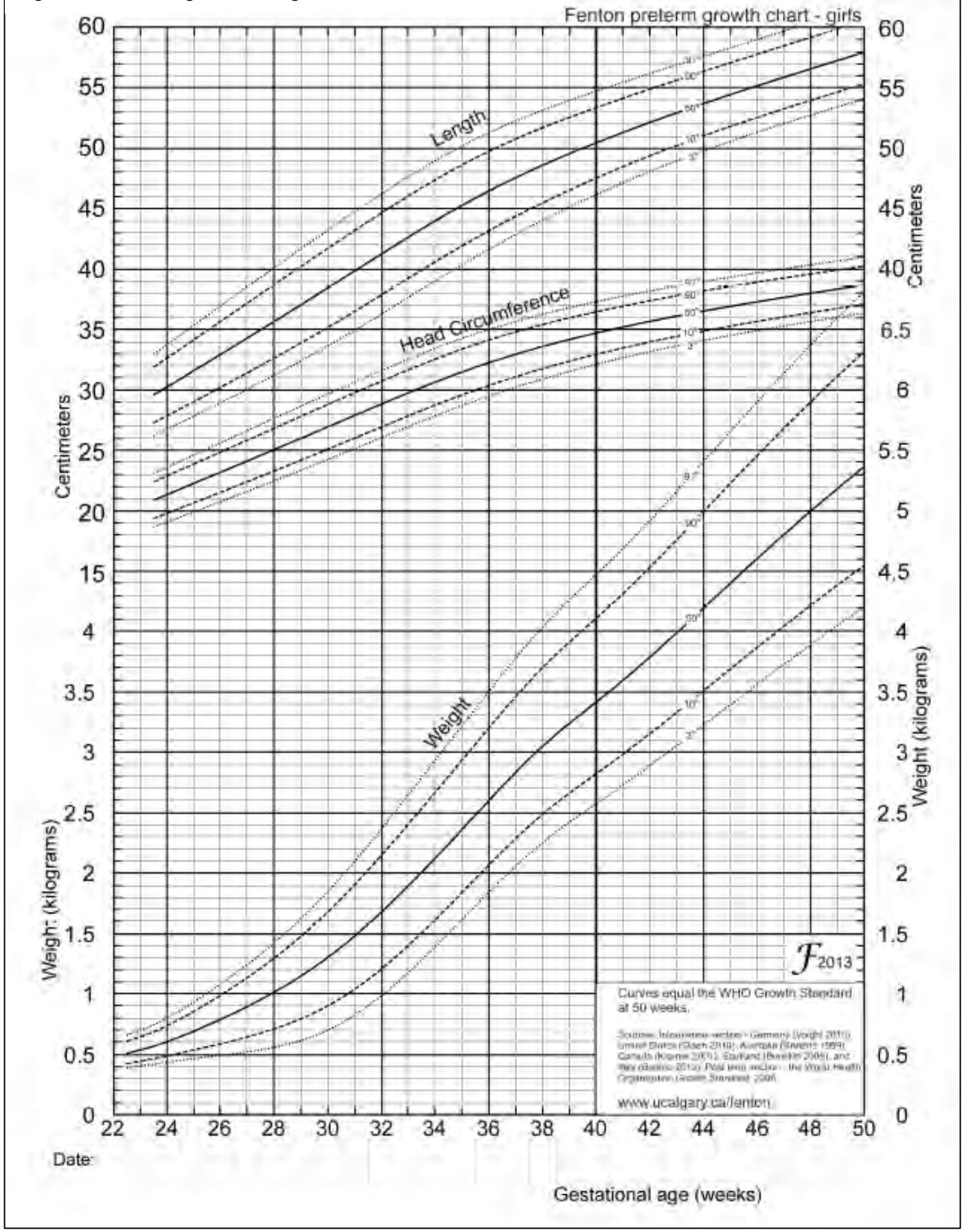
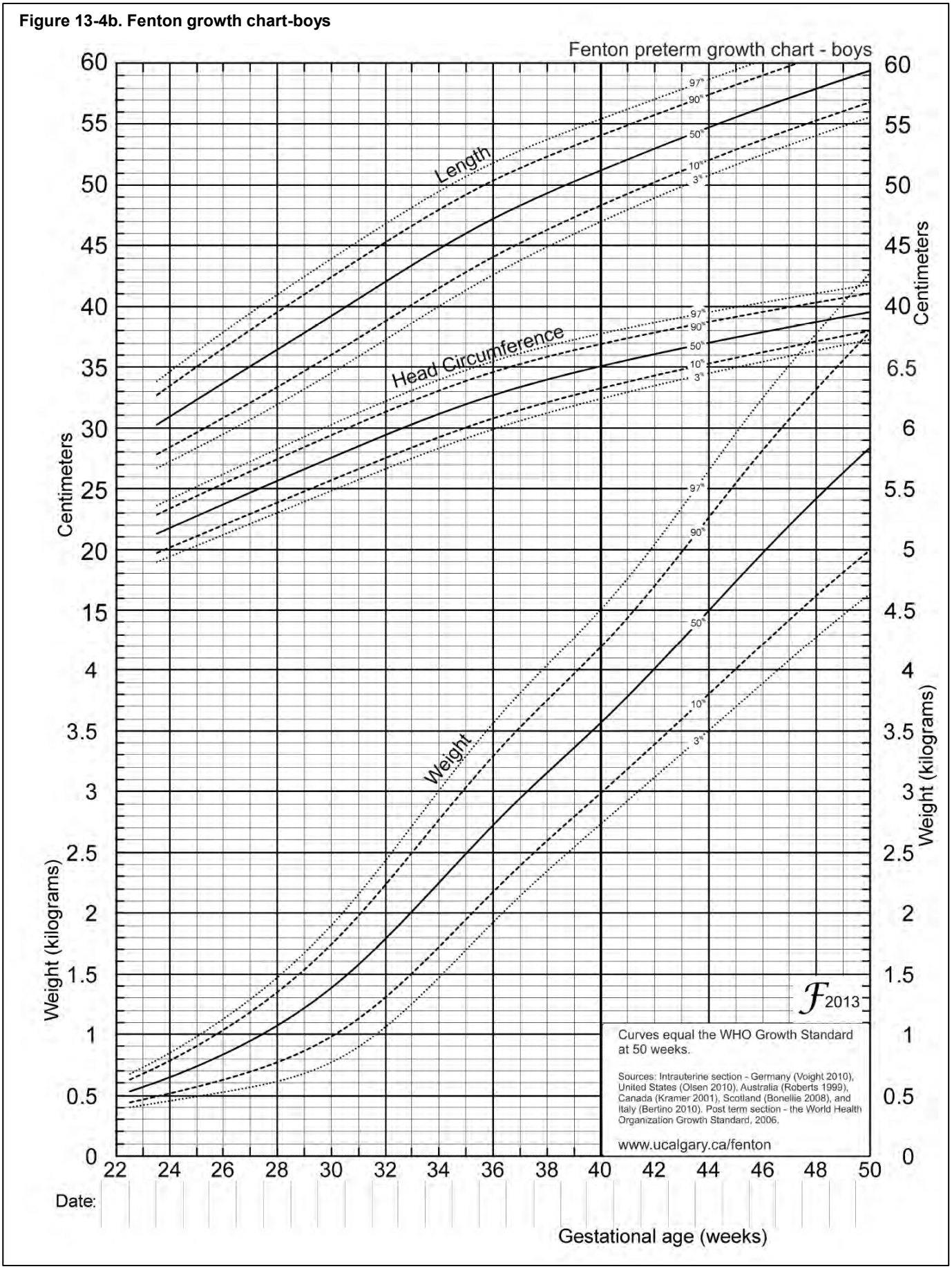


Figure 13-4b. Fenton growth chart-boys



Section 14: Palliative Care

Editors: Karen E. Johnson and Frank X. Placencia

14.1 Introduction

Palliative care is specialized care focused on supporting patients and families members of patients with chronic, life-threatening or terminal illness. Growing evidence suggests that families of children with life-threatening and chronic conditions benefit from palliative care and that earlier discussions and initiation can improve symptom management and quality of life.

The palliative care model is founded on the following principles:

1. Respect for the dignity of patients and families
2. Access to competent and compassionate palliative care
3. Support for caregivers
4. Professional and social support for families
5. Continued improvement of pediatric palliative care through research and education

Palliative care includes pain/symptom control and management, enhancement of quality of life, assessment and treatment of the body, mind, and spirit to prevent suffering for children and families living with life-threatening or terminal conditions. AAP supports an integrated model of palliative care that begins when illness is diagnosed, continues through the disease trajectory and often co-exists with conventional treatments, and continues through and after death.

Domains of Palliative Care

The National Consensus Project (NCP) published clinical practice guidelines (updated in 2018 and endorsed by AAP) for quality palliative care by outlining 8 domains of care.

The domains of care include:

1. Structure and Processes of Care
2. Physical Aspects of Care
3. Psychological and Psychiatric Aspects of Care
4. Social Aspects of Care
5. Spiritual, Religious and Existential Aspects of Care
6. Cultural Aspects of Care
7. Care of the Imminently Dying Patient
8. Ethical and Legal Aspects of Care

Further information may be found at www.nationalconsensusproject.org

Qualifying Patients

Patients who may benefit from palliative care include:

1. Newborns at the threshold of viability (<24 weeks or <500 grams)
2. Newborns with complex or multiple congenital anomalies
3. Newborns not responding to Neonatal Intensive Care interventions (either slow deterioration or an acute life threatening event) or those deemed to have a terminal or irreversible condition
4. Newborns with a severe complex chronic illness which may become life-threatening

Palliative Care in the Hospital Setting

Palliative care provided in the tertiary hospital setting is best coordinated through the use of an interdisciplinary palliative care team which includes a physician, nurse and/or nurse practitioner, social worker, spiritual advisor, and a child life therapist. Other members of the team may include a family advocate, clinical pharmacist, dietician, bioethicist, and psychiatrist or psychologist. Because palliative care patients receive interventions from diverse disciplines, it is important that the primary care physician/team coordinate these efforts.

Palliative Care Consultations

Perinatal Pediatric Advanced Care Team (PPACT) consultations are available for Fetal Center outpatient consults.

TCH Newborn Center (NICU 2, 3, 4) palliative care consultations, call the **Pediatric Advance Care Team (PACT)** at 832-822-7228 Monday through Friday or for urgent questions or concerns, call 281-763-4622.

Perinatal Palliative Care Consultations are also available at Ben Taub General Hospital through an interdisciplinary team. **(Ch 14.8-Circumstances Unique to BTGH)**

14.2 Assessment of Pain and Discomfort

Pain is one of the most common symptoms experienced by infants with serious or life-threatening conditions. Unfortunately, much of pediatric pain is undertreated. It is important to recognize and treat all types of pain, including acute pain, chronic pain, recurring pain, procedure related pain, and end-of-life pain. Physiologic indicators such as vital sign changes or behavioral indicators such as facial grimacing may not be as reliable or may be absent in a chronically or critically ill infant. In order to treat pain effectively, it must be accurately assessed. Multiple validated neonatal pain assessment tools are available. At Texas Children's Hospital the CRIES and PIPP instruments are used.

CRIES Scale

The CRIES scale is used for infants > than or = 38 weeks of gestation. Characteristics of crying, oxygen requirement, changes in vital signs, facial expression, and sleep state are scored. A maximal score of 10 is possible. If the CRIES score is > 4, further pain assessment should be undertaken. Analgesic administration is indicated for a score of 6 or higher. **(Table 14-1)**

PIPP Scale

The PIPP scale is used for infants < or = 37 weeks of gestation. To use the PIPP scale, the behavioral state is scored by observing the infant for 15 seconds immediately before and after a painful event, and before and after pain medication is given (30 minutes after intravenous and 1 hour after oral medication). The baseline heart rate, oxygen saturation, and facial expression are assessed. Any changes from baseline should be noted for 30 seconds **(Table 14-2).**

Table 14-1. Cries Scale						
Date/Time						
Crying – Characteristic cry of pain is high pitched 0 – No cry or cry that is not high-pitched 1 – Cry high pitched but baby is easily consolable 2 – Cry high pitched but baby is inconsolable						
Requires O_2 for SaO_2 <95% - Babies experiencing pain manifest decreased oxygenation. Consider other causes of hypoxemia, e.g., over sedation, atelectasis, pneumothorax) 0 – No oxygenation required 1 – <30% oxygenation required 2 – >30% oxygenation required						
Increased vital signs (BC+ and HR+) - Take BP last as this may awaken child making other assessments difficult 0 – Both HR and BP unchanged or less than baseline 1 – HR or BP increased but increase <20% of baseline 2 – HR or BP is increased >20% over baseline						
Expression – The facial expression most often associated with pain is grimace. A grimace may be characterized by brow lowering, eyes squeezed shut, deepening naso-labial furrow, or open lips and mouth. 0 – No grimace present 1 – Grimace alone is present 2 – Grimace and non-cry vocalization grunt is present						
Sleepless – Scored based upon the infant's state during the hour preceding this recorded score. 0 – Child has been continuously asleep 1 – Child has awakened at frequent intervals 2 – Child has been awake constantly						
Total Score						

The total pain score is then calculated:

- **6 or less =** Minimal to no pain
- **7-12 =** Mild pain
- **>12 =** Moderate to severe pain
- **N-PASS** is the pain scale used in the BTGH NICU for all patients**. (Table 14-3)**

Table 14-2. PIPP Scale

Gestational age	≥ 36 weeks	32-35 weeks	28-31 weeks	<28 weeks
Behavioral state	Active awake Eyes open Facial movements	Quiet awake Eyes open No facial movements	Active sleep Eyes closed Facial movements	Quiet sleep Eyes closed No facial movements
Maximum heart rate	0-4 BPM increase	5-14 BPM increase	15-24 BPM increase	≥ 25 BPM increase
Maximum oxygenation saturation	0-2.4% decrease	2.5-4.9% decrease	5.0-7.4% decrease	≥ 7.5% decrease
Brow bulge	None 0-9% of time	Minimum 10-39% of time	Moderate 40-69% of time	Maximum ≥ 70% of time
Eye squeeze	None 0-9% of time	Minimum 10-39% of time	Moderate 40-69% of time	Maximum ≥ 70% of time
Nasolabial furrow	None 0-9% of time	Minimum 10-39% of time	Moderate 40-69% of time	Maximum ≥ 70% of time

Neonatal Abstinence Syndrome (NAS)/Withdrawal Assessment Tool (WAT) scoring should not be used for pain assessment.

Pharmacologic Management

Once identified, it is important to alleviate pain in acute, chronic or life- threatening illness. To achieve adequate analgesia/sedation, medications optimally should be scheduled or given by continuous infusion with intermittent bolus doses as needed in order to avoid fluctuations in blood levels and breakthrough pain or discomfort. In addition, infants should always receive a bolus dose of narcotic or sedative prior to starting or increasing the infusion rate.

The intravenous route is the preferred delivery route. Intranasal administration is an alternative option for patients who do not have intravenous access. In general, IM or SC injections should only be used as a last resort to avoid additional discomfort to the patient. Oral medications may be used if patient has no IV access, but will not provide as rapid relief as IV medications. Please also refer to **Table 14-4** for further dosing information.

Narcotic Analgesics

Morphine has several advantages over other narcotics. It provides pain relief, elicits a sense of euphoria and promotes histamine release, which results in vasodilatory properties. These properties may decrease venous return, thereby decreasing cardiogenic pulmonary vascular congestion and resultant respiratory distress. Morphine may be less tolerance inducing than the synthetic opioids, given its longer half-life and therefore, should not have to be titrated up as quickly as the synthetic opioids. **(Table 14-4)**

- In general, narcotic dosing should be titrated to effect. There is no set maximum dose. If a patient is habituated on an opioid infusion, the hourly dose of the infusion can be used for bolus dosing.

Sedatives - Benzodiazepines

These agents have specific anxiolytic effects in addition to sedative effects but do not provide pain relief.

Alternative Route Medications

In the patient who does not have intravenous access, oral morphine or intranasal medications may be used.

- Intranasal administration of fentanyl and midazolam has been found to be effective in pediatric palliative care.

Adjunct Medications

- Acetaminophen 10mg/kg to 15 mg/kg PO, PR may be given every 4 to 6 hours for mild discomfort. See TCH Formulary for specific weight and age based dosing.
- Sucrose 24% 1 mL to 2 mL PO every 6 hours for term babies and 0.1 mL to 0.4 mL PO every 6 hours for preterm babies may be given while if providing nutritive or non-nutritive support.

14.3 Understanding and Communicating at the End-of-Life

Introduction

Death in a tertiary care center neonatal intensive care unit is unfortunately a common occurrence. More children die in the perinatal and neonatal period than at any other time in childhood. Extremely premature infants and those with congenital anomalies serve to dramatically increase the mortality rate in the NICU setting. It is therefore vital that the neonatal intensive care physician is well-versed in the grief process, and able to address end-of-life care issues with the family in a culturally sensitive manner.

Definitions

- **Grief** - intense sorrow or deep mental anguish; arising from the loss of someone or something loved, usually through death.
- **Mourning** - a cultural complex of behaviors in which the bereaved participate, or are expected to participate.
- **Bereavement** - the period of time during which grief is experienced and mourning occurs.
- **Hospice** - provides support and care for patients and their families in the final phase of a terminal disease so that they can live as fully and comfortably as possible.

Attachment in Pregnancy

Attachment to the baby begins before birth. The mother usually bonds closely with her baby while pregnant. Thus, the death of a fetus or infant means the loss of both the baby and the parents' hopes and dreams for their baby and leaves them with an overwhelming sense of grief.

Professional and Societal Perceptions of Death and Grieving

Expectant parents have faith in modern medicine and are not likely to think that their child may die, especially after the first trimester of pregnancy. Further, in our culture, there is significant social pressure to believe in miracles and use as much technology as possible to save lives. Parents may feel obligated to choose to continue extensive and invasive medical interventions because these are seen by society as "heroic" and "courageous" choices. Parents who choose other options often feel judged, isolated and unsupported by their families, friends, and by society in general.

Table 14-3. N-PASS: Neonatal pain, agitation and sedation scale

Assessment	Sedation		Normal	Pain/Agitation	
Criteria	-2	-1	0	1	2
Crying Irritability	No cry with painful stimuli	Moans or cries minimally with painful stimuli	Appropriate crying Not irritable	Irritable or crying at intervals Consolable	High-pitched or silent-continuous cry Inconsolable
Behavior State	No arousal to any stimuli No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	Appropriate for gestational age	Restless, squirming Awakens frequently	Arching, kicking Constantly awake or Arouses minimally / no movement (not sedated)
Facial Expression	Mouth is lax No expression	Minimal expression with stimuli	Relaxed Appropriate	Any pain expression intermittent	Any pain expression continual
Extremities Tone	No grasp reflex Flaccid tone	Weak grasp reflex ↓ muscle tone	Relaxed hands and feet Normal tone	Intermittent clenched toes, fists or finger splay Body is not tense	Continual clenched toes, fists, or finger splay Body is tense
Vital Signs HR, RR, BP, SaO_2	No variability with stimuli Hypoventilation or apnea	< 10% variability from baseline with stimuli	Within baseline or normal for gestational age	↑10-20% from baseline SaO_2 76-85% with stimulation – quick ↑	↑ > 20% from baseline $SaO_2 \leq 75\%$ with stimulation – slow ↑ Out of sync with vent
Premature Pain Assessment	+ 3 if < 28 weeks gestation / corrected age + 2 if 28-31 weeks gestation / corrected age + 1 if 32-35 weeks gestation / corrected age				

Table 14-4. Pharmacologic management for neonatal end-of-life care

Class		Route	Dosing	Frequency	Important Features
Narcotics					• There is no set maximum dose. • Meds should be titrated to effect
	Morphine	IV, IM, SC	0.1 mg/kg/dose	Q 2-4 hours	• Pain relief, euphoria and vasodilatory effects • Decreases air hunger • Less tolerance inducing • Longer half-life
		IV	0.03 mg/kg/hr	continuous	
		PO	double IV dose		
	Fentanyl	IV	1-2 mcg/kg/dose 1-2 mcg/kg/hr	Q 2-4 hours	• May not provide adequate pain control due to short half life • Infants receiving a fentanyl infusion should also receive a morphine bolus immediately prior to discontinuation of support • May give up to 3 doses in 30 minutes for labored breathing, concern for pain/discomfort (specifically for intranasal fentanyl in NBs with comfort care plan)
		Intranasal	1-2 mcg/kg/dose	Q 10 minutes	
Benzodiazepines	Lorazepam	IV	0.1-0.2 mg/kg/dose	Q 2-4 hours	• May be used in conjunction with narcotics to achieve moderate sedation • Anxiolytic and sedative properties but no pain control
	Midazolam	IV	0.1-0.2 mg/kg/dose 0.06 mg/kg/hr	Q 1-2 hours continuous	• Shorter duration of action than lorazepam
		Intranasal	0.2-0.3 mg/kg/dose Give half of dose in each nare		
Habituated patients	Phenobarbital	IV	1-3mg/kg/hr	continuous	• May be helpful in patients who are narcotic or benzodiazepine resistant
	Propofol Dexmetatomidine				• May be required in rare cases as an anesthetic agent; an anesthesia/pain service consult should be obtained.
Patients with no IV access	Chloral hydrate alternating with morphine	PO or PR for chloral hydrate	25-50 mg/kg/dose		
Adjunct medications	Acetaminophen sucrose 24%	PO, PR, PO	10-15 mg/kg 1-2 mL 0.1-0.4 mL (for preemies)	Q 4-6 Q 6 Q 6 hours	

** Due to the unique nature of the palliative care setting, medication dosing may differ from the usual recommendations for analgesia or conscious sedation in neonates.

Health professionals frequently are uncomfortable with the thought of death or grieving. Historically, professional support for grieving families and caregivers has been lacking. Grief education is not routinely included in medical training. In addition, parents sometimes perceive healthcare provider behaviors to be thoughtless and insensitive.

Communication Strategies at the End-of-Life

Parents facing the potential death of their newborn need professional and empathetic communication. There is little data on the optimal way to approach these discussions, but the following acronym **(SOBPIE)** may help structure these discussions:

Situation: What is the situation? Decide what information needs to be conveyed to the family and what decisions need to be made.

Opinions/Options: What are the medically and ethically supportable alternatives on the table? How might my biases influence how I view those alternatives?

Basic Human Interactions: Ensure that only critical personnel are present, e.g. bedside nurse, chaplain, etc. Find a quiet, private place for the discussion without distractions such as cell phones. Use the infant's name. Introduce everyone and their role. Tolerate moments of silence, as this provides people to process the information and resultant emotions.

Parents: Elicit the parents' understanding of their child's situation, their questions and concerns, and what they need from the healthcare team. Provided honest and balanced information, avoiding personal biases.

Information: Tailor information to the parents' needs and individualize it for the patient's condition. Many families want a recommendation. If the clinical scenario supports a particular recommendation, it should be offered.

Emotions: We must recognize that emotions play a large part in our decision making, especially for momentous decisions. Sensitivity to this allows for better understanding of parental decisions.

Faith and cultural tradition play an important role for many people, especially in times of crisis. Members of the healthcare team may feel uncomfortable navigating unfamiliar traditions and rituals. Texas Children's offers access to *Culture Vision*. This resource, available from the TCH *Connect* site under "*Clinical Resources*" offers helpful information about different ethnic, cultural, and religious groups. The use of a cultural broker can also be helpful. A cultural broker is a person affiliated with the hospital from the family's cultural or faith group who can serve as an intermediary between the healthcare team and the family.

A useful communication strategy when working with families for whom faith plays a prominent role is the **AMEN** protocol.

This mnemonic represents four components:

- **Affirm** the patient's/family's belief. Validate his or her position, "Ms. X, I am hopeful too."
- **Meet** the patient or family where they are: "I join you in hoping (or praying) for a miracle."
- **Educate** from your role as a medical provider: "And I want to speak to you about some medical issues."
- **No matter what**; assure the family you are committed to them: "No matter what happens, I will be with you every step of the way."

14.4 Determination of Limitation or Redirection of Life Sustaining Treatment

Forgoing of life sustaining treatment for newborns (which includes non-initiation or withdrawal) must consider several key points:

1. Decisions about forgoing life sustaining treatment should be made by the health care team in collaboration with the parents, who must be well-informed about the condition and prognosis of their infant.
2. Parents should be involved in the decision-making process to the extent that they choose.
3. Compassionate comfort care should be provided to all infants, including those for whom intensive care is not provided.
4. It is appropriate to provide intensive care when it is thought to be of benefit to the infant, and not when it is thought to be harmful, of no benefit, or futile. Deference should be given to the parents' perception of what is beneficial.

The goal for the primary team, and subspecialty consulting services in partnering with the parents, is to design a course of action that is in the baby's best interest. Goals of care should be mutually agreed upon by all involved. In 2017, the AAP updated its policy on forgoing life-sustaining treatment**.**

The Texas Advance Directives Act and its Application to Minors

If an infant is to be transitioned from curative to comfort care and this entails forgoing of life-sustaining treatment, it is important to determine if s/he is a qualified patient under the *Texas Advanced Directives Act* (TADA). The TADA states that a qualified patient is one with either an irreversible or a terminal condition.

An **irreversible condition** is one that may be treated but is never eliminated, leaves a person unable to care for or make decisions for him- or herself, and is fatal without life-sustaining treatment provided in accordance with the prevailing standard of medical care.

A **terminal condition** is an incurable condition caused by injury, disease or illness that according to reasonable medical judgment will produce death within six months, even with available life-sustaining treatment provided in accordance with the prevailing standard of medical care.

The baby's mother, legal father, or legal guardian may sign or verbally agree to an advanced directive or make treatment decisions for the affected infant. The TADA also allows the attending physician to invoke an institutional review process if parents persist in demanding interventions that the attending physician believes to be inappropriate. However, this option

should not be undertaken lightly and only used as an option of last resort. Timely consultations to Palliative Care and Clinical Ethics can prevent the need to utilize this approach.

Special Circumstances Surrounding Delivery Room Resuscitation

No federal law or Texas state law mandates delivery room resuscitation in all circumstances. According to the *Neonatal Resuscitation Program* (NRP), it is ethically and legally acceptable to withhold or withdraw resuscitative efforts if the parents and health professionals agree that further medical intervention would be burdensome, merely prolong dying, or would not offer sufficient benefit that would improve the baby's outcome.

Parents and health care providers must have accurate and current information regarding potential infant survival and outcomes. Joint decision making by both the parents and the physician should be the standard. Given the uncertainties of gestational age assessment and fetal weight determination, it may be necessary to examine the baby at birth before making firm statements to parents and others regarding providing or withholding resuscitation.

In specific cases when parents request that all appropriate resuscitative measures be performed in the face of a high or uncertain morbidity and/ or mortality risk, it may be appropriate to offer the infant a trial of intensive care that may be discontinued later. Alternatively, some parents may not want full resuscitation of their child; the appropriate response in these cases will depend upon the circumstances. Ethical and legal scholars agree that there is no distinction between withholding and withdrawing life-sustaining treatments.

Developing Consensus between the Medical Team and the Family

All members of the medical team should meet prior to meeting with the family to reach an agreement regarding recommendations for redirection of care. One spokesperson (usually the attending physician of record) should be established to maintain continuity of communication. In addition, a necessary component in preparing for such discussions is to clarify the family values and beliefs. In these circumstances, it is not uncommon for parents to rely on family members for help with these difficult decisions. As long as these family members are acting to support the parents' autonomy and not trying to override parental decisions, this is permissible, perhaps even advisable.

Disagreement between the Medical Team and the Family

The infant's parents serve as legal and moral fiduciaries for their child, and the relationship of parents to children is a responsibility, not a right. Because infants are incapable of making decisions for themselves and because their parents are assumed to be the best judges of what is in their infant's interests, the parents become their surrogate decision makers. The physician serves as a fiduciary who acts in the best interest of the patient using the most current evidence-based medical information. In this role as an advocate for their patients, physicians oversee parental decisions.

Even in the best of circumstances people of good conscience may disagree. If individual caregivers' ethical standards conflict with those of the parents or the primary team, the caregiver is free to remove herself or himself from the care of the patient in accordance with hospital and unit policies. In circumstances of disagreement between the family and medical team, other professionals (e.g., social worker, family relations team, chaplaincy, palliative care and/or ethics) may be of help in further discussions. In both instances, the director of nursing and the medical director should be notified. Early involvement of these services can often prevent conflict escalation.

The AAP and other organizations support addressing these considerations with the utmost regard for families' viewpoints, continuing a process of respectful and honest information sharing as the patient's condition and the family's understanding evolve over time. Differences between family caregivers or between the care team and family decision-makers can be approached by using basic principles of negotiation and conflict resolution.

It is often helpful to discuss ethical cases with colleagues with particular ethics expertise, or with a larger group. The monthly Newborn Center Ethics Rounds is an ideal forum for these discussions.

Ethics Consultation

To make a request for an ethics consultation, please page them through the page operator:

At Texas Children's Hospital:

David Mann, MD, DBe
Chair Clinical Ethics Committee

At Ben Taub General Hospital:

Joey Fisher, MD, MPH
Please page for an ethics consult through the Ben Taub page operator 713-873-2010.

If the parents request full resuscitative measures in direct opposition to the opinion of the medical team and the infant is responsive to those measures, the infant should continue to be supported while the ethics committee's deliberations are ongoing.

Patients in Child Protective Services Custody

Policy of the Texas Department of Family and Protective Services is that any decision to withdraw or redirect care of a qualified patient in the custody of CPS must have the concurrence of an ethics committee with knowledge of the patient's case, and must also be approved by a court.

Withdraw of Life Sustaining Therapy (WOLST) Documentation

When the family agrees to a withdraw of life sustaining therapy **(WOLST)** the attending physician of record must complete the proper documentation in EPIC.

This is a 4-step process:

- **First:** Create a note that describes the conversation with the surrogate decision maker(s) (in the NICU, the surrogate decision maker will almost always be the parents), including why the patient qualifies for redirection of care. You may use the dot phrase "**CODESTATUSNOTE**" to help frame the details of the note, however, feel free to put any details that are relevant. Be sure to "tag" the note by clicking the tag icon

in the upper right hand corner, and choose "*Code/RRT*" to make it easier for others to find the note.

- **Second:** Enter the appropriate order in EPIC. Under "*Order Sets*" enter "*Inpatient Code Status Panel*." Options are: "*Full Code,"* "*Intubation Only*," "*No CPR*," and "*No Escalation.*"
- **Third:** Create the **FYI** flag. Click "*FYI*" on the left side of the screen, then click "*New Flag."* The Flag Type should be "*End of Life Care*." In the body of the text, include the key details from the previously created note, and include the **DATE** of the note created in the first step for easy reference. A shortcut to creating an "*FYI*" can be found in the **End of Life Navigator** (described later in this section).
- **Fourth:** Once plans for proceeding with WOLST have been determined, create a WOLST note. Using the dot phrase "**WOLST**" will help create a checklist of important items to consider.

End of Life Navigator – EPIC

The **End of Life Navigator** in EPIC is a useful repository of end of life resources.

It is divided into four sections:

- **"*Consult*"** and is used primarily by the PACT team. However, it does include a shortcut to create the "*FYI*" flag described in the third WOLST documentation step.
- **"*Bereavement Support Checklist"*** and will primarily be used by nursing and ancillary staff (**Ch 14.6 Death of the Infant**).
- **"*Consent Forms*"** includes various forms including LifeGift, autopsy consent, and funeral home information.
- ***"LifeGift Coordinator Documentation"*** and is to be used by the LifeGift representative.

14.5 Transition to Comfort Care

Supporting the Family

The time surrounding the death of a child is of profound importance. Most parents are in a deep state of shock at the time the baby dies, and immediately afterward. Medical caregivers are to guide parents and family members through the process of making memories of their child.

Parents being present and able to participate in the care of their dying infant, at the level with which they are comfortable, is extremely important in the experience of anticipatory mourning, fosters a sense of control, and facilitates preparation for the event of death.

1. The sequence of events should be described to parents in advance, and they may express preferences about the process. The parents should be educated about what to expect during the dying process and that not every newborn dies immediately after the ventilator is removed.
2. In WT NICU and PFW NICU, patients may be moved to the "Butterfly room" for end of life care. At PFW on the MBU the mother's door will be marked with the Newborn Center bereavement heart logo as a signal to all hospital staff to respect the family's space with their dead or dying infant.
3. Visiting restrictions should be relaxed, and the parents should be provided with an environment that is quiet, private and will accommodate everyone that the family wishes to include. Child life specialists may help counsel siblings prior to the death of the infant. The hospital chaplain can assist with spiritual needs.
4. A quiet, private space for family members should be provided
5. One nurse and one physician should be available to the family at all times, and if possible the patient's primary nurse and physician should be present at the time of the death.
6. Alarms disabled and pagers/phones silenced of those in attendance.
7. If no family is available, a staff member should hold the baby as he or she dies.
8. A memory box should be created and given to the family based on their wishes before leaving the hospital, which may include:
    - Hair locks
    - Hand, foot, ear, lip and buttock prints, if desired
    - Hand and foot molds
    - Record of baby's weight, length, and FOC
    - Identification bracelets
    - Cap and blanket
    - Photography or videography
    - Texas Children's Hospital and The Pavilion for Women have a digital camera for this purpose.
    - Multiples should be photographed together, whether living or dead.
9. The family should be encouraged to hold, bathe, dress and diaper their infant.
10. The family should be accompanied to their car by a member of the Texas Children's Hospital staff. The assigned or on-call social worker should be contacted for parking validation.
11. The Perinatal Bereavement Committee provides parents with a bereavement support packet and canvas bag containing resource materials, funeral information, their child's memory box, and a teddy bear.
12. The infant's bed space should not be cleaned until the parents have left the unit.
13. The physician of record should notify the obstetrician, pediatrician, and any referring physicians of the infant's death.
14. The death summary should designate who the follow up doctor will be to contact the family one month after the death and following autopsy completion.

Care of the Dying Infant

Care should focus on keeping the infant comfortable. The baby should be swaddled in warm blankets while being held. All painful interventions including blood draws should be

discontinued and all monitoring devices removed from patient. Vascular access can be maintained to administer medications.

PPACT patients with a Birth Plan for palliative care/comfort care only will address all care issues as chosen by parents. Intramuscular vitamin K administration or erythromycin eye prophylaxis may not be necessary. Breast, bottle, or naso- or orogastric feedings and pacifier use may provide comfort. However, as per AAP guidelines it is medically appropriate to forgo feeds of any kind if anticipated imminent death. Gentle suctioning should be used as indicated.

It is important to differentiate symptoms of respiratory distress including increased work of breathing, grunting, and nasal flaring from agonal reflexive respirations that occur sporadically with long periods of accompanying apnea. Respiratory distress indicates that the patient is experiencing air hunger that should be immediately treated with a dose of morphine. Agonal respirations usually occur when the patient is unconscious and should not be a source of discomfort.

Pharmacologic Management at the End of Life

Although end-of-life care does not immediately dictate the need for medication, it is important to alleviate pain at the end-of-life by achieving moderate to deep sedation in the affected patient, but respiratory depression is also a known side effect of many narcotics and sedatives. However, evidence from retrospective reviews and the neonatology literature suggests that the use of narcotics and sedatives does not shorten time to death. Moreover, the *Doctrine of Double Effect* states that "a harmful effect of treatment, even resulting in death, is permissible if it is not intended and occurs as a side effect of a beneficial action." Thus, the main goal of medication use at the end-of-life is to keep the infant comfortable despite any known side effects.

Medical management should include both sedation with benzodiazepines and pain relief with narcotics. Narcotics alone may be insufficient in the management of air hunger and respiratory distress at the end-of-life. Habituated patients or those who are difficult to sedate are candidates for evaluation by Anesthesia/Pain Management specialists. Because of the unique nature of the palliative care environment, medication dosing frequently differs from usual recommendations for analgesia or conscious sedation in neonates. If planning a compassionate extubation, it is important to anticipate the acute symptoms. First doses of medication should be given prior to extubation, and an adequate level of sedation should be achieved to avoid patient air hunger.

All medications other than those needed to promote comfort should be discontinued, unless otherwise requested by the family. Exceptions may include anti-epileptics, which offer seizure control and provide some level of sedation but should not be considered the primary sedative. There is no role for paralytics in end-of-life care as they prevent the medical team from adequately assessing the patient's level of sedation or pain. If the infant was receiving neuromuscular blockade prior to the transition to comfort care, special attention should be paid to assure patient comfort under any residual paralytic effect.

Of note, morphine has several advantages over other narcotics in end-of- life care, and is especially effective at decreasing shortness of breath and air hunger. Fentanyl bolus dosing may not provide adequate pain control for a dying infant secondary to its short half-life. Infants receiving a fentanyl infusion should also receive a bolus morphine dose immediately prior to discontinuation of support, or in the event of observed distress.

14.6 Death of the Infant

Brain Death

There are no accepted guidelines to declaring brain death in neonates less than 37 weeks gestational age. Therefore, it is uncommon to declare brain death in the NICU. The process for declaring brain death is detailed in Texas Children's Hospital's ***"Determination of Brain Death" Procedure #1951.*** Per the policy, at least two different services must perform the brain death exam. Along with Neurology, it is advisable to consult with a member of Critical Care Medicine due to their expertise in assessing brain death. See "EPIC Resources" in the Appendix for information on documentation in EPIC.

Transitioning to Conventional Ventilation, Decreasing Ventilatory Support, and Removal of Endotracheal Tube

If the infant has been maintained on high frequency oscillatory ventilation, they should be transitioned to conventional ventilation to facilitate parental holding and bonding prior to extubation. The ventilator settings may be gradually decreased over a short period of time to assure that pain management and sedation is adequate; if the infant appears uncomfortable the titration of medications should be increased prior to the removal of the endotracheal tube. There is no need to monitor blood gases or chest imaging while weaning the ventilator prior to extubation. The process of weaning the ventilator will also increase hypoxemia and hypercarbia, which may contribute to the level of sedation.

Pronouncing the Death

The physician of record or fellow acting under the physician of record should always document the time of death in the chart.

This can be done in EPIC. Declaring the patient's time of death should not interfere with parental bonding.

The Option of No Escalation of Care

Parents faced with the prospect of their infant's death may not be able to join in the decision to discontinue life support altogether. The family should again be informed that despite all available interventions, the known outcome for their infant remains unchanged. The option of continuing current support to give the parents time for memory-making with their baby may be offered as a bridge to the transition to comfort care.

Organ Donation

LifeGift Organ Donation Center should be notified within one hour of the patient meeting an imminent death trigger or at cardiac time of death. Imminent death triggers at Texas Children's Hospital are as follows; prior to first brain death testing, changing the status of a ventilated patient to DNR, or after a transition of care meeting in the NICU. The phone call should be documented on the ***Inquiry for Organ/Tissue Donation and Consent for Postmortem Procedures*** including phone caller's name, time of the call to LifeGift, the LifeGift coordinator's name, referral number and the response.

If the patient is a potential organ donor, LifeGift will "follow" the patient and will consult regularly with the medical team. All cardiac times of death should be called into LifeGift on any patient 19 weeks of gestation or older.

Texas Children's Hospital:
LifeGift Liaison:
Katie Barrett
425 623-8879(mobile)
713-328-0662 (office)

Ben Taub General Hospital:
Larry Leblanc
504-941-0050 (mobile)
lleblanc@lifegift.org

Special Considerations Regarding Family Staying with the Body

Grieving after the death of a child or newborn can take many forms, and will vary across religions and cultures. Some families will want to stay with the body of their dead child for longer than others, and we should take appropriate measures to accommodate this request. Nevertheless, we must comply with *Texas Administrative Code § 181.4* (2018) which states that a deceased body cannot be kept unpreserved for more than 24 hours.

Medical Examiner

The medical examiner should be notified by the physician of record or the fellow acting under the physician of record after an infant death has occurred. The medical examiner is available 24 hours a day, 7 days a week including all holidays. In the State of Texas, notification of the medical examiner is required for all dead children under 6 years of age. The medical examiner's office will determine if the body may be released to Texas Children's Hospital or Ben Taub General Hospital. If the body is not released, the medical examiner will perform a mandatory autopsy. No parental permission is required.

Autopsy

If the body is released by the medical examiner, parental consent for an autopsy should be discussed shortly after death. Written or witnessed telephone consent is acceptable. Parents are often receptive to knowing that an autopsy will help them to clarify many aspects of their child's disease process, in addition to providing insight as to why their child died.

Studies have consistently shown that in approximately 30 to 50% of cases, the diagnosis of the infant was changed or new information was found at autopsy. Although autopsies may only be helpful in informing the family predicting recurrence risk in future pregnancies and future diagnostic testing of siblings in 6-10% of cases, the information may still be helpful.

It is also important to discuss that autopsy is not disfiguring. Although restrictions may be placed on the extent of the examination, an unrestricted, complete examination will provide the most comprehensive information and will have no impact on an open casket viewing. The procedure is completed within 3 to 4 hours, and the body is available to the funeral home on the same day. Limited autopsies regarding a tissue or organ of interest are also possible. In these cases, the pathology department does request that the chest of the infant is included in the evaluation if the parents agree. Genetic testing on blood or tissue may also be obtained without performing a complete autopsy. Imaging autopsy is also available for the perinatal population at TCH

Physicians and medical professionals caring for the patient are encouraged to attend the autopsy and discuss specific questions to be addressed with the pathologist. A verbal report is usually available in 72 hours and preliminary results within 7-10 days. The final autopsy report is complete in 6 to 8 weeks. The Texas Children's Hospital pathology department performs autopsies for inpatients at no charge. Autopsies can be done on patients discharged home from TCH in hospice care. Consent may be obtained prior to, or at the time of death. The "follow-up" physician is responsible for contacting the family and initiating a post-autopsy consultation. Parents should be provided with a copy of the autopsy report at the time of the meeting.

If there are additional questions regarding an autopsy at TCH, contact:

Debra L. Kearney, M.D.
Associate Professor of Pathology
832-824-2250
832-824-1876
kearney@bcm.edu

Post Death Follow-Up

The death of an infant is a traumatic experience for any parent. As part of the healing process, it is common for parents to have questions about their infant's hospital stay. Or they may want the opportunity to visit with hospital staff who cared for their child. As physicians it is our obligation to aid parents in the grieving process to the extent they desire. At Texas Children's Hospital, in order to facilitate providing this aid, the following should occur:

On the Death Summary and the autopsy form, the "follow-up" attending should be identified. This attending is also responsible for signing the Death Certificate. The follow-up attending should be the regular daytime attending assigned to the infant, and not necessarily the attending on-call. This is consistent with the Texas Department of State Health Services, *Handbook on Death Registration*. In the event that it is unclear who should be designated as the follow-up attending, consider the following in order:

1. The daytime attending on-service assigned to the infant
2. A previous daytime attending if the infant died soon after the attendings switched rotations (especially if the decision to forgo life-sustaining therapy (LST) was made by the previous attending).
3. The attending who led the discussion in which it was agreed to forgo further LST
4. The on-call attending when the infant died
5. The admitting attending
6. The L&D attending if the infant died in L&D.
7. Whomever signed the death summary but failed to identify one of the above.

In the event that a follow-up attending is not identified, Denita Wallace and Frank Placencia will use their discretion in identifying the follow-up attending.

The social workers routinely contact all families of deceased infants 1 month after death. At that contact, they will ask the family if they wish to be contacted by the follow-up physician. That information will be forwarded to the follow-up attending who will call interested families and offer to meet with them. It is advisable to have the social worker present during the phone call and meeting to address issues beyond the scope of our training. This meeting is in addition to the autopsy review meeting, which usually happens closer to 2-3 months after death. These meetings can be combined if that is the parents' wish. After the phone call and/or meetings, a note should be entered into the chart for documentation purposes.

Though this process is specific to Texas Children's Hospital, we encourage colleagues at our sister institutions to develop similar approaches to helping parents through the grieving process.

Hospice

Hospice care refers to a package of palliative care services (including durable medical equipment, diagnostic and therapeutic interventions), generally provided at a limited per diem rate by an interdisciplinary group of physicians, nurses, and other personnel, such as chaplains, health aides, volunteers and bereavement counselors. Hospice care provides a support system for families with children discharged from the hospital with an irreversible or terminal condition. There are no time limits for referral to hospice care, and this care may be provided in a facility or at home. The assigned social worker can help with placement, and should be contacted for all referrals. Although it is not a prerequisite for hospice enrollment, an outpatient ***DNAR*** form should be completed prior to discharge if the family agrees. All prescription medications should also be filled prior to discharge. The family should be instructed to call the hospice rather than emergency personnel in the event of a home death.

Perinatal Hospice

Some parents confronted with a lethal fetal diagnosis may decide to continue their pregnancy to its natural conclusion. These families are best served through an interdisciplinary team (MD/RN/SW/CCLS) palliative care team, and PPACT is often consulted in these circumstances.

The goals of perinatal hospice include shared decision-making with the family regarding pregnancy management, after-birth care, and preparation for the loss that is consistent with the family's wishes and values. The mother should be encouraged to make a birth plan for her baby's care after delivery. A hospice packet is available for parents in the TCH Newborn Center. Consideration of hospice care is appropriate if the baby does not expire soon after birth.

Funeral Homes

The family will be assisted with obtaining a funeral home for their deceased child by the appointed social worker or nursing staff. Funeral information is also provided in the bereavement support packet. In addition, Texas Children's Hospital volunteer services department has a fund to assist families in financial need with $300 towards a funeral or cremation costs. Disbursement is coordinated by the appointed social worker.

Nursing Bereavement Support Checklist

The nursing staff is guided by a checklist which enables them to deliver care at the time of death in a uniform fashion to each family, including bereavement support materials, a sympathy card, and information on funeral homes in English or Spanish. In compliance with nursing guide- lines, the physician of record should notify the obstetrician, pediatrician, and any referring physicians of the infant's death. The checklist is available in the *End of Life navigator* in EPIC.

14.7 The Grief Process

Timing and Stages of Grief

There is no particular way that anyone "should" grieve. Elisabeth-Kubler Ross proposed five stages of grief as a pattern of phases that affected people experience, not always in sequence, when faced with their own or a loved one's death. These stages are denial, anger, bargaining, depression and acceptance and are not always experienced in a linear fashion. Glen Davidson's phases of bereavement suggest that shock and numbness are most intense in the first 2 weeks, followed by searching and yearning from the second week to 4 months, then disorientation from 5 to 9 months, and finally reorganization/resolution at 18 to 24 months. However, bereavement is unique to each individual. Up to one quarter of bereaved parents may display severe symptoms years after the death of their baby. Bereavement has been described as "relearning the world." Parents' ability to maintain a continued bond with their deceased child and integrate memories into a new reality is considered central to parental bereavement and adjustment.

Special Circumstances Relating to Fetal or Infant Death

Coping with the baby's death is especially difficult because the length of time spent with the child is brief and few memories have been created. Parents may also feel responsible and guilty that their child has died. Support systems for bereaved parents may be weak, and community insensitivity is not uncommon. Bereaved parents often face caring for other children while mourning one or more who died, especially in cases of multiple births with one or more losses. Parents anticipating the death of their child may feel conflicting emotions of relief intermixed with sadness at the time of death. In addition, parents may grieve in different ways, and may not be available to each other as sources of support while experiencing their individual sorrow. Unresolved or delayed grief may result in a complicated grief reaction, and additional stressors including mental illness, low socioeconomic background, or a history of substance abuse can prolong and negatively impact the resolution of grief and integration of the loss. Psychiatric referral should be made for parents or family members experiencing atypical grief patterns. The Women's Place at the PFW offers psychiatric care to mothers followed in the Fetal Center and mothers of our NICU patients as well.

Religious, Cultural, and Socioeconomic Differences Surrounding Death and Grieving

Religion and spirituality can be a source of comfort in the midst of loss. Customs and rituals of the individual family

should be honored. Asking open-ended questions such as "What are your beliefs and how can we meet your spiritual needs?" is more effective than "Do you want your baby to be baptized?" or "Do you need a chaplain?" Religious references, even though well-intentioned, may cause offense. Families should be reassured that spiritual crises and questions such as "why me?" or "what did I do wrong?" are part of normal grief reactions.

The nursing staff is responsible for contacting the chaplain at the beginning of the dying process, regardless of the family's faith tradition. The chaplain is trained to make an assessment and provide the family with appropriate spiritual care and religious resources. At the family's request, contact the chaplain to help arrange a special service in the hospital's chapel or to officiate the funeral.

For some families, eye contact and touch may be expected; for others it may not be appropriate in their culture. When an infant is born with malformations, the mother may be blamed by other family members and education of the family may be necessary. Many cultures express discomfort with death. Some cultures forbid autopsy, some parents may not wish to hold their dying or dead infant.

In families of lower socioeconomic status, they may view the cessation of intervention as a cost-cutting measure aimed at them. It will be necessary to explain to parents that their ability to pay is not the factor that determines goals of care for their child. These types of issues exemplify the importance of providing culturally competent care in this setting.

Language barriers may also be present. A hospital-employed medical interpreter should always be used for conversations regarding end-of-life care.

Self-Care

Working with the bereaved makes us aware of our personal experiences and feared losses. If we have not appropriately mourned and re-located our own grief, it will be re-experienced in our interactions with families and predispose us to burn-out and compassion fatigue. Thus, it is important to consider the healthcare provider's feelings, coping styles, and behavior while communicating with parents at the end of their infant's life. Debriefings to review end of life care cases may be helpful for staff and note the PACT service has monthly Palliative Care sessions to address these issues. Frank Placencia is the Newborn Center liaison for these sessions.

To help support NICU staff, the Newborn Center hosts a '*Remember Me Always'* event each year.

14.8 Circumstances Unique to BTGH

Ben Taub Women's and Infant's Services has an active interdisciplinary palliative care team. Most of our services are provided to inpatients, but outpatient consultation is available for birth plan discussions with families whose fetus has been given a life limiting diagnosis and expects to deliver at BTGH.

In cases where comfort care is planned from delivery, the mother's OB is the physician of record for baby when born alive until assumption of care by our faculty neonatologist/fellow is requested. NICU staff are always available to support and to answer questions from TCN, OB, or family members; and/or for orders, for palliative medications, transfer of infant to MBU with mother after her recovery, or to the NICU when mother chooses not to have her baby rooming-in with her.

All babies with comfort care plans admitted to MBU have the NICU physicians as their care team until attending to attending sign-out can occur with the faculty neonatal hospitalist covering MBU during the daytime on weekdays. The NICU also provides nursing support to the TCNs and MBU nursing staff as needed but is not directly responsible for patient care.

A ***Perinatal/Neonatal Nursing End-of-Life-Care Checklist*** is available in EPIC and bereavement supplies on our unit for our nursing staff to use for providing care at the time of death in a uniform fashion. This includes: notification of key members of the palliative care team – chaplain, social, work, and child life – as well as Life Gift and Now I Lay Me Down To Sleep; memory making; best practices for providing a supportive environment for family to grieve; and the appropriate paperwork required after each death.

If parents consent to an autopsy, the attending neonatologist must write **"***Requesting autopsy to determine cause of death***"** in a progress note or attestation of the death note in addition to autopsy consent being filled out appropriately. Imaging only autopsies are not available at BT, but limited autopsies are permitted though full autopsies preferred. For deaths outside L & D, the physician of record should notify the obstetrician and any consulting physicians of the baby's death, and is responsible for contacting the family to offer to meet with them to discuss autopsy findings.

Each family is provided with bereavement support materials, a sympathy card, and information on the grieving process and support services outside the hospital in English or Spanish prior to discharge. All families that provide contact information with our team receive follow up phone calls and sympathy cards at key points in their grieving process.

Suggested Reading

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Section 15: Respiratory Care

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15.1 Delivery Room Stabilization

Overview

In the delivery room, 4-10% of all term and late preterm newborns receive positive-pressure ventilation (PPV), but only 1 to 3 per 1000 receive chest compressions. NRP prepares team members to respond to resuscitations in a standardized format and encourages using teamwork behaviors to communicate effectively with each other. We describe here evidence based approaches to stabilizing a newborn's respiratory and cardiovascular status in the delivery room.

Continuous Positive Airway Pressure (CPAP) First

The CPAP first approach with rescue surfactant therapy has been shown to be superior to intubation and prophylactic surfactant administration for prevention of bronchopulmonary dysplasia (BPD). Preterm infants treated with early CPAP in the delivery room are not at greater risk for any major adverse outcomes. Randomized clinical trials have demonstrated that premature infants of gestational age (GA) 24 weeks and above can be effectively stabilized on CPAP without intubation or surfactant administration. Thus, a spontaneously breathing preterm newborn should be stabilized on CPAP first when possible.

In practical terms, a CPAP first strategy requires team effort and coordination. It takes time for a preterm infant to transition and demonstrate consistent respiratory effort, establish lung volume and maintain stable oxygen saturations.

1. We recommend that all neonates ≤30 weeks GA be placed on CPAP immediately on arrival to the warmer in the delivery room. Neonates who are between 30 and 34 weeks GA should be stabilized with CPAP if signs of respiratory distress are noted.
2. The initial steps of the NRP algorithm, including assessment of respiratory effort and heart rate, can be performed while the baby is receiving CPAP.
3. PPV is indicated before 60 seconds of life if the infant is gasping, not breathing, or if the heart rate is <100 beats per minute (bpm). Neonates may require alternating PPV and CPAP until a consistent spontaneous breathing pattern is established.
4. For the initial resuscitation of newborns ≥35 weeks GA, set the blender to 21% oxygen. For the initial resuscitation of newborns <35 weeks GA, set the blender to 21-30% oxygen.
5. Adjust FiO2 during resuscitation using the minute specific saturation targets specified in the NRP guidelines. It is common for newly born preterm infants to temporarily require higher FiO2 to achieve target saturations until the lungs are optimally recruited. Providers may wait and administer surfactant after NICU admission if high oxygen requirement is the only indication for intubation.
6. Infants who are ≥30 weeks GA may be able to wean from CPAP in the delivery room. Monitor closely for symptoms of loss of functional residual capacity, hypoxia, and increased work of breathing during the weaning process.

CPAP failure can occur in up to 50% of babies stabilized with a CPAP first approach. Therefore, it is critical that strategies aimed at optimizing CPAP delivery are not limited to the delivery room and are continued during and after NICU admission. Early caffeine administration can be considered to decrease the likelihood of CPAP failure.

Positive Pressure Ventilation (PPV)

"Ventilation of the newborn's lungs is the single most important and effective step in neonatal resuscitation" – NRP guidelines.

Providing effective ventilation is the foundation for resuscitation in the delivery room. PPV or delivery of a set pressure can be accomplished using devices such as a flow inflating (anesthesia) bag, T- piece resuscitator, or self-inflating bag to move air in and out of the lungs. In the delivery room, the starting pressures used for resuscitation are a PEEP of 5 cm H_2O and PIP of 20-25 cm H_2O. Great caution should be taken to limit lung injury during resuscitation by ensuring excessive pressures are not delivered intentionally or unintentionally. Using the T-piece resuscitator allows users to set PIP and PEEP. When using the other resuscitation devices, providers must closely monitor the pressure gauge to deliver consistent and safe pressures with each breath and not rely on subjective measures or the "feel" of lung compliance. There is little evidence comparing the outcomes for flow-inflating bags to T-piece resuscitators and therefore it is unclear if one is superior to the other.

PPV is indicated if the infant is gasping, not breathing, or if the heart rate is <100 bpm and should be started within 60 seconds of life. The most important indicator of effective ventilation is a rising heart rate. Thus, after 15 seconds of PPV, the heart rate response should be assessed. ECG can be used for continuous and accurate assessment of heart rate. If the heart rate is **NOT** rising after providing PPV for 15 seconds, then chest rise must be assessed. If the heart rate is **NOT** rising but there IS good chest rise, then ventilation may be effective and the patient may need more time to show a response. Continue with PPV that moves the chest for a total of 30 seconds before deciding on further interventions. If the heart rate is **NOT** rising and the chest is **NOT** moving then ventilation is NOT effective. The most likely reasons for ineffective mask ventilation are leak around the mask, airway obstruction (by neck position, secretions, or glottic closure), and insufficient ventilating pressure. Take corrective steps using the mnemonic MR. SOPA **(Fig. 15-1)** until you are able to provide PPV that moves the chest for 30 seconds. After performing the M and R steps, try ventilating again while watching for chest movement. If the chest is not moving, proceed to the next 2 steps. After performing the S and O steps, trying ventilating again. If the chest is not moving, increase the pressure by 5 to 10 cm H_2O increments until you achieve chest movement. The maximum recommended pressure is 40 cm H_2O for a term newborn.

Placement of an end-tidal carbon dioxide detector between the facemask and PPV device can aid detection of effective ventilation. As with intubation, the detector will turn yellow during exhalation during effective ventilation. Note that a purple or blue color with chest rise may indicate circulatory failure in the presence of effective ventilation.

Figure 15-1. The ventilation correction steps

M	Mask adjustment
R	Reposition airway
S	Suction mouth and nose
O	Open mouth
P	Pressure increase
A	Alternative airway

Alternative Airway

If PPV by face mask does not result in adequate chest rise or has not increased the heart rate, then an alternative airway such as an ETT or an LMA should be placed.

The LMA is used infrequently in the neonatal population. However, it should be considered in cases where the provider is unable to ventilate effectively and unable to place an ETT. A Cochrane review comparing LMA and bag mask ventilation noted comparable efficacy and decreased resuscitation and ventilation times as well as the decreased need for endotracheal intubation with LMA use (weak recommendation, low to moderate quality evidence).

NRP no longer recommends routine intubation for the presence of meconium stained amniotic fluid. However, if an infant is not responding to PPV and airway obstruction due to meconium is suspected, a meconium aspirator can be used after intubation to suction and clear the airway. Suctioning of meconium should occur after providing PPV via ETT that still does not improve the patient's condition when an obstruction is still suspected.

Circulatory Resuscitation

When optimizing ventilation does not adequately stabilize an infant, circulation must be supported by chest compressions to deliver 100% oxygen and medications (primarily epinephrine) to the coronary arteries. The NRP algorithm emphasizes the need for an alternative airway **BEFORE** beginning chest compressions, highlighting the importance of providing effective ventilation and the difficulty of coordinating optimal positioning for chest compressions with bag mask ventilation.

If the heart rate of an infant is <60 bpm despite effective ventilation (which is 30 seconds of PPV via an alternative airway that moves the chest), then chest compression with 100% oxygen should be initiated and continued for at least 1 minute and until the heart rate is >60 bpm. The ratio of coordinated chest compressions to breaths is 3:1. As approximately 1 minute is required to raise diastolic blood pressure to coronary perfusion pressure with chest compressions, coordinated blocks of chest compressions with ventilation should be at least 60 seconds in length without interruption. If the need for resuscitation is thought to be primarily of cardiac origin, then NRP recommends a higher ratio of 15:2, as dictated by PALS algorithm, may be used.

If chest compressions do not result in heart rate >60 bpm, epinephrine should be given IV or IO (0.1 to 0.3 mL/kg of 1 mg/10mL concentration) as the first line medication while compressions are in progress. The heart rate should be checked 1 minute after IV or IO epinephrine administration. If the heart rate remains <60 bpm, IV or IO epinephrine can be repeated every 3 to 5 minutes.

If the heart rate is persistently <60 bpm after IV or IO epinephrine, volume expansion is indicated if the newborn has signs of shock or a history of acute blood loss. Volume expanders should not be given routinely in the absence of shock or a history of blood loss because giving a large volume load to a heart that is injured may worsen cardiac output. Normal saline is recommended for acutely treating hypovolemia but packed red blood cells should be considered when severe anemia is expected.

Notable NRP 8th Edition Updates

1. Umbilical cord management plan replaces "How many babies?" in the 4 pre-birth questions.
2. An ECG monitor is recommended earlier in the algorithm, when an alternative airway becomes necessary.
3. IV/IO epinephrine flush volume increased from 0.5-1 mL to 3 mL normal saline (applies to all weights and gestational ages). In animal studies, this flush volume better delivered epinephrine to the heart and improved return of spontaneous circulation.
4. Initial epinephrine doses are recommended, however the dosage range is unchanged. The suggested initial IV/IO dose is 0.2 mL/kg (range 0.1 to 0.3 mL/kg). The suggested initial ETT dose is 1 mL/kg (range 0.5 to 1 mL/kg).
5. The timeframe for cessation of resuscitative efforts increased to 20 minutes of life (with the confirmed absence of HR after all appropriate steps have been performed).

15.2 Apnea of Prematurity

Control of breathing in the newborn involves functioning of three major components: the controllers (respiratory center), sensors (peripheral and central chemoreceptors) and effectors (respiratory muscles). An apneic spell is defined as the complete cessation of breathing for 20 seconds or longer, OR a shorter pause accompanied by bradycardia (<100 bpm), cyanosis or pallor. Apnea may be central (no breathing effort) or obstructive (obstruction to airflow, usually at the pharyngeal level) or mixed. In premature neonates, the majority of the apneic events are mixed. Periodic breathing on the other hand is defined as regular cycles of respiration approximately 10 to 18 seconds in length, interrupted by pauses at least 3 seconds in duration, with this pattern recurring for at least 2 minutes.

Apnea of Prematurity

Central respiratory drive and upper-airway patency are poorly integrated in infants less than 34 weeks gestation. Thus, the incidence of apnea is high in such infants. Infants born at 25 weeks gestation or less may continue to exhibit immature control of breathing at term and occasionally up to 44 weeks PMA.

Environment and other preventive measures

All infants with apnea should be nursed in a stable thermal environment using servo-controlled incubators. It is critical to avoid flexion of the neck and airway closure. Assure adequate oxygenation in an infant with apnea or periodic breathing both while awake and asleep. Some apneic infants may not maintain desired target oxygen saturation and thus best practices would indicate the need to treat the underlying cause e.g. V/Q mismatch, central apnea, etc.

Xanthines

These agents enhance rhythmic respiratory drive, enhance CO_2 response, reduce REM sleep, enhance resting pharyngeal muscle tone, and strengthen force of contraction of the diaphragm. They affect both central and obstructive apnea. Caffeine citrate is the drug of choice for apnea of prematurity because of its wide therapeutic index and reduced adverse cardiovascular effects. It increases respiratory rate and minute ventilation with little effect on tidal volume or heart rate. It may be given intravenously or enterally. In our unit, caffeine is routinely started in all babies <1250 gms for prevention of BPD. In neonates >28 weeks of gestation not needing positive pressure support, the clinician may consider waiting for the occurrence of apnea before initiating therapy.

Nasal CPAP

Nasal CPAP enhances rhythmic control of breathing primarily by opposing pharyngeal collapse and minimizing obstructive apnea. Initiate CPAP with 5-6 cm H_2O pressure. Increase pressures if necessary but levels above 8 cm H_2O should be needed only rarely. Immature infants requiring CPAP to control their apnea often need it until they reach a gestational age at which pharyngeal muscle control begins to mature (32-34 weeks). However, in babies born at 27 weeks' gestation or less the need for CPAP may persist for a much longer duration.

Role of Anemia

Anemia, particularly progressive physiologic anemia of prematurity, may exacerbate the frequency or severity of apnea. Transfusion of PRBCs may produce a short-term reduction in the frequency of apnea in such infants. There is no evidence to support long-term resolution of apnea following transfusion. Neither the incidence of apnea nor the response to transfusion is related to the actual hematocrit value.

Role of Gastroesophageal Reflex

There is no evidence of a causal relationship between GER and apnea of prematurity. There is no relation between reflux frequency or duration and apnea frequency or severity. Current evidence does not support the use of anti-reflux medications to treat apnea of prematurity and these medications may be associated with increased morbidity.

Medications

Caffeine Citrate

Loading dose is 20 mg/kg followed by an initial maintenance dose of 5 mg/kg given once daily. If apnea persists, maintenance dose may be increased to maximum of 10 mg/kg/day. The therapeutic range for serum levels is 10 to 20 mg/L but current evidence does not support routine monitoring of serum caffeine levels because of poor correlation between serum levels and adequacy of control of apnea. Trial off therapy may be considered after a clinically significant apnea-free period (off positive pressure) of 5 to 7days or 33 to 34 weeks' PMA, whichever comes first. Cardiopulmonary monitoring should continue for another 7 days after discontinuation of the medication.

Preparation for Discharge

Most preterm infants achieve physiologic stability between 36-37 weeks PMA. Approximately 80% of premature infants are free of apnea/bradycardia by the time they are otherwise ready for discharge. However, maturation of respiratory control may be delayed up to 43-44 weeks PMA in babies born at very early gestational ages or those with a complex medical course. Otherwise, healthy preterm infants, who are off xanthines have a low risk of significant episodes of recurrent apnea if they are apnea free for an observation period of 5 to 7 days. The following events are common in convalescent preterm infants and generally need not delay discharge according to the AAP COFN 2016 recommendations: brief, isolated bradycardic episodes that spontaneously resolve, feeding-related events that resolve with interruption of feeding

Please note that bouts of apnea may be increased in very preterm infants associated with elective surgical procedures (hernia repair), ophthalmologic exams and 2-month vaccinations (rarely after 4-month vaccinations).

Home apnea monitors are rarely indicated in management of persistent apnea of prematurity and should not be used to facilitate home discharge in infants who have not achieved stability of respiratory control. They are also not indicated for prevention of SIDS in preterm infants. Pneumograms are of no value in predicting SIDS and are not helpful in identifying patients who should be discharged on home monitors.

Polysomnography

Polysomnography is a tool that can be used to diagnose and monitor sleep-related breathing disorders. The study records several physiological parameters, including electroencephalographic signals, oronasal airflow, abdominal and chest wall movements, heart rate, oxygen saturation etc. The study components and their interpretations are well defined, and their diagnostic ability is well established in older children and adults. However, their utility in preterm and term infants is not well studied for several reasons. First, the normal values of the study components in our patient population are unknown. Second, most of the prematurity-related cardiorespiratory events improve over time. Third, use of polysomnography does not reduce the risk of mortality. Finally, the American Academy of Pediatrics does not recommend the routine use of this study in our preterm infants. For the select population who may benefit from this study in the NICU, infants with severe obstructive sleep apnea or persistent apnea in infants > 48 weeks post-menstrual age, we recommend consultation with the pulmonology team before performing a polysomnography

Oxycardiorespirogram (OCRG)

OCRG is a multichannel (3-lead) study that measures a patient's heart rate, rhythm, and chest movement during periods of sleep, wakefulness and feeding. Patients are monitored during the study period using pulse oximeter, EKG, and chest impedance band. The study can last 4-8 hours and a report of events such as apnea, bradycardia, and desaturations noted during the study period is produced. This is not to be confused with polysomnography and does not differentiate between types of apnea such as central and obstructive apnea. In addition, this is not an oxygen titration study that can be used to determine the oxygen requirements of a particular patient.

The utility, reliability, and positive predictive value of OCRG in the neonatal population is unknown and has not been studied. Currently, there is no evidence to suggest that an OCRG at the time of discharge will improve patient outcomes or reliably identify an infant's home oxygen requirement or minimize risk of neonatal morbidities after discharge from the NICU.

15.3 Management of Neonatal Respiratory Distress

The primary disorders producing respiratory symptoms during the newborn period are Respiratory Distress Syndrome (RDS), retained fetal lung fluid or transient tachypnea of the newborn, (TTN), Pneumonia, and Meconium Aspiration Syndrome. Many of these conditions have overlapping presentations and can be managed using the following strategies.

"CPAP First" Strategy

Current evidence indicates that early CPAP is an effective strategy for providing respiratory support for preterm infants, even for those who are extremely low birth weight (ELBW infants). CPAP initiated immediately after birth, with

subsequent selective use of surfactant has been noted to be at least as safe and effective as intubation and prophylactic surfactant administration. Preterm infants treated with early CPAP alone are not at increased risk of adverse outcomes. Further, early CPAP reduces the need for subsequent surfactant treatment or mechanical ventilation. A recent meta-analysis demonstrated that early CPAP combined with selective surfactant use results in lower rates of death or BPD as compared to intubation and prophylactic surfactant administration. This strategy of using CPAP first has also been endorsed recently by AAP.

Surfactant

Surfactant administration to preterm infants with RDS reduces mortality, incidence of pulmonary air leaks and risk of death or CLD at 28 days of life. Recent evidence indicates early CPAP combined with selective use of surfactant if RDS develops (rescue strategy) is the optimal strategy to reduced risk of death or BPD. **(Sec 1-Care of Preterm Infant)**

Rescue Treatment

We recommend surfactant treatment for VLBW infants who require 40-60% O_2 despite optimizing CPAP delivery. Rescue surfactant given within the first two hours of life to infants with established RDS is associated with reduced risk of death, air leaks and death or BPD compared to delayed treatment. Some treated infants may benefit from 2 or more doses. Repeat dosing is recommended 12 hours after the first dose for patients with a continued oxygen requirement of 40-60%.

- Spontaneously breathing infants with RDS requiring 40-60% oxygen despite nasal CPAP are candidates for endotracheal intubation, mechanical ventilation and surfactant therapy or **INSURE** (intubation, surfactant treatment, extubation to CPAP) technique. Dosing should be repeated as needed for up to 3 total doses (Curosurf®), although most infants require only one dose. Lung mechanics may improve rapidly, requiring rapid weaning of FIO_2, PIP (or Vt), or ventilator rate. Continue positive pressure ventilation until weaned to minimal settings, then attempt extubation and place infant on nasal CPAP

Surfactant Product Selection and Administration

Always ensure proper endotracheal tube position (by auscultation) prior to treating with surfactant in order to avoid unequal delivery of the medication to both lungs.

Commonly used surfactant products include those of bovine origin (Survanta®, Infasurf®) and porcine origin (Curosurf®). A recent meta-analysis reported a reduction in mortality, need for repeat dosing and duration of mechanical ventilation associated with use of porcine surfactant versus the bovine product beractant.

Curosurf®

Curosurf® has the additional benefit of lower dosing volume, longer half-life and more rapid onset of effect. Initial dose is 2.5 ml/kg (using birth weight). Up to 2 subsequent doses of 1.25 ml/kg may be given at 12 hour intervals. There may be a situation in which a patient born at an outside hospital may receive a dose of beractant (Survanta®) prior to transfer to TCH and need a second dose of surfactant. In this situation, we would give poractant (Curosurf®) 1.25 ml/kg/dose when second dose of the original product is due.

During or immediately following the dosing procedure lung compliance may improve rapidly. An ABG should be obtained soon after dosing to avoid hyperventilation or over distension of the lungs associated with surfactant administration. Continued monitoring of chest excursion and pCO_2 is essential to allow rapid reduction in ventilator support as the lung compliance improves.

Surfactant Replacement for Term Infants with Hypoxic Respiratory Failure

Current evidence indicates surfactant treatment improves oxygenation and reduces the need for extra-corporeal membrane oxygenation (ECMO) in term babies with hypoxic respiratory failure associated with RDS, meconium aspiration, pneumonia, sepsis, and some cases of idiopathic PPHN. Benefits are greatest for infants requiring positive pressure ventilation with oxygenation index of 15 on 2 consecutive measurements. In this setting, up to 3 doses of surfactant may be necessary. No benefits of surfactant therapy have been reported in infants with CDH.

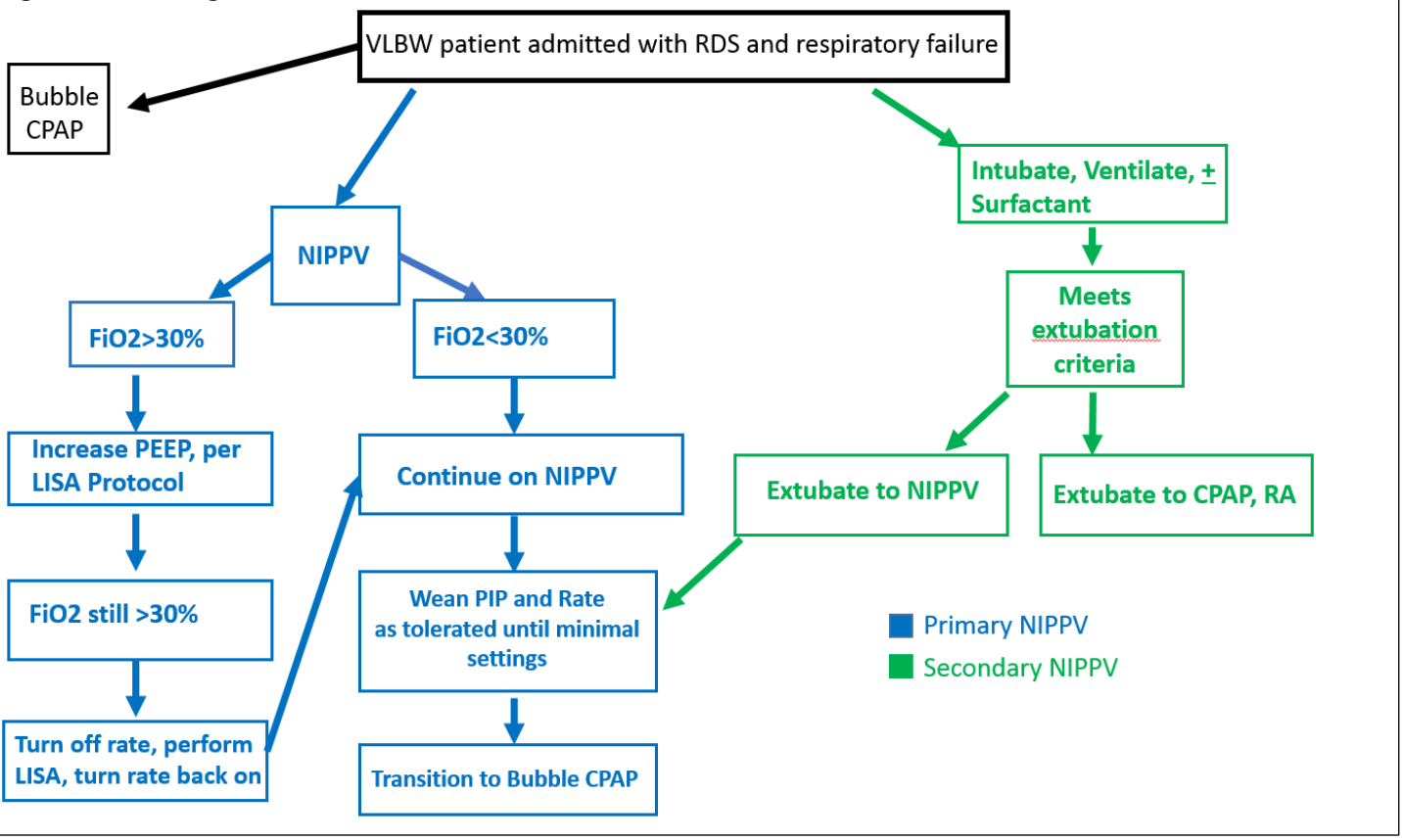
15.4 Non-Invasive Respiratory Support

Nasal Intermittent Positive Pressure Ventilation (NIPPV)

NIPPV is a form of non-invasive ventilation that delivers intermittent positive pressure without using an endotracheal tube. It is an alternate mode of non-invasive ventilation that's comparable to CPAP. It can be used as primary mode of respiratory support for infants with RDS (as an alternative to CPAP) or as secondary mode of respiratory support or post-extubation support. **(Fig 15-2)** The equipment needed includes the Ventilator, patient interface, and an orogastric tube. Contraindications to using NIPPV include conditions that prevent an adequate seal between the patient and the NIPPV interface (ex. choanal atresia, severe cleft lip, cleft palate), cardiorespiratory instability, and conditions that prevent adequate venting of the GI tract (ex. patient with esophageal atresia in whom OG/NG not possible). Potential complications of NIPPV include skin breakdown from the patient interface, abdominal distension, and feeding intolerance.

NIPPV has been studied extensively and its safety and efficacy has been compared to CPAP in randomized controlled trials. A meta-analysis in 2016 showed that early NIPPV is better than CPAP in treating preterm infants with RDS and preventing the need for intubation and ventilation (moderate quality evidence). A Cochrane review from 2017 reports that NIPPV reduces the incidence of extubation failure within 48 hours and up to 7 days after extubation. The number needed to treat with NIPPV to prevent one extubation failure is 8. A new meta-analysis from 2021 showed less risk of developing BPD and a lower extubation failure rate in premature patients extubated to NIPPV vs CPAP (moderate to low quality evidence). While it seems to be beneficial as primary mode of respiratory support and for post-extubation support, it's unclear if the same benefits extend to the indication of CPAP rescue. Since this indication has not been studied, we cannot recommend NIPPV as a CPAP rescue modality. Clinicians will have to evaluate the pros and cons of NIPPV on a case by case basis if considering it for the indication of CPAP rescue.

Figure 15-2. Using NIPPV in VLBW infants



Of note, NIPPV has been mostly been studied in preterm population (infants with gestational age ≤ 32 weeks) requiring positive pressure ventilation for respiratory failure or apnea. Therefore, it's unclear if the benefits and safety profile extend to full term patients or older, former preterm patients. Currently, we recommend using NIPPV as an alternative to CPAP, either as primary mode of respiratory support (upon admission to our NICU) or as secondary mode of support following extubation of a VLBW infant.

Initial Settings

Unlike Conventional Ventilation, NIPPV will not significantly support Minute Ventilation. It serves to increase MAP in infants with apnea or periodic breathing. Suggested initial settings are listed in **Table 15-1**. A higher i-time is required (than typically used for conventional mechanical ventilation) due to the higher resistance in the circuit. We recommend checking a blood gas within 60 minutes of starting a patient on NIPPV (and at least once daily thereafter) to assess adequacy of ventilation and to adjust settings as necessary.

Table 15-1. Initial settings for NIPPV

NIV Settings	Primary NIPPV	Secondary NIPPV
PIP	20-25	2 above PIP reached on Vent
Peep	5-6	Same as on vent
Rate	20-30	20
Ti	0.5	0.5
FiO_2	As needed to maintain targeted goal oxygen saturations	As needed to maintain targeted goal oxygen saturations

Maintenance of NIPPV

Always ensure that a properly functioning OG/NG is in place to vent stomach. The PIP can be increased by 1-2 cm H_2O up to a max of 26. We do not recommend increasing above 26 as this may worsen gastric insufflation. Using a rate higher than 30 may also result in inability to achieve set PIP. If FiO_2 is high, increase PEEP by increments of 1 (up to a max PEEP of 8) to optimize MAP. Consider daily blood gas for 2-3 days after starting NIPPV.

Weaning from NIPPV -Transition to CPAP

NIPPV breaths are unsynchronized and can be uncomfortable for the patient or result in increase in WOB. Therefore, we recommend choosing a rate that allows NIPPV to coincide with patient's spontaneous respiratory rate as much as possible. Attempt to wean NIPPV once per day based on blood gases, either PIP by 2 or rate by 5. Patients may also be weaned clinically based on FiO_2 and frequency of apnea. Transition patients to CPAP once the PIP is down to 16-18, the rate is 10-15, and the PEEP is less than 7. We recommend that NIPPV is used as a bridge to CPAP/HFNC or room air for a period of 7-14 days and not be used continuously for a prolonged period of time. Consider reintubation if the patient has moderate to severe WOB, frequent apnea/bradycardia/desaturation (more than 3 per hour), or events requiring bagging.

Nasal CPAP

Nasal constant positive airway pressure (CPAP) is used for managing apnea of prematurity, maintaining lung recruitment in premature infants, and for early intervention in acute respiratory distress syndrome (RDS).

There are various types of devices and patient interfaces available to deliver CPAP. Continuous flow CPAP is the mode delivered by most neonatal ventilators. **Bubble CPAP** is a specific type of continuous flow CPAP that is thought to be superior to ventilator delivered CPAP based on observational studies reporting enhanced gas exchange with bubble CPAP as compared to conventional delivery systems (low grade evidence). **Bubble CPAP delivery system is currently the method of choice in the Baylor NICUs.** The continuous flow should be adequate to produce bubbling most of the time, but this varies with infant position and opening of the mouth. Begin with 5 to 6 cm H_2O pressure and increase by 1- to 2-cm increments. CPAP pressures of 5 to 8 cm H_2O usually are optimal to manage apnea or acute lung disease with continuous flow devices, however pressures greater than 8 cm H_2O are needed rarely.

Patient Interface

Currently mask is the preferred interface for delivering CPAP in our NICU. Recent evidence suggests that CPAP delivered by nasal mask may be more beneficial. Four randomized control trials compared CPAP failure rate, defined as the need for mechanical ventilation within 72 hours, between patients treated with masks versus prongs interface. When the results of these studies are combined, patients receiving CPAP via mask had a lower CPAP failure rate than those receiving CPAP via nasal prongs (low quality evidence). There are 6 randomized trials that included the outcome of nasal injury. There was no difference in nasal injury rate between the two interfaces (low quality evidence). Clinicians may consider using prongs transiently for special circumstances where an infant is unable to tolerate mask. Please refer to our unit specific CPAP interface algorithm for details on CPAP interface use and skin scoring system to monitor for nasal injury **(Fig 15-3).**

Indications for CPAP

Apnea of Prematurity

CPAP reduces the frequency of the obstructive component of mixed apnea of prematurity. The primary effect is to maintain upper airway patency until hypopharyngeal function matures. A secondary effect is to maintain adequate lung volume. Pharyngeal function usually improves after 31-32 weeks PMA.

Maintenance of Lung Recruitment

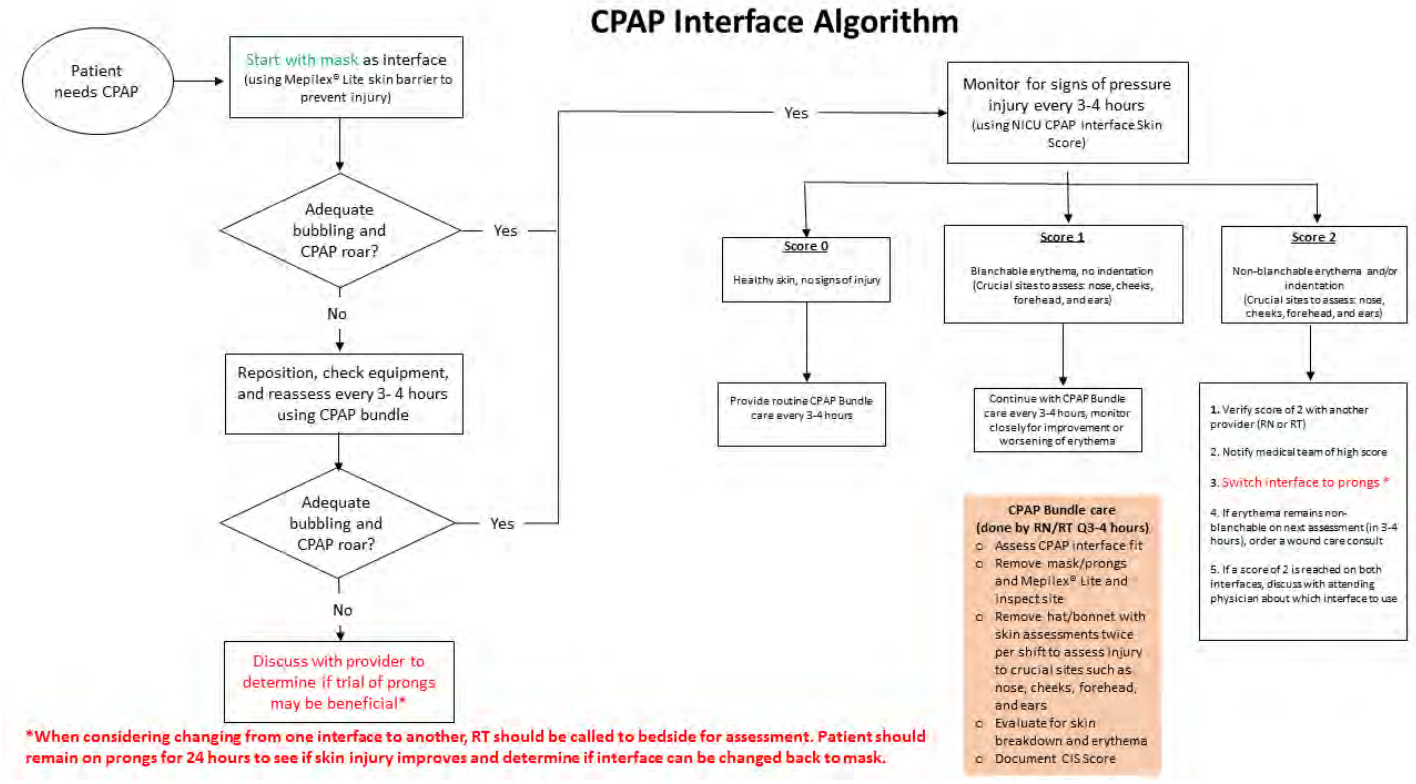
CPAP is used in this setting to oppose high chest wall compliance and low lung volume in infants. Infants are placed on CPAP at birth to maintain lung recruitment especially if they appear immature, have RDS or are at risk for postnatal chest wall dysfunction or apnea. CPAP may also be used for maintaining lung recruitment post-extubation.

Acute Lung Disease

We recommend a trial of non-invasive respiratory support for premature infants with respiratory distress and oxygen requirement of 40% or greater to maintain appropriate lung recruitment and oxygen saturation.

With continuous flow devices, begin with 5 cm H_2O. Pressures of 5 to 8 cm usually are adequate; pressures over 8 cm H_2O are rarely indicated. In some patients, lung over distension may occur at these levels. Inadequate response to CPAP includes persistent O_2 requirement above 40 % or severe apnea.

Figure 15-3. CPAP interface algorithm



Home CPAP

For patients in whom tracheostomy is thought to be not ideal due to greater risk than benefit, or in cases where parents refuse tracheostomy, or for special circumstances involving discharge to hospice care, the option of home CPAP can be considered. While there is no reports of efficacy or safety of delivering CPAP at home for newborns, home CPAP use has been facilitated for a small number of babies being discharged from the NICU. Since this is not a routine practice, we recommend working with pulmonary team to determine which device and interface are suitable for these rare circumstances when patients are discharged with CPAP. It's important for clinicians to be aware that this option is available, feasible, and is being requested by families on occasion. Further study is needed to understand the risks and benefits of home CPAP delivered non-invasively versus. CPAP delivered via tracheostomy.

High Flow Nasal Cannula

Two primary mechanisms of action have been described for HFNC.

CPAP Effect

Pharyngeal end expiratory pressure during HFNC is dependent upon gas flow and degree of leak around the nasal cannula (NC). In presence of 30-50% leak (open system), only minimal distending pressure 0-3 cm H_2O is delivered. However, if a tight fitting NC is used (closed system) pharyngeal/esophageal pressures delivered may be quite high, especially as flow exceeds 1-2 LPM. This variation in delivered pressure and lack of ability to monitor pharyngeal pressures, makes it a challenge to use HFNC. Evidence regarding effects of HFNC on work of breathing in neonates is inconclusive and data are limited regarding effect on lung volume and recruitment. A randomized crossover study showed no difference between patients treated with CPAP and HFNC in WOB and thoraco-abdominal asynchrony or oxygen saturations.

Enhanced Dead Space Ventilation (Pharyngeal Washout) Effect

A different effect of HFNC is that of NC flow rates that exceed the patient's spontaneous inspiratory flow (> 2 LPM for neonates) and minimize entry of room air. Clinical studies suggest that gas flows of 3-8 LPM with 30-50% NC leak produces "purging" of nasopharyngeal dead space during expiration with enhancement of CO_2 elimination. Evidence suggests this effect may be the primary mechanism for reported benefits of HFNC therapy in adults and older pediatric patients. However, evidence in neonates regarding this mechanism is limited. Washout times for HFNC and CPAP, with open and closed mouth were significantly longer for CPAP versus HFNC in the closed mouth setting.

Use in Neonates

Use of HFNC in the NICU environment has increased over the years, but the primary mechanism of action in neonates has not been well understood. Studies have compared HHNC therapy to various forms of conventional CPAP in premature infants.

Infants ≤28weeks

A meta-analysis of 15 studies examined evidence on HFNC use for post extubation respiratory support. CPAP has been noted to be superior for post extubation support of babies < 26 weeks and ELBW infants. In a retrospective analysis, ELBW infants who received HFNC had higher rates of death or BPD when compared to infants who received CPAP alone. Infants in the HFNC group also had more days of mechanical ventilation, use of postnatal steroids, and days on supplemental oxygen. Time to initiate and achieve full PO feeds was also longer in the HFNC group. At present, we do not recommend HFNC as primary support for the management of infants <28 weeks with RDS. In a 2016 meta-analysis of HFNC versus CPAP for extubation failure, two studies reported data on infants <28 weeks gestation. There was no difference between post extubation treatment failure (re-intubation within 7 days of trial therapy), death, or chronic lung disease. At present, we do not have enough evidence to provide a recommendation for the use of HFNC in the management of respiratory distress as post extubation support in infants <28 weeks.

Infants > 28 weeks

Per Cochrane Review done in 2016, when HFNC is used for post extubation support (6 studies), there was no difference in rate of treatment failure, need for re-intubation, death or BPD. However, nasal trauma was significantly lower among patients treated with HFNC, when compared to patients treated with CPAP. Several of these studies allowed "rescue" with CPAP or NIPPV for patients failing HFNC, resulting in comparable need for re-intubation in both groups (patients treated with CPAP vs HFNC).

A meta-analysis of studies comparing HFNC versus CPAP as primary mode of respiratory support of early neonatal respiratory disorders found no difference in primary outcome of death or BPD or pneumothorax. HFNC resulted in longer duration of respiratory support. For the treatment of early RDS, in the first 72 hours, a RCT from 2018 demonstrated HFNC was inferior to CPAP in avoiding the need for escalating respiratory support. Another RCT including 28 to 42 weeks gestational age infants reported similar efficacy and safety of HFNC and CPAP in treating early respiratory failure. A multicenter, randomized, non-inferiority trial included new born infants who are ≥31 weeks of gestation and less than 24 hours of age. These infants with respiratory distress were randomized to HFNC or CPAP and more infants were reported to have treatment failure with HFNC at 72 hours, compared to CPAP (20.5% in HFNC group vs. 10.2 % in CPAP group, RD of 10.3, 95% CI: 5.2 to 15.4). At present we do not recommend using HFNC as a primary mode of respiratory support in VLBW infants with respiratory distress.

15.5 Weaning from CPAP and Nasal Cannula

Based on the best available evidence, the following recommendations were developed to wean infants from CPAP and nasal cannula oxygen therapies. The goal of this protocol is to promote a safe and effective weaning of CPAP and oxygen therapy in preterm infants in order to decrease oxygen toxicity (and its effects on ROP and chronic lung disease), reduce unnecessary use of positive pressure and oxygen, prevent exacerbations of underlying lung disease, and avoid CPAP-related nasal and facial injuries.

Eligibility Criteria

Infants can be considered to be safe to trial off CPAP if they meet **all of the following criteria**:

- PMA ≥ 30 weeks
- $FiO_2 \leq 40\%$
- No respiratory distress (RR<60/min; no significant chest retractions)
- No concurrent treatment for PDA or sepsis
- Absence of significant apneas and bradycardias
- Absence of major congenital abnormality

Choosing between Heated Humidified High-Flow Nasal Cannula (HFNC) vs Low-Flow Nasal Cannula (LFNC)

Typically, oxygen requirement in infants is reflective of the severity of the underlying lung disease: therefore, the greater the oxygen requirement, the more severe the lung disease and greater the need for respiratory support. Based on available evidence, we recommend that infants on CPAP requiring FiO_2 of 21%, < 30%, and 30–40% can be weaned to room air, LFNC, or HFNC, respectively. If the infant meets the criteria for LFNC therapy, we suggest that you refer to **Tables 15-2a** and **15-2b** to determine the flow that is required to deliver < 30% FiO_2 and titrate to maintain SpO_2 in the target range.

Weaning HFNC and LFNC

The recommended SpO_2 targets are between 90 – 95% in infants receiving supplemental oxygen. Refer to the algorithm **(Fig 15-4)** for guidance on titrating and weaning off HFNC and LFNC. Once you are down to 1L/min NC flow, we suggest that you can either wean the flow **(Fig 15-4)** or use a blender to titrate oxygen delivery. Using a blender at very low flow rates, under 0.5L/min, seems to be equivalent of giving no respiratory pressure support.

Table 15–2a. Calculation of effective FiO_2, Step 1

	Factor With Weight (kg) of								
	0.7	1.0	1.25	1.5	2	2.25	3	3.5	4
Flow, L/min									
0.01	1	1	1	1	1	0	0	0	0
0.03 (1/32)	4	3	2	2	2	1	1	1	1
0.06 (1/16)	9	6	5	4	3	2	2	2	2
0.125 (1/8)	18	12	10	8	6	4	4	4	4
0.15	21	15	12	10	8	6	5	4	4
0.25 (1/4)	36	25	20	17	13	10	8	7	6
0.5 (1/2)	71	50	40	33	25	20	17	14	13
0.75 (3/4)	100	75	60	50	38	30	25	21	19
1.0 (1.0)	100	100	80	67	50	40	33	29	25
1.25	100	100	100	83	63	50	42	36	31
1.5	100	100	100	100	75	60	50	43	38
2.0	100	100	100	100	100	80	67	57	50
3.0	100	100	100	100	100	100	100	86	75

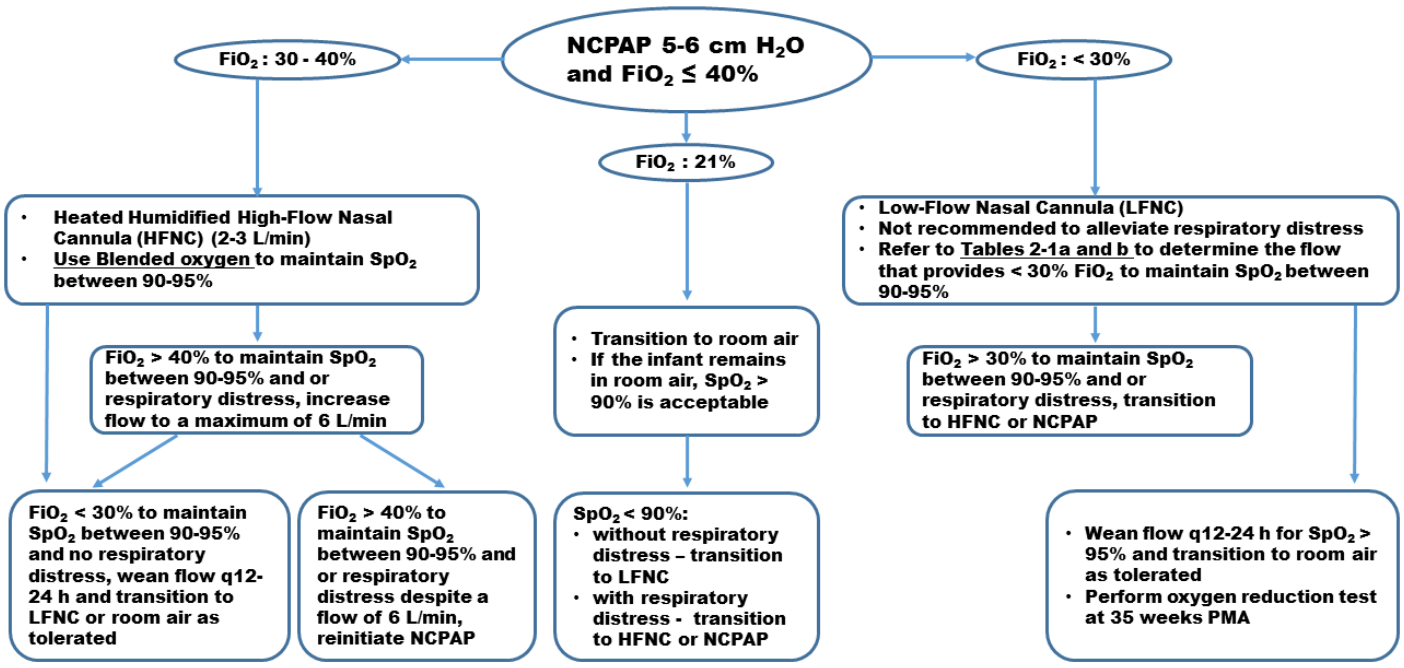
Adapted from equations 3 and 4 in ref 1 (of the source publication). The rule of thumb (implicit in the table) is that, for most infants in the STOP-ROP study, if flow (in liters per minute) exceeds body weight (in kilograms), then the effective Fio_2 equals the nasal cannula oxygen concentration.

Table 15–2b. Calculation of effective FiO_2, Step 2

	Effective FiO_2 With Oxygen Concentration of						
Factor	0.21	0.22	0.25	0.30	0.40	0.50	1.00
0	0.21	0.21	0.21	0.21	0.21	0.21	0.21
1	0.21	0.21	0.21	0.21	0.21	0.21	0.22
2	0.21	0.21	0.21	0.21	0.21	0.22	0.23
3	0.21	0.21	0.21	0.21	0.22	0.22	0.23
4	0.21	0.21	0.21	0.21	0.22	0.22	0.24
5	0.21	0.21	0.21	0.21	0.22	0.22	0.25
6	0.21	0.21	0.21	0.22	0.22	0.23	0.26
7	0.21	0.21	0.21	0.22	0.22	0.23	0.27
8	0.21	0.21	0.21	0.22	0.23	0.23	0.27
9	0.21	0.21	0.21	0.22	0.23	0.24	0.28
10	0.21	0.21	0.21	0.22	0.23	0.24	0.29
11	0.21	0.21	0.21	0.22	0.23	0.24	0.30
12	0.21	0.21	0.21	0.22	0.23	0.24	0.30
13	0.21	0.21	0.22	0.22	0.23	0.25	0.31
14	0.21	0.21	0.22	0.22	0.24	0.25	0.32
15	0.21	0.21	0.22	0.22	0.24	0.25	0.33
17	0.21	0.21	0.22	0.23	0.24	0.26	0.34
18	0.21	0.21	0.22	0.23	0.24	0.26	0.35
19	0.21	0.21	0.22	0.23	0.25	0.27	0.36
20	0.21	0.21	0.22	0.23	0.25	0.27	0.37
21	0.21	0.21	0.22	0.23	0.25	0.27	0.38
22	0.21	0.21	0.22	0.23	0.25	0.27	0.36
23	0.21	0.21	0.22	0.23	0.25	0.28	0.39
25	0.21	0.21	0.22	0.23	0.25	0.28	0.41
27	0.21	0.21	0.22	0.23	0.25	0.29	0.42
28	0.21	0.21	0.22	0.24	0.26	0.29	0.43
29	0.21	0.21	0.22	0.24	0.27	0.29	0.44
30	0.21	0.21	0.22	0.24	0.27	0.30	0.45
31	0.21	0.21	0.22	0.24	0.27	0.31	0.47
33	0.21	0.21	0.22	0.24	0.27	0.31	0.47
36	0.21	0.21	0.22	0.24	0.28	0.31	0.49
38	0.21	0.21	0.23	0.24	0.28	0.32	0.51
40	0.21	0.21	0.23	0.25	0.29	0.33	0.53
42	0.21	0.21	0.23	0.25	0.29	0.33	0.54
43	0.21	0.21	0.23	0.25	0.29	0.33	0.55
44	0.21	0.21	0.23	0.25	0.29	0.34	0.56
50	0.21	0.21	0.23	0.25	0.30	0.35	0.60
55	0.21	0.22	0.23	0.26	0.31	0.37	0.64
57	0.21	0.22	0.23	0.26	0.32	0.38	0.66
60	0.21	0.22	0.23	0.26	0.32	0.38	0.68
63	0.21	0.22	0.24	0.27	0.33	0.39	0.71
67	0.21	0.22	0.24	0.27	0.34	0.40	0.74
71	0.21	0.22	0.24	0.27	0.34	0.42	0.77
75	0.21	0.22	0.24	0.28	0.35	0.43	0.80
80	0.21	0.22	0.24	0.28	0.36	0.44	0.84
83	0.21	0.22	0.24	0.28	0.37	0.45	0.87
86	0.21	0.22	0.24	0.29	0.37	0.46	0.89
100	0.21	0.22	0.25	0.30	0.40	0.50	1.00

Adapted from equations 3 and 4 in and reproduced with permission from Walsh M, Engle W, Laptook A, et al. Oxygen delivery through nasal cannulae to preterm infants: can practice be improved? *Pediatrics* 2005;116:857-861.

Figure 15-4. Algorithm for weaning CPAP, heated humidified high-flow nasal cannula (HLNC) and low-flow nasal cannula (LFNC)



Irrespective of mode of weaning you choose (blender vs. flow), we suggest that you pay attention to the infant's saturations and ensure that they are in the target range. If the infant's oxygen saturations are persistently greater than 95%, wean delivered oxygen to avoid oxygen toxicity (e.g. ROP). We also recommend performing an oxygen reduction test at 35 weeks PMA based on the NICHD criteria as explained below to assess whether the infant actually needs supplemental oxygen to maintain the SpO_2 targets.

Oxygen Reduction Test

Infants consistently maintaining SpO_2 targets between 90 – 95% on a $FiO_2 \leq 30\%$ without any respiratory distress, apnea or bradycardias are eligible for this test. Infants requiring $FiO_2 >$ 30%, or any form of positive pressure (e.g. mechanical ventilation, CPAP, or HFNC); having respiratory distress, apnea, or bradycardias, increase in baseline oxygen requirements by > 10% in the past 24 h; or those with congenital anomalies are not eligible for this test. Before performing the test, please ensure that the infant is: not been fed in the past 30 minutes (timing is irrelevant for infants on continuous feeds), on continuous cardio-respiratory monitoring, and supine. The test can be conducted either in sleep or awake state. For eligible infants receiving low-flow nasal cannula oxygen therapy, decrease flow by 0.1 L/min every 5 minutes until the flow is 0.1 L/min. Then reduce the oxygen concentration by 20% every 5 minutes until the FiO_2 is 21% making sure that the infant is stable and the oxygen saturations remain ≥ 90%. It is recommended that the nasal cannula be removed from the nares but left affixed to the face, to not disturb the infant during the test. We recommend that the infant's heart rate, respiratory rate, oxygen saturation, and frequency of apnea and bradycardias be recorded every minute starting 15 minutes prior to the test (baseline),continue throughout the testing period (oxygen reduction phase) and for 30 minutes after weaning off the oxygen (room air trial phase).

The infant is considered to have passed the test if the oxygen saturation remains ≥ 90% in room air. A rapid pass is defined as oxygen saturation ≥ 96% for 15 minutes in room air. These infants need to be closely monitored in room air. The infant will be considered to have failed the trial and should be immediately placed back on their baseline oxygen need if they meet any of the following criteria: SpO_2 are < 90% for 5 consecutive minutes or < 80% for 15 seconds, and worsening apneas or bradycardias.

15.6 Airway Management

Intubation

Endotracheal intubation is a life-saving procedure that requires technical and behavioral skills as well as advanced planning to minimize adverse events. Odds of an adverse event increase four fold with an emergent intubation, compared to a planned intubation. Commonly encountered short-term complications of neonatal intubation include cardiopulmonary compromise – hypotension, bradycardia, and desaturations. An increased number of intubation attempts have been associated with an increase in risk of severe IVH in VLBW infants. Intubation success and safety can be improved by minimizing number of intubation attempts, limiting each attempt to 30 seconds, by using premedication whenever possible, and by preparing team members for the procedure in advance.

Table 15-3. ETT size selection

Weight/Post Menstrual Age	Tube Size (ID, mm)
<1kg or 22-28 weeks	Size 2.5
1 to <2 kg or 29-34 weeks	Size 3.0
≥2 kg or 35+ weeks	Size 3.5
Post term or larger babies	Size 4.0

Preparing for intubation:

- Discuss indications, risks and benefits with the bedside team
- If difficult or critical airway is anticipated, discuss who should be called in case of unsuccessful intubation or in case of an emergency (at TCH this includes GOAT team and ENT).
- Look for bedside signage to see if patient had previously been labeled to have "*critical airway*"
- Prepare your team by assigning roles to each individual participating in the procedure.
- Determine the size of ETT needed **(Table 15-3)** and the depth of insertion.
- Check equipment and ensure medications are readily available for premedication.

Premedication for Non-Emergent Endotracheal Intubation

Premedication for **elective** intubation improves physiologic stability during the procedure and decreases incidence of complications such as bradycardia and need for multiple attempts.

Premedication strategy based on 2011 AAP recommendations:

1. Atropine 0.02 mg/kg IV PUSH - vagolytic agent to reduce bradycardia and secretions.
2. Fentanyl 1-2 mcg/kg IV INFUSION 3-5 minutes - opioid to provide analgesia and sedation.
3. ± Vecuronium 0.1 mg/kg IV PUSH - muscle relaxant to decrease patient movement.

Premedication strategy for infants without intravenous access:

- Fentanyl 1.5mcg/kg/dose INTRANASAL (do not dilute), - opioid to provide analgesia and sedation.
- ± Midazolam 0.2-0.3mg/kg/dose INTRANASAL - benzodiazepine to provide sedation.
- ± Succinylcholine 2mg/kg/dose IM - muscle relaxant to decrease patient movement.

Of note, for LISA or INSURE procedures, premedication with atropine and fentanyl **(not vecuronium)** should be used to facilitate early extubation of infant following the procedure. Fentanyl for LISA or INSURE can be given at 0.5-1 mcg/kg.

Potential adverse events related to premedication:

1. Fentanyl-induced chest wall rigidity. Avoid incorrect doses and rapid infusion of fentanyl to prevent chest wall rigidity. If patient experiences chest wall rigidity, treat with vecuronium 0.1mg/kg IV PUSH. If persists consider a second dose of vecuronium or naloxone.
2. Failure to intubate after administration of a muscle relaxant. Maintain effective ventilation with bag mask ventilation via facemask or LMA. Short-acting agents may be reversed with neostigmine.
3. Succinylcholine is contraindicated in preterm infants, patients with hyperkalemia, or cardiac disease/myopathy.

Stylet use

Using a stylet to facilitate intubation has been associated with injury to the trachea. However, stylets can be used safely if providers take precautions to follow proper technique and ensure that the tip of the stylet is always proximal to the end of the ETT.

ETT placement

Placement of ETT can be confirmed by improvement in heart rate and color change in CO_2 detector (yellow means successful intubation). Indirect signs of successful intubation include symmetric chest rise and auscultation of breath sounds bilaterally. ETT should be positioned so that the tip of the tube on a chest radiograph is above the bifurcation of the trachea, at T3 - T4. Chest X-ray should be done with midline head position (not flexed or extended) and arms at the sides to facilitate accurate assessment of ETT tip positioning. If a patient gains a significant amount of weight (~500g) over the course of mechanical ventilation, consider a repeat X-ray to reassess tube position.

ETT Securement

ETT can be secured with NeoBar® or tape. Proper securement is critical for prevention of complications such as tube dislodgement and unplanned extubation. Respiratory therapists will follow unit guidelines to secure ETT and nursing staff will monitor for proper securement during each shift.

Alternate Airways

Laryngeal Mask Airway (LMA)

LMA can be used in the setting of unsuccessful tracheal intubation, especially in patients with upper airway malformations. Two sizes of LMA are available, size 1 is indicated for any infant < 5 kg and size 1.5 for infants 5-10 kg. During placement, LMA can be obstructed at the base of the tongue or due to the epiglottis being "down folded." If malposition is suspected, deflate and remove LMA and replace it using proper technique. Monitor for gastric insufflation in the setting of prolonged ventilation with LMA. For instructions on LMA placement visit https://www.youtube.com/watch?v=DCLiznDpNzs.

Oral Airway

Two sizes of oral airway devices are available - infant (green) and neonate (clear). Consider an oral airway placement when unable to ventilate a baby with upper airway obstruction, such as a patient with posteriorly displaced tongue or laryngeal anomaly. For instructions on airway placement visit https://www.youtube.com/watch?v=2r14qWHDToE

Management of Neonates with Pierre Robin Sequence (PRS) and Severe Micrognathia

Pierre Robin sequence (PRS) is defined as micrognathia, glossoptosis and upper airway obstruction with or without cleft palate. It can present as an isolated anomaly or may have an underlying genetic etiology such as Stickler syndrome and velocardiofacial syndrome. The incidence in US is approximately 1 per 5,000-7,000 live births.

Between 46-85% of neonates with PRS have upper airway obstruction and it can be treated with conservative management (positioning to optimize airway patency) or surgery based on the severity and clinical symptomatology. Mandibular distraction osteogenesis (MDO) is a surgical technique in which the mandible is gradually lengthened to relieve airway obstruction and reduce feeding difficulties over time.

Prenatal consultation

- When anomaly is diagnosed prenatally and found to be severe, an EXIT-to-airway procedure is sometimes considered.

Postnatal Assessment

- In order to determine candidacy for MDO, consultation of following services should be considered:
  - Otolaryngology
  - Plastic Surgery
  - Genetics
  - Ophthalmology (to evaluate for Stickler syndrome)
  - Pulmonary
- The following studies are typically used to determine candidacy for surgical intervention:
  - Multi-positional sleep study - to evaluate for obstructive apnea.
  - Feeding evaluation by speech therapy and swallow study to evaluate patient's ability to swallow safely during oral feedings.
  - Audiology evaluation – for hearing screen.
  - CT maxillofacial without contrast with 3D reconstruction - to evaluate mandible, airway, and assess degree of obstruction.
  - Bronchoscopy – to assess severity of airway obstruction and evaluate need for tracheostomy. Of note, for patients who undergo airway evaluation, a "Difficult airway" or "critical airway" sign should be placed at bedside based on findings on bronchoscopy and ENT recommendations.

Patients with airway obstruction are typically managed by placing in prone or lateral positioning or using nasopharyngeal airway until surgical candidacy is determined. Determining candidacy for MDO is a multidisciplinary process that includes input from Plastic Surgery and ENT services as well as results of the testing listed above.

Postoperative Care after MDO:

- Following surgery, infant will return to the NICU and remain intubated until cleared by Plastic Surgery and ENT services.
- **Antimicrobial prophylaxis** – treat with cefazolin until external distractors are removed.
- **Pain management** - Sedatives and narcotics are used for treating post-operative pain and keeping patient comfortable and minimizing agitation. For the first few days after surgery, suggest using scheduled or continuous infusions of narcotics and sedatives to minimize risk of inadvertent extubation. After 2-3 days postop, consider adding acetaminophen and weaning narcotics as tolerated prior to planned extubation attempt. In addition, premedication with Tylenol and/or opiates is recommended prior to daily distractor manipulations, preferably given 30 minutes prior to each manipulation.

  Planned extubation - patients will return to the OR 5 days after the procedure for a controlled extubation attempt. Typically, these planned extubations are scheduled early in the morning so that infant can be observed closely for respiratory failure and need for reintubation. Treatment with dexamethasone (0.25 mg/kg x 3 doses) is recommended to facilitate a successful extubation attempt.
- **LMA** is placed at bedside throughout the NICU course to ensure easy access in case of an emergent episode of airway obstruction.
  - **Feeding**- Consider starting NG feedings within 12-24 hours after surgery if no other contraindications. Modified Barium Swallow study can be considered to re-evaluated safety of oral feedings after surgery. If no improvement in oral feeding after 2-3 weeks, consider discussing the option of G Tube placement with the family.
- **Anti-acid therapy** - PPIs are used as a first line therapy to prevent acid related erosive esophagitis. If PPIs are contraindicated or unavailable H2 blockers may be used
- If a patient should require a return to the OR for any reason, plastic surgery attending and ENT attending should be notified in advance so that arrangements can be made with the anesthesia team regarding appropriate anesthetic management.

Discharge preparation:

- Medications for treatment of GE reflux are to be continued post discharge based on Plastic surgery/ENT recommendations.
- Follow up PSG can be considered after 8 weeks post-distraction.

Tracheostomy

Determining candidacy for tracheostomy and home ventilation is a complex process that requires careful patient selection, frank discussions with family members, and education for providing this complex home care. Only a small proportion of infants requiring chronic mechanical ventilation are suitable candidates for tracheostomy. The optimal timing of tracheostomy placement is unclear but some studies have reported that early tracheostomy placement (< 120 days) reduced the risk of subglottic stenosis, decreased the need for sedation, and improved patient comfort.

It is important to note that infants with severe BPD requiring tracheostomy and long term mechanical ventilation are at risk for a number of adverse outcomes. They are at increased risk for hospitalizations with 2 year readmission rates reported to be ranging between 43-63% and also develop more frequent lower respiratory tract infections. On the other hand, there may be short-term neurodevelopmental benefits of improved growth and increased participation in development-promoting activities by facilitating the transition to homecare. NICHD Neonatal Network reports indicated that after adjustment for potential cofounders, odds of death or NDI are higher in patients with tracheostomy. Overall there is limited information on long-term pulmonary and neurodevelopmental outcomes of neonates with tracheostomy and a careful consideration of risks and benefits for each individual patient and family, along with the input of the multidisciplinary care team, should guide this complex decision making process.

Steps to consider in identifying candidates for tracheostomy placement:

- Family involvement
  - Understanding goals of the family
- Assessment
  - A multidisciplinary family meeting should be considered-neonatology team, all subspecialists (ENT, Pulmonology, Pediatric Surgery if GT placement

occurring, nursing manager, tracheostomy educator, and social worker
    - Consider patient's overall prognosis and discuss role of neuroimaging in facilitating discussions regarding risk of neurodevelopmental impairment.
    - Social Services can be involved to evaluate family circumstances and home environment.
    - Pediatric Pulmonology consult to determine the ideal home ventilator mode and settings for each patient, timing and duration of home ventilator trials in the NICU and readiness for discharge home on the chosen mode/settings.
    - Pediatric Surgery consult
        - Assess need for g-tube placement at the time of tracheostomy.
- Tracheostomy educators
    - This team of nurses provides extensive education and training for families who are considering tracheostomy and home ventilator. They provide hands on training and simulations to prepare families to tackle and anticipate problems that could occur at home.
- Scheduling tracheostomy
    - Primary neonatology attending attends the *"Multidisciplinary Pretracheostomy Conference"* at TCH and presents to the group each patient that is being considered for tracheostomy. The required form for this meeting walks you through the steps of assessing patient and family candidacy and readiness for this procedure.

Peri-operative preparation for Tracheostomy

Access

Consider obtaining a midline PICC catheter if the patient does not already have a central catheter due to the need for stable access for 5-7 days after the procedure.

Sedation

Sedation should be selected according to patient's prior medication exposure and history.

Medications

- Acetaminophen 10-15mg/kg/dose q6-q8h IV (analgesia)
- Opioid continuous drip (to provide analgesia/sedation, selected based on prior exposure)
- Midazolam continuous drip (sedation ONLY)
- Additional pharmacotherapy should be discussed in conjunction with clinical pharmacist

Home Ventilation

- Minimal weight for home ventilation is usually 2500 g. Specifications for most home ventilators recommend weight 5 kg/above to allow delivery of minimal TV of 50 ml. However, these devices can deliver lower TV to smaller infants if operated in pressure control or pressure support mode.
- Most patients initially will receive SIMV/PSV but some may be moved to volume control ventilation on their conventional ventilator and average expired tidal volume recorded for several days. If patient is stable with a pediatric circuit then may be placed on the conventional ventilator. Adjustments in machine Vt again may be required. If patient remains stable he may then be switched to the home ventilator. This often requires additional adjustments in machine Vt. After a stable period on the home ventilator, infant seat/car seat testing of SpO_2 and PCO_2 in the semi-upright position should be performed. Modified positioning, as well as special infant seats, car seats or strollers may be required. At this point an HME may be introduced for short test periods to determine tolerance and proper size.

Equipment

- Pulse oximeter
- Suction device and supplies (including replacement tracheostomy tubes)
- Portable O_2 tank
- Tracheostomy care supplies
- O_2 concentrator
- Mask/bag

Other considerations

- Humidification – standard ventilator humidifier will be used for the ventilator at home.
- HME's (heat moisture exchanger) are used for short-term periods when patient and ventilator travel outside the home. If patient is stable, a period of 1-2 hours without humidification is acceptable.

Criteria for Discharge to Home Ventilation

- The AAP recommends training at least **TWO** family caregivers and assessment of their ability prior to discharge- one family member should be completely trained in all aspects of home ventilator care and a second family member should be trained in infant CPR, recognition of airway emergencies and replacement of tracheostomy tube. Acquisition of caregiver skills should be documented in the nursing discharge teaching records.
- Evaluation of physical adequacy of home setting by the home care company (lighting, power supply, access to emergency hospital facilities, etc.), social services, discharge coordinator are necessary. Medical care team should make formal request to the electric power provider company to place patient on a priority list for assistance in case of prolonged outage.

15.7 Conventional Ventilation of Preterm and Term Neonates

Importance of Adequate Lung Recruitment

In order for effective ventilation and pulmonary gas exchange to occur, lung inflation and recruitment must be adequate. In neonatal mechanical ventilation, this "open lung" strategy is achieved by applying adequate levels of PEEP (or MAP during HFOV). In infants without lung disease, appropriate PEEP is 4-5 cmH_20. For those with poorly compliant or atelectatic lungs, PEEP levels up to 8 cm H_2O may be necessary. Infants with severe airway anomalies from chronic lung disease, acquired or congenital tracheobronchomalacia, may need higher levels of PEEP to prevent airway closure and gas trapping. This should be differentiated from atelectasis and de-recruitment, as there is no lung collapse. Caution should be used when using excessive levels of PEEP, as they can be counterproductive with impaired hemodynamics and lymphatic drainage, and lung over distension causing decreased pulmonary blood flow with tamponade physiology.

Overview of Mechanical Ventilation

The preferred strategy for majority of neonatal patients is volume-targeted ventilation with Assist Control (A/C + VG) or SIMV (SIMV + VG). Volume targeted ventilation involves targeting a set tidal volume and adjusting other ventilator parameters to provide adequate minute ventilation with the lowest effective PIP.

HFOV is reserved as a rescue strategy for neonates who are unable to ventilate or oxygenate adequately on conventional ventilation. It should also be considered for infants requiring high pressures on conventional ventilator (and therefore at high risk for barotrauma), for patients with congenital anomalies such as CDH, and for infants with signs of severe air leak.

Volume Guarantee (VG)

"Volume-targeted" ventilation (VTV) allows inspiratory pressure to fluctuate to maintain a set tidal volume. A recent Cochrane meta-analysis of 12 studies reported significant reduction in death or BPD, severe IVH and air leak with VTV strategies as compared to traditional TCPL ventilation.

The VG mode on the Drager VN500 ventilators maintains consistent Vt delivery in the face of changing lung mechanics. In VG mode, the operator selects a target Vt and a pressure limit (Pmax) up to which the inflation pressure can be increased by the ventilator to achieve the targeted volume. Measurements of exhaled volume are made at the ventilator Y-connector, and the microprocessor adjusts working pressure to maintain the target volume. VG significantly reduces the proportion of delivered ventilator breaths that are outside the target range, promotes more stable oxygen saturation and reduces working pressures. The VG lowers the working PIP as lung compliance improves ("self-weaning") and may be a useful as a safety feature during periods of rapid change in compliance (such as following surfactant administration). VG can be used with A/C, SIMV or PC-PSV modes.

We recommend PC-A/C + VG as primary mode of ventilation for babies $\leq$ 32 weeks PCA. As with all modes of mechanical ventilation, blood gases, chest x-rays and indicators of ventilation must be monitored closely to avoid over ventilation.

Initial Settings

Mode: PC-A/C + VG with Dräger VN500

Vt Target: 4.0-6.0 ml/kg (for infants <1000g: 4.5-5.0 ml/kg and for infants >1000g: 4.0-4.5 ml/kg)

Adjustments: Vt can be changed in increments of 0.5 ml/kg.

Pmax (PIP limit): Initially set at 25-28 cm H_20. This allows the ventilator to choose adequate "working" PIP to deliver target Vt and overcome variable ET tube leaks. "Working" PIP will usually be below this set value. Subsequently, adjust Pmax to 3-5 cm above the "working" PIP.

Note: If the manual inflation button on the ventilator is pressed, the manual breath will be delivered at the set Pmax. Ventilator delivered manual breaths are not volume-controlled. For patient safety, adjust Pmax downward as lung compliance improves and as working PIP decreases. Maintain ~ 3-5 cm H_2O difference between Pmax and "working" PIP.

PEEP: $\geq$5cm

Table 15–4. Useful respiratory equations

Respiratory acidosis and pH	$\Delta pH = \Delta PCO_2 \times 0.008$
Mean airway pressure	$MAP = PEEP + \{(PIP - PEEP) \times [T_i / (T_i + T_e)]\}$
Oxygen content	$CO_2 = (1.39\ mL/g \times SaO_2 \times Hb) + (0.003\ mL/mm\ Hg \times PaO_2)$
Alveolar air equation	$PAO_2 = FIO_2(71\ 3) - PaCO_2 / 0.8)$
A-a oxygen gradient	$AaDO_2 = PAO_2 - PaO_2$
Oxygen index	$OI = MAP \times FIO_2 \times 100 / PaO_2$
Airway resistance–laminar flow	$R = (8 \times length \times viscosity) / (\sim \times radius^4)$
Compliance	$C = \Delta V / \Delta P$
Pressure drop as gas (of given density and viscosity) Flows through a tube (of given length [L] and radius [r])	$\Delta P = resistance \times (flow)^2$
	$Resistance = 0.32\ density \times L \times (Reynolds\ Number)^{-1/4} / (4 \sim {}^2r^5)$
	$Reynolds\ Number = 2 \times density \times (flow \times \sim r^{-1} \times viscosity^{-1})$

Low Tidal Volume Alarm: activated – this will alarm if expired Vt < 90% of set Vt

Trigger Sensitivity: set at highest sensitivity initially

Ti (Inspiratory Time): 0.3 sec (if slope 0.08 sec)

If Ti $\leq$ 0.25 sec is used, it may be necessary to decrease slope to 0.02-0.04 sec

Ventilator Back Up Rate (BUR): Use of 30/min has been associated with optimal spontaneous breathing and patient triggering of breaths. Infants with apnea or very low spontaneous breathing rate may require higher back up rates to maintain adequate minute ventilation. Back up breaths are unsynchronized and are reported to require higher working PIP to deliver target Vt.

Circuit Gas Flow: 6-8 LPM

Maintenance of VG Ventilation

"Low Tidal Volume" Alarm – can indicate Pmax is too low, presence of large ET tube leak, ET tube malposition, forced exhalation, abdominal "splinting", deterioration of lung mechanics or inadequate Ti to achieve pressure plateau.

ETT Leak - large leaks around ETT impair delivery of adequate Vt in any ventilator mode. VG usually can be used with up to 45-50% leak. DrägerVN500 provides automatic leak compensation by increasing inspiratory gas flow and wave form pattern. If persistent large leaks generate frequent Low Tidal Volume alarms or impair adequate ventilation, ensure proper ET tube position and adjust patient position. On occasion, persistent large leaks may require re-intubation with larger size tube.

Adjusting Ti - Effect of Ti can be evaluated with the ventilator graphic display. If Ti is too long, pressure plateau is held after cessation of inspiratory flow and there is no further increase in Vt.

Weaning VG Ventilation

When a patient is on VG mode, PIP is automatically weaned as lung compliance improves. In A/C mode, the infant controls the respiratory rate and therefore ventilator rate. Reducing the BUR has no effect on delivered rate and ventilation unless the infant's spontaneous respiratory rate is low or absent. Therefore, the main parameters reduced during weaning are FiO_2 and the target Vt. Do not wean target Vt $\leq$ 4 ml/kg because working inflation pressure will be very low and the infant will be breathing essentially on ET-CPAP with increased work of breathing and risk of fatigue or atelectasis. Under such circumstances, consider extubation. **(Table 15-5)**

Table 15-5. Assessing readiness for extubation				
	AC-VG	**SIMV-VG**	**SIMV-PC**	**AC-PC**
Tidal Volume or PIP	4-5 ml/kg (generating PIP <25)	4-5 ml/kg (generating PIP <25)	20	20
Mean Airway Pressure	8-10	8-10	8-10	8-10
PEEP	5-6	5-6	5-6	5-6
Rate	Spontaneous breathing above back up rate of 30	20-25	20-25	Spontaneous breathing above back up rate of 30
FiO_2	≤ 30%	≤ 30%	≤ 30%	≤ 30%

Indications for Extubation

- **Table 15-5**

Prolonged Mechanical Ventilation

Transitioning from acute phase to chronic phase:
The strategy for respiratory support in the acute phases of extreme prematurity is to avoid unnecessary intubation and mechanical ventilation to prevent secondary ventilator-associated lung injury. However, at some point during the respiratory course of premature infants with evolving BPD, lung structure and function may become sufficiently abnormal that attempts at extubation to nasal CPAP are not feasible. At this point, the goals of care need to be focused toward optimizing management on mechanical ventilation to support adequate gas exchange, reduce the work of breathing, and optimize growth and healing of the injured lungs.

Determining the specific type and level of respiratory support for infants with sBPD is challenging, as an optimal ventilator strategy required by these infants is frequently dramatically different than the strategy utilized in the first few weeks of life. **(Table 15-6)** The strategy must reflect the transition from lung mechanics in the first few days of life, which are dominated by low compliance, relative homogeneity, and normal airway resistance, to the mechanics that are seen in sBPD, dominated by high airway resistance, air trapping, and heterogeneous aeration. In the first week of life, lung mechanics suggest that a ventilator strategy aimed at the relatively uniform respiratory system with short time constants is reasonable and would include a fast rate, low tidal volume (Vt), short inspiratory time (Ti) strategy. In sBPD, the lung is characterized by different combinations of lung regions with different levels of airway resistance and altered distal lung compliance, which leads to highly diverse time constants. Thus, to enhance gas exchange, reduce the risk for atelectasis, decrease dead space ventilation, and perhaps lower pulmonary vascular resistance, the ventilator support strategy needs to change to high Vt and prolonged Ti strategy for chronic disease. (Weak recommendation, low quality of evidence).

Synchronized Ventilation

Synchronized modes are preferred in acute and chronic ventilation of infants to improve consistency of oxygenation, reduce work of breathing and reduce discomfort on the ventilator. VN500 ventilators detect patient respiratory efforts by measuring ET tube airflow with a hot wire anemometer.

Table 15-6. Comparison of ventilator strategies and goals during progression of early disease to established BPD.	
Early (BPD prevention)	**Strategies to prevent acute lung injury** 1. Low tidal volumes (5-8 ml/kg) 2. Short inspiratory times 3. Increased PEEP as need for lung recruitment without over distention (as reflected by high peak airway pressures) 4. Achieve lower FiO_2 **Strategies for gas exchange:** 1. Adjust FiO_2 to target SpO_2 (range: 91%-95%) 2. Permissive hypercapnia
Late (established BPD)	**Strategies for effective gas exchange:** 1. Marked regional heterogeneity • Larger tidal volumes (10-12 mL/kg) • Longer inspiratory times (≥0.6 s) 2. Airways obstruction • Slower rates allow for better emptying, especially with larger tidal volumes (10-20 bpm) • Complex roles for PEEP with dynamic airway collapse 3. Interactive effects of ventilator strategies • Changes in rate, tidal volume, inspiratory and expiratory times, and pressure support are highly interdependent • Over distension can increase agitation and paradoxically worsen ventilation 4. Permissive hypercapnia to facilitate weaning 5. Adjust FiO_2 to target high oxygen saturations
Adapted and modified from Abman SH and Nelin LD. Management of the infant with severe bronchopulmonary dysplasia. In: Bancalari E, ed. The newborn lung: neonatology questions and controversies. Philadelphia (PA): Elsevier Saunders; 2012. p. 407-25. ©2020 Elsevier	

Current evidence is limited to observational studies, which report reduced mean airway pressure, reduced work of breathing, reduced need for sedation, less fluctuation in cerebral blood flow velocity, and reduced ventilator days associated with use of synchronized ventilation as compared to non-synchronized ventilation. Most current neonatal ventilators provide synchronized ventilation as SIMV, Assist–Control (A/C) or Pressure Support Ventilation (PSV). In each of these modes, the patient breathes spontaneously while triggering some or all of the ventilator support breaths. Each of these modes of synchronized ventilation provide for a mandatory back up ventilation rate in case of apnea.

SIMV

In SIMV, the patient's spontaneous respiratory efforts trigger a preset number of mandatory breaths per minute (usually set at 20 - 40). In between mandatory ventilator breaths additional spontaneous breaths occur entirely with patient's effort, without support. The operator sets the ventilator breath rate, PIP (or Vt) and Tinsp.

Initial Ventilator Settings

Mode	SIMV + PEEP (VG preferred)
Rate	20 to 40 per minute
PIP	20 to 25 cm H_20
	(if VG not used, adjust PIP as needed to achieve a tidal volume of 4-6 ml/kg)
PEEP	5 cm H_2O
Ti	0.3 -0.4 seconds
FiO_2	Adjust for desired saturation

Ventilator Adjustments

Oxygenation is a function of FiO_2 and mean airway pressure, which is determined by the PIP, PEEP, and the inspiratory time. These parameters influence PaO_2.

Ventilation (minute ventilation) is a function of respiratory rate and tidal volume. These settings influence $PaCO_2$. In general, moderate hypercarbia (PCO_2 ~ 60 mmHg) is acceptable, but hypocarbia (PCO_2 less than 35 mmHg) should be promptly corrected since it can be reflective of over distention of the lung by high-volume ventilator breaths and hypocarbia can cause decrease in cerebral blood flow. Continued vigilance is necessary to detect improving lung compliance to avoid lung over distention and alveolar rupture. This may occur rapidly after a dose of exogenous surfactant.

If oxygenation remains poor or severe hypercapnia occurs on SIMV, alternative management may be required. If PIP of 30 cm H_2O or greater or MAP >12 to 14 cm H_2O is necessary with conventional ventilation, or if severe hypercapnia persists, the patient is a candidate for rescue HFOV.

Indications for Extubation

Table 15-5 displays ventilator settings for which to consider extubation in most term and preterm infants. Depending on the clinical situation, some infants may either tolerate extubation at higher settings or be suboptimal candidates for extubation at these settings for non-respiratory reasons.

Assist–Control (A/C)

In A/C mode, the patient breathes at his own spontaneous rate and each patient breath triggers a ventilator breath. A backup mandatory IMV rate is set by the user in case of apnea. In theory, A/C mode optimizes synchronization of patient and ventilator breaths and unloads work associated with asynchronous breathing. One observational study reported lower PIP, reduced variability of oxygenation and reduced work of breathing with AC + VG as compared to SIMV + VG. However, no specific long-term benefits have been established for this technique.

In SIMV mode, when a patient triggers a breath over the set rate, the machine will not give a breath (but can support it with Pressure Support, if set). In A/C mode, the machine will give a full machine breath for every breath effort. Both A/C and SIMV are Pressure Controlled modes and differ on the amount of support delivered for each patient effort above the set rates. The full ventilator breath can be set for PIP, or for Vt if VG function added. The Pressure support component will always be a level of pressure over PEEP.

Pressure Support Ventilation (PSV)

PSV is a patient triggered mode of ventilation similar to A/C. However, unlike A/C, the patient's own breathing pattern determines the inspiratory flow pattern, Tinsp, Texp and I:E ratio. With each breath, inspiratory gas flow is delivered at a set pressure until that inspiratory flow decreases to a predetermined level (usually 15-25% of peak flow). PSV may be used alone or in combination with SIMV. In adult studies, PSV reduces work of breathing, improves patient comfort and allows better patient control of respiratory rate and flow characteristics during spontaneous breaths. In limited studies in neonates, SIMV + PSV has been associated with improved consistency of SpO_2 values and reduced need for mechanical ventilation on day 28 of life compared to SIMV alone. However, total duration of mechanical ventilation and oxygen dependency at 36 weeks GA was unchanged. PSV levels $\geq$10cm H_2O above PEEP may be necessary to overcome work of breathing of most ventilator circuits and small ET tubes. Levels of 10-15 cm H_2O are associated with optimal patient comfort and reduction in work of breathing.

Chronic Mechanical Ventilation

Infants with severe BPD may require a more prolonged period of mechanical ventilation. Poor chest wall function with atelectasis and pulmonary edema causing low lung compliance are dominant features of this disease process known as "new BPD". As a group, such infants have significantly reduced ventilation and effective tidal volumes. During this period, continuing acute care ventilator strategies such as A/C + VG or SIMV + VG are appropriate for many. Attempts to minimize FiO_2 and Vt should continue, but current evidence suggests that Vd/Vt worsens and target Vt necessary to maintain adequate ventilation rises with advancing postnatal age in ventilator dependent ELBW infants. Target Vt required averages 6 ml/kg (range 5-8 ml/kg) beyond 3 weeks of age. Most of these infants progressively improve over a variable period of time. As lung function improves they can be weaned by reductions in PIP or target Vt (VG mode) and vent rate.

A small proportion of infants remain ventilator dependent and evolve into "classic BPD". During this evolution, uneven airway resistance and anatomic / physiologic dead space increase. Continued use of the AC + VG mode in patients with significant uneven airway obstruction and long airway time constants may result in progressive gas trapping and hyperinflation. These patients should be evaluated closely to

identify a long-term ventilator strategy. Uneven airway obstruction and high Vd/Vt are major components of the pulmonary physiology of "classic" BPD, and some develop symptomatic bronchomalacia. Chronic ventilation represents a significant challenge. Some patients require a more selective ventilator strategy with slower ventilator rates, longer inspiratory time and splinting of airways with moderately high levels of PEEP. This often necessitates use of higher tidal volumes (10-12 mL/kg) than those employed for acute care ventilation and longer inspiratory times (≥0.6 s). These patients may benefit from a demand flow ventilator which allows for the combination of SIMV + PSV + PEEP which matches inspiratory gas flow more closely to patient demands. Use of volume-targeted ventilation or VG is desirable in attempt to maintain consistency of delivered tidal volume, but only bedside evaluation can determine whether a pressure-controlled or volume-targeted strategy maintains the best combination of patient comfort, stability of minute ventilation and adequate oxygenation. Pressure controlled TCPL ventilation may be superior for optimizing distribution of ventilation in patients with severe uneven airway obstruction. Gas trapping can occur if ventilator rates greater than 20-30/min are employed in face of severe, uneven airway obstruction. Likewise, if rapid spontaneous breathing continues after initiating PSV, inadequate expiratory time and lung hyperinflation may occur.

Close monitoring is necessary in attempt to optimize oxygenation and reduce hypoxia, minimize PVR and risks of high RV afterload leading to cor pulmonale. Reductions in FiO_2 or ventilator support should be done in small increments with several days of observation for signs of deterioration between weaning of each parameter.

Over time, lung growth and remodeling result in increasing stability of oxygenation and improving lung mechanics. When oxygen requirements fall to 50% or less, the patient can be "tested" for improvement by a small reduction in ventilator rate or PIP (Vt). Infants on SIMV + PSV + PEEP can be slowly weaned by increasing spontaneous breathing time on PSV alone every few days. **Weaning must be done carefully because several days may be required for these patients to exhibit signs of clinical deterioration after a small reduction in level of support.**

After weaning from mechanical ventilation, most infants with moderate-severe BPD require supplemental oxygen for additional weeks or months. Close monitoring of SpO_2 to detect subtle hypoxia is critical **(Ch 15.9-Bronchopulmonary Dysplasia)**. The role of CPAP or HFNC for post extubation support in BPD infants is poorly studied. CPAP devices may produce agitation in older infants. Although the theoretical benefits of enhanced diffusive effects and CO_2 removal reported for HFNC systems seem desirable, little objective data exists at present to guide use of this technique in infants with BPD.

15.8 High-frequency Oscillatory Ventilation (HFOV)

HFOV is a technique for maintaining effective gas exchange and oxygenation with lower tidal volumes than those usually employed for conventional mechanical ventilation. This may reduce airway distension during tidal ventilation and potentially reduce airway injury.

Some centers use HFOV electively as a primary ventilation strategy for RDS. Current evidence does not demonstrate any long-term benefits for this strategy when compared to rescue use. Although individual studies have reported a reduction in risk of BPD or long-term airway dysfunction, this effect was inconsistent across studies. Pulmonary air leaks occurred more frequently in the HFOV group.

Complications include tracheal injury, pulmonary hyperinflation, and air leak. Over distension of the lung with impairment of thoracic venous return could increase risk of IVH in preterm infants.

Indications for Use

- **Respiratory failure:** infants who are ≥ 34 weeks GA and at high risk for requiring ECMO, with or without iNO, can benefit from HFOV**.** This includes infants with PPHN, sepsis, pneumonia, RDS, meconium aspiration, CDH or pulmonary hypoplasia. One study reported a reduced need for ECMO in patients in these categories treated with HFOV plus iNO as compared to either modality alone. Of note, iNO can be delivered via HFOV.
- **Severe, acute lung disease**. HFOV should be considered when conventional ventilator PIP reaches or exceeds 28- to 30- cm H_2O or mean airway pressure exceeds the 12- to 14-cm H_2O range (10 cm H2O in babies < 1000 g) (weak recommendation, low quality evidence). This strategy attempts to minimize peak airway pressures applied to the lung. Although short-term improvement in oxygenation or patient status at 28 days of age has been reported, meta-analysis of studies using the current recommended lung recruitment strategy has not demonstrated any superiority in long-term survival, neurologic status, or lung function.
- **Severe air-leak syndrome** producing persistent hypoxemia despite conventional fast-rate ventilation with short inspiratory times may benefit from HFOV, but no superiority of this technique for management of air leaks has been demonstrated.

Physiology

Gas exchange on the oscillator appears to result from bias flow in the airway tree induced by the high-frequency pulsations as well as by enhancement of molecular diffusion. These effects are superimposed upon the usual mechanisms of pendelluft, cardiogenic mixing, and convective flow to short pathway lung units. The basic concepts of the three-compartment lung model remain operative in oscillator decision making. Open, poorly ventilated lung units determine PO_2 and well-ventilated units determine PCO_2. In some PPHN patients, distribution of ventilation is uniform (e.g., "pure" PPHN), while in others it is not uniform (e.g., meconium aspiration syndrome). It is important to differentiate this before initiating HFOV, just as with conventional ventilation, because the ventilator strategy will be influenced by characteristics of regional time constants in the lung. Just as with conventional mechanical ventilation, the approach to ventilation (PCO_2) and oxygenation (PO_2) should be evaluated independently as each is influenced by specific parameters.

Management

Current clinical guidelines are based primarily upon strategies for the Sensor Medics oscillator. The device has six controls. For most clinical situations, only mean airway pressure (Paw) and oscillatory pressure amplitude (ΔP) are varied. Frequency is less often changed based on PCO_2. Bias flow, piston centering, and percent inspiratory time are set initially and rarely vary throughout the course.

Ventilation (PCO_2)

Manage ventilation by adjusting ΔP. At a given mean airway pressure, CO_2 removal occurs via the high-frequency tidal volume (bias flow) created by the ΔP. With a 3.5 mm ET tube, 80% of the proximal oscillatory pressure will be attenuated across the tube. With a 2.5 mm ET tube, 90% will be lost. Thus, it is desirable to use the largest, shortest ET tube possible and to be certain the tube is as straight as possible.

Increasing ΔP improves ventilation and lowers PCO_2. If PCO_2 remains excessive despite maximum ΔP, the frequency may be reduced to take advantage of the frequency dependence of ET tube attenuation. At lower frequency, there is less ET tube attenuation and a larger distal ΔP (and oscillatory tidal volume) in relation to proximal ΔP. This secondary strategy may lower PCO_2 and increase PO_2 levels, particularly if uneven airway obstruction is present. If ventilation is excessive (PCO_2 too low), lower ΔP.

Control of Oxygenation (PO_2)

Oxygenation is managed by changes in mean airway pressure (Paw). Increasing Paw improves PO_2. The general strategy is to recruit and maintain normal lung volume using relatively high Paw during the acute phase of lung disease. Paw is then weaned as the disease process improves.

Begin HFOV with Paw set 1 to 2 cm H_2O higher in VLBW infants and 2 to 3 cm H_2O higher in term babies than the previous level on the conventional ventilator just before initiating HFOV. Increase the Paw until adequate oxygenation is achieved. In multicenter studies, the average Paw for initial treatment was 11 to 19 cm H_2O, however some patients may require higher levels. When adequate oxygenation occurs, concentrate on weaning FiO_2. When FiO_2 falls below 60% to 70%, begin to wean Paw in 1- to 2-cm H_2O decrements.

Monitoring

- blood gases – to monitor PCO_2 and PO_2
- chest X ray – to estimate lung volume
- pulse oximetry – to monitor saturations

Special Considerations

- In non-homogeneous lung diseases such as meconium aspiration, pneumothorax, and pulmonary interstitial emphysema (PIE), emphasize weaning Paw and ΔP, while accepting higher $PaCO_2$, lower PaO_2, and $FIO_2 > 0.7$. These disorders have uneven expiratory time constants and therefore at increased risk of gas trapping.
- Remain vigilant to avoid over-inflating the lung on HFOV. Inadvertent increases in lung volume and intrapleural pressure associated with improving compliance could decrease venous return and circulatory function, increase cerebral vascular congestion, or result in air leak.
- Serial chest X-rays are necessary to monitor for hyperinflation. A suggested schedule is:
  - first chest x-ray within 1 to 4 hours of initiating HFOV
  - every 12 hours during the first 24 hours on HFOV
  - then once daily and as needed based on clinical picture
- On chest radiograph, the diaphragms should be at the T8.5 to T9 level, if lung anatomy is normal. In pulmonary hypoplasia or CDH, this estimate cannot be used, so do not try to inflate the lungs to these volumes.
- Maintain an unrestricted airway during HFOV. Limit suctioning to minimal frequency necessary to maintain airway patency.
- Sudden, unexplained bradycardic events that occur with no other demonstrable cause might signal rapid improvement in lung compliance and the need to wean pressures more aggressively. Sudden increase in PCO_2 and decrease in PO_2 usually indicates airway obstruction, which may be due to secretions in the airway or inadequate positioning of the ETT.
- Patient and head position should be rotated every 3 to 4 hours with cares to avoid pressure injuries to the skin and dependent atelectasis. Use of a swivel on the end of the HFOV tubing facilitates rotation of the head in infants who are unstable.

Weaning

Wean to conventional ventilation when:

- air leak, if present, has resolved,
- Paw has been weaned to the 10- to 12-cm range,
- ΔP has been weaned to less than 30 cm, and
- blood gases are stable.

High-frequency Jet Ventilation (HFJV)

High frequency jet ventilation (HFJV) is a form of high frequency ventilation used in conjunction with a conventional ventilator. HFJV operates in conjunction with a conventional ventilator to provide gentle ventilation that may be beneficial in certain patients such as those at risk for air leak.

The Bunnell LifePulse® 204 Jet Ventilator is used in Baylor nurseries. It is a pressure-limited and time-cycled ventilator with an adjustable rate, PIP, and I-time. Inhalation is generated by a pinch valve to generate a stream of high frequency pulses. Gas is delivered into the airway at a very high velocity via an endotracheal tube adapter which produces flow streaming with gas flowing down the core of the bronchial tree. Exhalation occurs passively, swirling around this inner inhalation stream. A conventional ventilator is used in tandem with the Jet ventilator to generate PEEP and conventional mechanical breaths (or sigh breaths).

Certain differences exist between the oscillator and the jet. HFOV provides both active inhalation and exhalation while the jet allows for passive exhalation. The I:E on the oscillator is usually at 1:2 (Ti 33%) whereas on the jet it can be adjusted between 1:4 to 1:12. The jet is used in conjunction with a

Table 15-7. Initial jet ventilator settings

Jet Parameter	Recommended setting	Comments
Rate	360-420	Usually start with 420 and adjust in increments of 60
Ti	0.02	Don't change
PIP	20-25	Usually 1-2 below PIP on conventional ventilator
CMV Parameter		
Rate	0-5	Avoid sigh breaths if possible
PEEP	5-12	Initiate PEEP based on approximate MAP provided by CMV
Ti	0.4-0.6	
PIP	50% of Jet PIP or 5-8 above PEEP	Can cause lung injury and shearing

conventional ventilator allowing for the option of sigh breaths to assist in lung recruitment if needed.

Indications for Use

- **Target population:**
  - Patients who have failed conventional ventilation or are requiring high support on conventional ventilation that could cause lung injury
  - Patients who have failed high frequency oscillatory ventilation
- **Indications:**
  - Air leak syndrome: PIE, pneumothorax, and lung blebs
  - Non-homogenous lung disease: MAS, CDH

Management

- **Initiation of Jet Ventilation**
  - The initial recommended settings for the jet ventilator are in **Table 15-7.**
  - Obtain a blood gas within 30 minutes of starting jet ventilation and obtain a CXR within 1 hour.
- **Maintenance of Jet Ventilation**
  - General management strategies
    - » Jet ΔP (PIP-PEEP) is the primary determinant of $PaCO_2$. To optimize ventilation, adjust Jet ΔP.
    - » (For table 2-8, box should read Increase PEEP while keeping PIP constant. This increases the MAP to improve oxygenation and decreases ΔP to improve hypocarbia.)
    - » PEEP on conventional ventilator is the primary determinant of MAP and oxygenation. To optimize oxygenation, adjust PEEP on conventional ventilator.
    - » Avoid IMV or sigh breaths with the exception of using it temporarily for recruitment of collapsed airways/alveoli. For sigh breath PIP, can either use 50% of HFJV PIP or 5-8 cm H_2O above PEEP.
  - **Blood gases:** consider frequent blood gas monitoring to titrate ventilator support based on changing compliance and lung mechanics.
    - » Titrating support **Table 15-8**
- **Weaning from Jet ventilation**
  - Jet can be weaned to either extubation or conventional ventilator
  - **Oxygenation:** Once oxygenation is adequate and the patient is ready to be weaned, follow these steps:
    - » Only wean FiO_2 until ≤ 0.50, unless over-inflated
    - » Once $FiO_2 \leq 0.50$ and CO_2 is acceptable, decrease PEEP and Jet PIP by 1 cm H2O Q4 - 8h
    - » If $FiO_2 \leq 0.30$ - 0.35, decrease PEEP and PIP by 1-2 cm H_2O Q2 - 4h to avoid over-inflation
    - » Also decrease PIP of conventional sigh breaths at the same time and by the same amount that you decrease the PEEP (e.g., PIP 16 and PEEP 10 to PIP 15 and PEEP 9).

Table 15-8. Titrating support

		Oxygenation		
		Inadequate or poor (increase FiO_2)	**Adequate or Good**	**Too Good (decrease FiO_2)**
Ventilation	**Over Ventilated CO_2 is too low**	Increase PEEP while keeping PIP constant. This increase MAP while decreasing ΔP to prevent hypocarbia	Decrease ΔP by decreasing PIP and consider increasing PEEP if needed to keep the MAP constant to prevent atelectasis. If over inflated just decrease TV	Decrease PIP until CO_2 is acceptable, If still over inflated decrease PIP and PEEP by the same amount
	Appropriate Ventilation CO_2 is adequate	Increase both PIP and PEEP by the same amount to keep ΔP unchanged while increasing the MAP	**No changes**	Decrease PEEP and PIP by the same amount to decrease MAP to avoid over inflation. This keeps ΔP unchanged
	Under Ventilated CO_2 is too high	Increase both MAP and ΔP by increasing PIP until CO_2 is acceptable. If oxygenation is still poor increase both PIP and PEEP by the same amount to keep ΔP constant while increasing MAP	Increase ΔP by increasing PIP	Increase ΔP by decreasing PEEP to avoid over inflation until CO_2 is acceptable. If still over inflated decrease both PIP and PEEP by the same amount to decrease MAP

Table 15-9. Extubation Criteria	
Parameter	**Setting**
PIP	< 20
PEEP	< 7-8
ΔP	< 10
FiO_2	≤ 0.35

- Ventilation
  - » Reduce Jet PIP (ΔP) at least 1-2 cm H_2O per change whenever $PaCO_2$ decreases below threshold, until minimal PIP (< 20) is reached, with a ΔP < 10.
  - » If $PaCO_2$ is still too low (< 35 mm Hg) on minimal PIP and minimal ΔP (3 cm), and if the infant is not ready for extubation, decrease rate to 300 bpm and then to 240 bpm to decrease alveolar ventilation.
- Extubation
  - » Patients are ready for a trial of extubation when they meet the criteria in **Table 15-9.**

Special Considerations

- **Atelectasis –** increase PEEP, utilize CMV sigh breaths (use it with great CAUTION and temporarily)
- **Hypotension –** decrease PEEP and PIP to decrease MAP or decrease rate (lowest of 240) to minimize air trapping
- **Over-inflation –** first limit or eliminate IMV, then consider decreases in PEEP, PIP, or Jet rate
- Servo pressure monitoring: represents gas flow to the patient to achieve set PIP
  - Servo Pressure increases with improving lung compliance or airway resistance as well as increasing leaks in vent circuit
  - Servo pressure decreases with worsening lung compliance/resistance, obstructed ETT, secretions, tension pneumothorax, right main stem intubation
- Chest vibration ("wiggle")
  - If decrease in chest wiggle, consider suctioning to relieve ETT obstruction and checking ETT positioning
  - If increase in chest wiggle, check a blood gas and wean

15.9 Bronchopulmonary Dysplasia

Bronchopulmonary Dysplasia is an important morbidity in preterm infants that results from altered course of lung development and disruption in the balance between lung injury and repair mechanisms. Despite its complexity, the disease has been defined simply by the type of treatments used to address its symptoms rather than the intricate pathophysiology.

BPD was initially described by Northway in 1967 and the definition has since been modified in 1978, 1988, 2001, and 2018. Currently, the definition that is commonly used for research purposes is the NICHD definition from 2001 which classifies infants requiring at least 28 days of oxygen as having BPD and categorizes the severity of disease based on respiratory support at 36 weeks PMA. On the other hand, the definition that many units use to track their outcomes over time is oxygen requirement at 36 weeks PMA. The latest NICHD consensus based definition is listed below **(Tables 15.10a and 15.10b).**

Table 15-10a. Definition of BPD	
Severity	**Definition**
None	O_2 treatment <28 days* and breathing room air at 36 wk PMA or discharge home, whichever comes first
Mild	O_2 treatment at least 28 days* and breathing room air at 36 wk PMA or discharge home, whichever comes first
Moderate	O_2 treatment at least 28 days* and receiving <30% O_2 at 36 wk PMA or discharge home, whichever comes first
Severe (type 1)	O_2 treatment at least 28 days* and receiving >30% O_2 or CPAP/HFNC at 36 wk PMA
Severe (type 2)	O_2 treatment at least 28 days* and receiving mechanical ventilation at 36 wk PMA

*A day of oxygen treatment is considered treatment with >21% inspired oxygen for more than 12 hours. The consensus workshop definition states that "infants treated with oxygen >21% and/or positive pressure for non-respiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress."

Table 15-10b. Suggested refinements to the definition of BPD

A premature infant (<32 weeks' gestational age) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks PMA requires 1 of the following FiO_2 ranges/oxygen levels/O_2 concentrations for ≥3 consecutive days to maintain arterial oxygen saturation in the 90%-95% range.

Grades	Invasive IPPV	N-CPAP, NIPPV, or nasal cannula ≥ 3 L/min	Nasal cannula flow of 1- <3 L/min	Hood O_2	Nasal cannula flow of <1 L/min
I	---	21	22-29	22-29	22-70
II	21	22-29	≥30	≥30	>70
III	>21	≥30			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (eg, necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc).				

*Excluding infants ventilated for primary airway disease or central respiratory control conditions. Values are percents.
CPAP, continuous positive airway pressure; *IPPV*, intermittent positive pressure ventilation; *N-CPAP*, nasal continuous positive airway pressure; *NIPPV*, noninvasive positive pressure ventilation.

Etiology and Pathogenesis

BPD results from immature lung's susceptibility to risk factors—both prenatal and postnatal. Prenatal factors include placental dysfunction, fetal growth restriction, chorioamnionitis, and genetic predisposition. Postnatal factors that potentiate lung injury include surfactant deficiency, mechanical ventilation, excessive oxygen administration, infection, microbial dysbiosis, and a hemodynamically significant patent ductus arteriosus. Mechanisms of injury include volutrauma, barotrauma, inflammation, impaired vasculogenesis, and arrested alveolar development.

Clinical Course

Most patients with BPD today have been exposed to antenatal steroids, received surfactant, and are usually premature infants with continued need for mechanical ventilation after the first 48 hours of life. This "new BPD" is characterized by impaired alveolarization and vascular growth. In the evolving phase, lungs are opaque on chest x-ray rather than exhibiting uneven hyperinflation. A subset of extremely immature infants may develop the more severe and prolonged "classic" course of BPD and require prolonged mechanical ventilation with high levels of support. Classic BPD is dominated by uneven airway obstruction, bronchomalacia, and hyperinflation.

Phenotypes of BPD

Because the etiology of BPD is complex and multifactorial, infants with the disease can have varied clinical manifestations. These manifestations are the result of *overlapping* phenotypes and the clinical course is dictated by the relative contribution of each component. Three different categories of disease have been described: lung parenchymal disease, pulmonary vascular disease, and airway disease. Therefore, it is important to avoid a "one-size-fits-all" approach to the management of these patients.

Acute Course and Diagnosis

An initially improving clinical course during the first 1 to 2 weeks of life is followed by deteriorating pulmonary function, rising oxygen requirements, and opacification of lung fields that were previously clearing on chest radiograph. Wide swings in PaO_2 and O_2 saturation values are characteristic. Despite treatment of PDA, management of apnea, and treatment of any infection, the infant remains ventilator-dependent.

Course of Chronic Ventilator Dependency

Features of this phase include bronchiolar metaplasia, hypertrophy of smooth muscle, and interstitial edema producing uneven airway obstruction with worsening hyperinflation of the lung. Obliteration of a portion of the pulmonary vascular bed is accompanied by abnormal growth of vascular smooth muscle in other sites. Active inflammation slowly subsides to be replaced by a disordered process of structural repair. During the early weeks of this phase, infants remain quite unstable with frequent changes in oxygen requirement and characteristic episodes of acute deterioration that require increases in ventilator support.

After 6 to 8 weeks, the clinical course becomes more static as fibrosis, hyperinflation, and pulmonary edema come to dominate the clinical picture. Increased airway smooth muscle is present and tracheobronchomalacia may become apparent as episodes of acute airway collapse with severe hypoxemia. This phase evolves over 3 to 9 months, during which time growth and remodeling of lung parenchyma and the pulmonary vascular bed is associated with gradual improvement in pulmonary function and heart-lung interaction.

Management of BPD

Primary goals of comprehensive BPD management include:

- **Optimizing respiratory support**
- **Optimizing nutrition for growth and repair**
- **Neurodevelopmental Support**, including treatment of narcotic or sedative habituation
- **Prevention of cor pulmonale**
- **Prevention of infection** with an emphasis on removing endotracheal tube as early as possible (as it is a portal of entry for organisms that could cause pneumonia)

Optimizing Respiratory Support

In babies with established severe BPD, appropriate tidal volume delivery, avoidance of atelectasis and minimizing oxygen toxicity should be incorporated in the ventilator management strategy. The lungs have high airway resistance, air trapping, heterogeneous aeration and altered distal lung compliance, which leads to highly diverse time constants. Thus, to decrease dead space ventilation, and lower pulmonary vascular resistance, the ventilator support strategy needs to change to high Vt and prolonged Ti strategy for chronic disease. (Weak recommendation, low quality of evidence). Assessment of the adequacy of respiratory support can be based on gas exchange, maintenance of oxygen saturations, work of breathing, and tolerance of routine care (including OT/PT and developmental care).

Oxygen Use and Monitoring

Oxygen use and monitoring is a critical component of BPD care. Chronic or recurrent alveolar hypoxia exacerbates pulmonary hypertension and increases mortality risk for patients with BPD. In moderate to severe BPD, supplemental oxygen is used to minimize pulmonary vascular resistance and prevent cor pulmonale. However, oxygen also may exacerbate lung injury and risk of retinopathy in preterm infants. In preterm infants with evolving BPD who have not reached full retinal maturation, adjust FIO_2 to maintain SpO_2 in the 90-95% range. Older infants with severe BPD or echocardiographic evidence of pulmonary hypertension require close attention to oxygen use and monitoring with daily review of oxygenation.

The need for supplemental O_2 often extends well beyond the period of positive pressure ventilator support. The impact of oxygen on the outcome of BPD cannot be overemphasized. Attempted reductions in FiO_2 must be monitored closely and adverse effects on PVR or pulmonary edema may not be apparent for several days after a reduction. **(Ch. 15.5-Weaning from CPAP and Nasal Cannula)**

Nutritional Support and Fluid Restriction

Infants with moderate to severe BPD may benefit symptomatically from fluid restriction to control pulmonary edema. The balance between fluid restriction, adequate growth, and stability of lung function requires careful consideration. In preterm infants, modest fluid restriction (150 ml/kg/day) and proper long-term nutrition often can be achieved using fortified human milk or one of the commercial mineral-enhanced premature formulas. These provide good quality protein intake,

trace nutrients, and increased calcium and phosphorus supplements to optimize bone mineral uptake. Severe impairment of lung mechanics may necessitate restricting fluids to 110-130 mL/kg/ day. **(Sec 13-Nutrition)** Patients should be weighed every 3-7 days; and length and head circumference measured weekly. Nutritional and growth parameters should be reviewed frequently with a pediatric nutritionist.

Neurodevelopment

The care environment is critical for chronically ventilator-dependent infants. The adverse impact of the intensive care environment upon development must be blunted during a long period of hospitalization.

The time course of evolving BPD coincides with critical period of neurodevelopment. Consequently, a primary goal of mechanical ventilation must be to support the infant's ability to derive optimal benefit from developmental therapies and maintain engagement with their environment, caregivers, and family. If support or oxygen is weaned too quickly as demonstrated by fatigue with developmental therapies, the infant's neurodevelopmental progress can be compromised.

A multidisciplinary team, directed by an experienced neonatologist and pediatric pulmonologist, can define each infant's needs and maintain focus on a consistent long-term plan of care. In hospital, parents and care providers must work together to plan a friendly, play-oriented environment that includes the infant's own toys and possessions when applicable. Control light and noise. Some patients have associated neurologic dysfunction, hearing deficits, or feeding disorders, and the resources to manage these problems must be integrated into weekly schedules.

Screening

Hearing screens (AABR) should be performed when the infant meets hearing screen criteria to allow early intervention by an audiologist, if needed. **(Ch 12.10-Newborn Screening)** Developmental assessment should begin during the hospital stay and continue as part of long-term follow-up after discharge. Specific attention to oral-motor dysfunction and feeding disorders may be necessary.

Surveillance and Management of Pulmonary Hypertension in the Patient with BPD

The presence of moderate to severe pulmonary hypertension in BPD patients has been associated with risk of mortality.

Diagnosis and Treatment:

- Echocardiography to assess for tricuspid regurgitant jet velocity, septal flattening, RV dilation, and other parameters of RV function. Cardiac catheterization should be considered prior to initiating long-term therapy to assess severity of disease and potential contributing factors, such as left ventricular diastolic dysfunction, anatomic shunts, pulmonary vein stenosis, and systemic collaterals
- If pulmonary hypertension present:
  - Evaluate and treat respiratory disease, , aspiration, and structural disease
  - Avoid hypoxemia (maintain oxygen saturation between 92% and 95%)
  - Consider therapeutic agents
- Therapies:
  - iNO at 20 ppm for symptomatic or severe pulmonary hypertension
  - Transition from iNO to sildenafil when feasible, starting at 0.5 mg/kg q8h and advancing to 2 mg/kg q6h. Monitor for desaturations secondary to V/Q mismatch and systemic hypotension.
  - If unable to wean from iNO, consider the addition of an ETRA or a prostacyclin analog. Liver function should be monitored closely if on an ETRA.
- Monitoring: Cardiac catheterization or serial echocardiography is recommended to monitor response to therapy.

Other associated cardiovascular abnormalities include left ventricular hypertrophy, systemic hypertension and development of systemic to pulmonary collaterals. The contribution of these collaterals to the course of BPD is poorly understood.

Medications

Diuretics

Systematic reviews have demonstrated improvement in short-term lung mechanics and reduced need for supplemental oxygen among premature infants with BPD treated with diuretics. Potential side effects include severe electrolyte imbalance, increased calcium loss and osteopenia, ototoxicity and nephrocalcinosis. The most commonly used diuretics are thiazides and furosemide.

Furosemide

Furosemide, a potent loop diuretic, improves short-term lung function by both its diuretic effect and a direct effect on transvascular fluid filtration. In a retrospective cohort study of infants with severe BPD, furosemide was noted to be one of the most frequently prescribed medications. Another retrospective cohort study of infants born at 23-29 weeks gestational age found an association between increase in the proportion of furosemide exposure days by 10 percentage points and decrease in incidence of BPD (4.6 percentage points, P=0.001) and BPD/Death (3.7 percentage points; P = 0.01). Intermittent use of furosemide when a positive fluid balance is associated with a deterioration in clinical respiratory status nay be considered by the neonatologist. If chronic therapy is initiated, serum electrolytes should be monitored at least on a weekly basis.

Thiazides

Thiazide diuretics act upon the early distal renal tubule. Hydrochlorothiazide (2 mg/kg per dose twice daily) or chlorthiazide (20 mg/kg per dose twice daily) are usually administered enterally. In some studies, this regimen has improved lung mechanics and reduced urinary calcium excretion; in other studies the regimen has been less effective. Thiazide diuretics may be associated with increased loss of potassium and phosphorus. These agents are less potent than furosemide.

Chloride Supplements

Chronic diuretic therapy induces hypochloremic metabolic alkalosis with total body potassium depletion. Infants receiving chronic diuretics need chloride supplementation of 2 to 4 mEq/kg/day in addition to usual nutritional needs. This should be provided as potassium chloride with no sodium chloride

provided unless serum sodium < 130 mEq/L. Serum chloride should be > 90 mg/dL and never maintained < 85 mg/dL. In general, total potassium and sodium chloride supplementation should not exceed 5 mEq/kg/day without consideration of reducing diuretic use. The combination of furosemide and thiazide is untested and may have a severe effect on electrolytes.

Inhaled Medications

It is important to note that although wheezing events are common, episodes of true reactive airway disease are uncommon during the first 2-3 months of life in most infants with BPD. Bronchomalacia and airway collapse are being recognized with increasing frequency in infants with signs of airway obstruction or sudden onset of reduced air flow.

Short Acting Beta-Adrenergic Agents

Cochrane meta-analysis found no effect of bronchodilator therapy on mortality, duration of mechanical ventilation or oxygen requirement when treatment was instituted within 2 weeks of birth. No beneficial effect of long-term B_2 bronchodilator use has been established and data regarding safety are lacking. In children with asthma, prolonged use of albuterol may be associated with a diminution in control and deterioration in pulmonary function in association with increased V/Q mismatch within the lungs. We do not recommend routine use of SABA's in management of BPD. Initial management of acute deterioration in chronically ventilator-dependent infants should include careful attention to airway patency, synchronized ventilation, consistency of oxygenation and fluid balance. Evaluation for possible infection should be done. In patients remaining unstable with progressive hypercapnia or high oxygen requirement, a short trial (48 hours) of a short acting beta agent (SABA) such as albuterol or an inhaled steroid (5-7 days) may be tried. However, a SABA should not be used for chronic maintenance therapy. Infants felt to need SABA's more than 1-2 times per week should receive further evaluation (including work up for bronchomalacia) and a defined plan for long-term care.

Postnatal Steroids to prevent/treat BPD:

The evidence and recommendations for the use of postnatal steroids at high risk of developing BPD or to treat BPD exacerbation summarized in **Table 15-11.**

Based on current evidence, clinicians should consider a course of corticosteroid therapy to those patients at high risk of BPD who cannot be weaned from mechanical ventilation (weak recommendation, moderate quality evidence).

In neonates < 30 weeks of gestation that remain on mechanical ventilation >14 days an objective assessment for the initiation of postnatal steroids is recommended. NICHD Web-based BPD estimator can be used to estimate risk of BPD (by severity) and death. This tool can be used in clinical practice to help identify infants at high risk for BPD who may benefit from steroid treatment.

If a decision is made to initiate corticosteroid therapy, we recommend low dose dexamethasone given twice daily according to the following tapering schedule derived from the DART Study, 2006, and Canadian Pediatric Society, 2015:

- 0.075 mg/kg/dose every 12 hours (6 doses)
- 0.05 mg/kg/dose every 12 hours (6 doses)
- 0.025 mg/kg/dose every 12 hours (4 doses)
- 0.01 mg/kg/dose every 12 hours (4 doses)
- Cumulative dose = 0.89 mg/kg

Once therapy is initiated, it is critical that check blood gases are followed closely and aggressive weaning from vent support is attempted with goal of extubating infant by day 3-4 of dexamethasone course.

Acute Exacerbation in BPD

Abrupt deterioration in pulmonary function may occur in older infants who have had a stable course and modest oxygen requirement for several weeks. Differential diagnosis includes acquired infection, worsening pulmonary hypertension, or the insidious onset of symptomatic cor pulmonale. However, many such episodes represent either accumulation of edema fluid in the lung or reactivation of the inflammatory process itself. These episodes may require significant increases in inspired oxygen concentration and ventilator support as well as additional fluid restriction and diuretics. Inhaled steroids or short-term albuterol may be required in select patients. Severe exacerbations in older infants occasionally require a pulse course of systemic corticosteroid therapy. Little published information is available to guide selection of rescue agents in the BPD patient during the first year of life. If systemic steroids are necessary for an infant with severe BPD who is beyond 44-48 weeks PMA, use of prednisone or methylprednisolone according to guidelines of Asthma Expert Panel III (2007) is recommended.

Management of Acute Reactive Airway Disease

Episodes of severe bronchospasm leading to respiratory decompensation are uncommon during the first 3 months of life. Acute episodes of poor air flow and hypoxemia are more likely to be result of airway collapse associated with tracheobronchomalacia. However, if an infant with BPD develops acute, persistent wheezing with gas trapping and deterioration in lung function, oxygen saturation should be closely monitored and a chest X-ray and measurement of PCO_2 should be obtained.

Emergency management of severe airway reactivity in infants with BPD is based upon consensus panel guidelines for asthma management published by the NIH. However, BPD is not asthma and these guidelines do not provide specific dosage recommendations for the first year of life. At present, albuterol (90 mcg per puff) or levalbuterol (45 mcg per puff) are the rescue agents of choice. Either may be given by MDI and spacer, 2 puffs every 4 to 6 hours for 24 to 48 hours, and then progressively weaned.

For severe episodes, either may be given by MDI and spacer, 2 to 4 puffs as frequently as every 20 minutes for 3 doses. Dosage should then be weaned to 2 puffs every 4 to 6 hours for 24 to 48 hours. Albuterol is not recommended for chronic maintenance therapy. If an occasional episode is particularly severe or persistent, addition of inhaled steroids may be necessary. Several studies suggest BPD infants with episodic wheezing are less responsive to bronchodilator therapy than asthmatic infants of similar age.

Tracheobronchomalacia (TBM)

15-34% of infants with ventilator dependent BPD have tracheomalacia or bronchomalacia, producing episodes of large airway collapse. These episodes are characterized by abrupt onset of increased work of breathing, cyanosis, and poor air exchange on auscultation. It is important to differentiate these events from reactive airway episodes because use of inhaled bronchodilators may worsen bronchomalacia. At present, bronchomalacia is much more common than reactive airway disease in BPD patients less than 6 months old. PEEP is the mainstay treatment for opposing airway collapse while awaiting growth and improved stability of the airway tree.

Evaluation of Airway Malacia

Infants with prolonged ventilator dependence are at high risk for TBM, demonstrated by collapse of the airway in expiration. Bronchoscopy has long been used to evaluate the airway of infants suspected to have TBM and identify the PEEP setting that results in ideal airway patency. Recent advances in CT imaging have led to newer diagnostic modalities such as Dynamic pulmonary CT. This CT study has been designed to detect excessive (≥50%) collapsibility of the airways and simultaneously evaluate lung parenchyma.

Table 15-11. Postnatal steroids for preterm infants (GA <30 weeks, BW <1500g) current evidence and recommendations

	Prominent Studies	Outcomes	Regimen	Recommendation
Early systemic steroids (<7 days of age)	**Dexamethasone** Cochrane meta-analysis (Doyle, 2017)	• Decreased BPD, no difference in mortality • Increased GI bleed and perforation • Long-term increased cerebral palsy and neurodevelopmental impairment	Not consistent	Not recommended
	Hydrocortisone Cochrane meta-analysis (Doyle, 2017) PREMILOC (Baud, 2016)	• Decreased death/BPD • No difference in cerebral palsy or neurodevelopmental impairment	Not consistent	• Not recommended • Limited data • Risks may be greater than Benefits
Late systemic steroids (>7 days of age)	**Dexamethasone** Cochrane meta-analysis (Doyle, 2017) DART (Doyle, 2006)	• Decreased death/BPD • Decreased extubation failure by 28 days • Increased transient hyperglycemia and hypertension • Increased severe ROP but not blindness	Low dose 10 day course per DART study and Canadian Pediatric Society	• Consider with parental discussion if: o Patient is at high risk for BPD based on NICHD BPD Outcome Estimator (or) o If patient requires mechanical ventilation > 14 days • Optimal timing for therapy: 2-6 weeks of age
	Hydrocortisone STOP-BPD (Onland, 2018) HCT for BPD (NICHD NRN, pending)	• No difference in death/BPD • Increased transient hyperglycemia requiring insulin • Long-term follow up pending	Not consistent	Not recommended (Limited data)
Inhaled corticosteroids	**Early** NEUROSIS (Bassler, 2015, 2018) Cochrane meta-analysis (Shah, 2017)	Increased mortality	Inhaled budesonide	Not recommended
	Late Cochrane meta-analysis (Onland, 2017) Cochrane meta-analysis (Shah, 2017)	• Compared to placebo or systemic steroids, no difference in death/BPD	Not consistent	Not recommended (Limited data)
BPD Exacerbation (>44 weeks PMA)	National Asthma Education and Prevention Program, NIH Expert Panel Report 3 (2007)		Methylprednisolone Prednisone Short course "burst": 1-2 mg/kg/day for 3-10 days	Consider for severe exacerbations

A recent study from Ngerncham and colleagues reported good correlation between CT and DB in a **select population** with TBM and esophageal atresia. In addition, Ullmann et al. studied 34 pediatric patients (average age 3.6 years) undergoing dynamic CT for the evaluation of TBM and identified bronchomalacia, stenosis, and parenchymal disease. The majority of the study population had respiratory distress within the first months of life, and only 35% of the patients had a history of prematurity (≤ 33 weeks gestation). Bronchoscopy was performed in 85% of these patients with good correlation between both diagnostic techniques. This is the largest pediatric study to date that compares dynamic CT to DB for suspected airway abnormalities. There are no studies evaluating safety, efficacy and utility of dynamic CT in preterm neonates.

Considering the lack of evidence suggesting benefit in the neonatal population, as well as lack of data correlating dynamic CT results with either short-term or long-term outcomes, and the risk of exposure to radiation that comes with a CT study, clinicians must exercise **great deal of caution** in ordering these studies and should carefully weigh risks and benefits for the population of interest.

15.10 Preventing Lung Injury

In our NICUs at Baylor a large quality improvement initiative is in progress by the 'Avoiding Lung Injury' or ALI team. This multidisciplinary team reviews local respiratory metrics, identifies areas in need of improvement and makes changes to care practices following the model for improvement (PDSA cycles). Please follow the protocols and algorithms that are being implemented as part of the QI projects closely to ensure that your practices are consistent with most recent unit recommendations.

Oxygen saturation targeting - Our current recommendation is to maintain the SpO_2 between 90-95%, especially if the eyes are not fully mature. In older patients with bronchopulmonary dysplasia and pulmonary hypertension SpO_2 should be maintained between 92-95%. To minimize oxygen toxicity, we strongly recommend to use blended oxygen to keep saturations within range.

Early nasal CPAP - Two meta-analyses have demonstrated a reduction in death or BPD associated with early application of CPAP in combination with selective use of surfactant. A failed trial of early CPAP should not preclude ongoing attempts to wean an infant from the ventilator.

Gentle Ventilation or Volume Targeted Ventilation - A recent Cochrane meta-analysis of 12 RCTs reported significant reductions in death or BPD associated with volume targeted ventilation (VTV). We recommended VTV in the form of Volume Guarantee (VG) as the default mode of ventilation for VLBW infants.

Minimizing Ventilator Days - Strongest evidence for preventing BPD includes limiting duration of mechanical ventilation. Therefore daily efforts should be made to assess ventilator requirements and adjust based on clinical parameters and blood gases. Once an infant is identified to meet criteria for extubation, attempt extubation immediately (rather than waiting for a convenient time or day). Optimizing caffeine dosing as well as using post-extubation respiratory support via CPAP or NIPPV can reduce chances of extubation failure in VLBW infants.

Caffeine - A multicenter randomized trial (CAP Trial) involving more than 2000 infants less than 1250 grams at birth reported a reduction in need for oxygen at 36 weeks PMA and improved neurologic outcome at follow-up in babies receiving routine caffeine administration initiated during the first 10 days of life. Based on two meta-analyses, **caffeine administration is recommended for all infants born < 1250 grams** (strong recommendation, moderate quality evidence,).

Vitamin A - Meta-analysis of 10 RCT's demonstrated a modest reduction in CLD at 36 weeks' PMA with administration of vitamin A to very low birth weight infants. We recommend administration of prophylactic vitamin A (if available) to babies < 1000 grams, beginning during the first week of life. Give 5000 IU intramuscularly Monday, Wednesday and Friday for a total of 12 doses (strong recommendation, moderate quality evidence).

15.11 Pulmonary Hypertension in Developmental Lung Diseases

Pulmonary hypertension (PH) or increased blood pressure in pulmonary vasculature increases morbidity and mortality in infants with developmental lung diseases, including BPD and CDH. Therefore, timely diagnosis and appropriate intervention for these infants is crucial. Inconsistencies in the criteria, method, and timing used for screening of PH in infants makes it difficult to characterize and generalize the prevalence of PH in infants with these lung disorders. The pooled prevalence of PH in mild, moderate, and severe BPD is 6%, 12%, and 39%, respectively. It's important to recognize that the relationship between PH prevalence and BPD severity is not always linear; 2% of extremely preterm infants without BPD develop PH, indicating that prematurity independently affects the development of pulmonary vasculature and increases the risk for developing PH. The pathogenesis and pathophysiology of PH-BPD differs from pulmonary arterial hypertension (PAH) and persistent pulmonary hypertension of the newborn (PPHN). The etiology of pulmonary vascular disease associated with BPD is multifactorial in nature; injury can result from both prenatal and postnatal factors. Prenatal risk factors include hypertensive diseases of pregnancy, intrauterine growth restriction, infection and/or genetic/epigenetic factors, while postnatal risk factors include hyperoxia, mechanical ventilation, infection, acute or chronic tissue hypoxia, cardiac dysfunction, and presence of shunts. These factors decrease angiogenesis and alveolarization, increase vascular tone and vasoreactivity, decrease alveolar-capillary surface area for gas exchange, and impair metabolic function of respiratory endothelium. The end result is pulmonary hypertension: a marked increase in pulmonary vascular resistance. The elevated resistance prevents forward flow of blood through the lungs, which manifests as worsening hypoxemia and right heart failure. The pathogenesis of PH in CDH is also multifactorial. A systemic review and meta-analysis of antenatal diagnostic tests in fetuses with isolated CDH indicated that there are no reliable antenatal predictors of PH in this population. The lung size and liver herniation did not predict development of PH in isolated CDH. The major pathogenic factors that contribute to PH in CDH are pulmonary endothelial cell dysfunction and increased pulmonary vascular remodeling, characterized by increased vascular smooth cell proliferation and vasoconstriction.

Diagnosis

Certain subsets of NICU patients are at risk for development of PH, especially those with history of oligohydramnios, IUGR, poor postnatal growth, congenital heart disease needing increased or persistent respiratory support, and moderate/severe BPD. Echocardiography (Echo) may demonstrate signs of PH, including increased tricuspid regurgitation and right ventricular ejection time to pulmonary artery acceleration time (RVET:PAAT) ratio; decreased tricuspid annular plane systolic excursion (TAPSE); and changes in the right ventricle shape/size/function, septal position (flattened or bowing into left ventricle), and direction of shunt flow (right to left). Echo can also be used to evaluate for "benign" shunts that may confound or contribute to development or severity of PH. In addition, interrogation of pulmonary veins for congenital or acquired stenosis by echocardiographic or angiographic studies should be sought, especially in infants with severe BPD and deteriorating lung function.

Recent PH guidelines released by the American Heart Association in conjunction with the American Thoracic Society recommend echocardiography screening of neonates with moderate/severe BPD at 36 weeks PMA.

Cardiac catheterization is the gold standard for diagnosis of PH. It can be used to confirm the presence and assess severity of PH; evaluate cardiac anatomy and assess for other abnormalities, including shunt lesion, systemic-pulmonary collaterals, and pulmonary venous abnormalities; assess hemodynamics including RV and LV function; and evaluate therapeutic responses. It is, however, an invasive procedure and is dependent on the clinical stability and weight of the infant (> 1.5 kg).

Cardiac catheterization is recommended if:

- Significant PH despite optimal management of lung disease and associated morbidities
- Anticipate long-term chronic PH therapy
- Unexplained, recurrent pulmonary edema

Management of PH in the NICU

- **Management of chronic respiratory failure-** This is a crucial and potentially curative component of PH management. Acute and/or chronic respiratory failure must be addressed quickly and appropriately to minimize impact on an abnormal pulmonary vascular system. Ensure adequate respiratory support using ventilator techniques which minimize under- or over-inflation because of the negative effects on PVR associated with low or high lung volumes (high quality evidence, strong recommendation).
- **Oxygen-** The goal is to reduce or eliminate hypoxemic episodes. Target saturation ranges in infants with PH should be set between 92-95%. Desaturations below 85% and hyperoxia >97% should be avoided (high quality evidence, strong recommendation)
- **Diuretics-** Titrated to effect, especially important in the setting of shunt lesions. Use can be considered as long as cardiac preload is adequate (low quality evidence).
- **Pressors-** Vasoactive therapies such as Pressors may be required to optimize cardiac function in addition to specific PH therapies to manage CDH or BPD infants with PH.
- **Inhaled nitric oxide-** iNO (1-20 ppm) is indicated if PaO_2 is <100 mmHg (while receiving 100% oxygen) or if oxygenation index is >25 (strong recommendation, high quality evidence).
- If the patient does not respond to the above interventions, consider PH team consult for further management. Potential therapeutic agents used by the PH team may include the following. It is important to note that although these medications are being used widely, the risk/benefit profile for many of them have not been studied extensively in preterm neonates. Therefore, caution should be exercised in using these medications in neonatal population.
    - **Phosphodiesterase inhibitors (e.g. *sildenafil*):** The PDE-5i group of drugs inhibit phosphodiesterase enzyme to allow increased nitric oxide concentrations within the pulmonary endothelium. These drugs are more selective for the pulmonary circulation but can have systemic effects. Sildenafil may be administered orally or intravenously and is typically dosed for body weight, given three to four times daily. Common side effects are hypotension and GE reflux. Sildenafil is the most widely used PH therapy in the BPD population (low quality evidence).
    - **Endothelin receptor antagonists (e.g. *bosentan*):** These drugs inhibit vasoconstriction of pulmonary vasculature and proliferation of vascular smooth muscle cells by blocking the action of endothelin hormone. Bosentan is administered orally and is dosed twice daily. Liver dysfunction is a common side effect; regular monitoring of hepatic enzymes is required. Other possible side effects include anemia and edema. Bosentan can be used alone or in combination with other PH medications (low quality evidence).
    - **Prostacyclins (*iloprost, treprostinil* and *epoprostenol*):** As a group, prostacyclins decrease PH by their vasodilatory, vascular remodeling, anti-inflammatory, and anti-thrombotic properties. Prostacyclins are generally reserved for severe PH and may be considered as add-on therapy for patient's refractory to other interventions (low quality evidence).
- **Interventional cardiology consult-** Consider for hemodynamic assessment, evaluation of shunts, and severe pulmonary vein stenosis.

Prognosis

It is important to recognize that the development of PH significantly increases the mortality and morbidity in infants with BPD and CDH. The increased risk of death is greatest in the first two years of life. Prompt recognition of PH and comorbid factors such as poor growth, inadequate respiratory support, shunts, and pulmonary vein stenosis are crucial to minimizing mortality risks. Over time, PH-associated morbidity and mortality decrease and few infants will require chronic PH medical therapies past early childhood. However, the risk for acute PH (i.e., associated with acute respiratory failure in the setting of a respiratory infection) remains high in the first few years of life.

15.12 Congenital Diaphragmatic Hernia (CDH)

When CDH is diagnosed before birth, fetal MRI is typically obtained at our center. The percentage of herniated liver (% HL) and observed-to-expected fetal lung volumes (O/E) from MRI are used in prenatal counseling to educate families on disease severity and mortality risks in CDH patients (strong recommendation, moderate quality of evidence).

Important consideration in characterizing the type and severity of defect include: side of the defect, total lung volume (TLV), lung-to-head ratio (LHR), observed-to-expected lung-to-head ratio (O/E-LHR), stomach position, and lung-to-thorax ratio. The presence of a major cardiac anomaly has been associated with an increased risk of mortality.

Management of Infants with CDH

- **Delivery Room -** At the time of delivery, immediate intubation should occur to avoid bag-mask ventilation and related lung injury. A pre-ductal saturation monitor should be immediately placed. A 10 French Replogle tube should be placed to suction for gastric decompression. Peripheral venous access should be established in the delivery room and umbilical lines and elective/non-emergent procedures should be reserved to be done in the NICU
- **Oxygenation -** Initial ventilation should be with 100% FiO_2 (strong recommendation, low quality of evidence). Monitor pre-ductal oxygen saturations for primary decision making. Pre-ductal saturations should be targeted to > 70% for the first ten minutes after birth, increasing thereafter to > 80% for the first two hours of life and > 85% after first two hours (strong recommendation, low quality of evidence). The oxygenation index should be used for management decisions in CDH patients. A trial of iNO may be considered based on oxygen index, but evidence of benefit in patients with CDH is lacking.
- **Ventilation -** Use gentle ventilation strategies (volume targeted, low tidal volume, high rate) in an attempt to minimize barotrauma since these patients have hypoplastic lungs and are particularly prone to ventilator related lung injury. Caution should be exercised during delivery room resuscitation not to inadvertently delivery high PIP either via bag mask ventilation, T-piece resuscitator, or mechanical ventilation. CDH patients should be initially ventilated with the conventional ventilator using AC/VG mode with the initial settings listed below. If pre-ductal saturation remains below target and/or pH is < 7.20 (or not slowly improving), increase TV in 0.5 ml/kg increments up to a "working" PIP with max PIP of 28 cm H2O (strong recommendation, low quality of evidence).

Goal parameters

- pH 7.20 or greater with lactate 3mmol/L or less
- PCO_2 50-70 mmHg, PO_2 40-90 mmHg
- Pre-ductal saturations > 80% (first 2 hours of life)
- Pre-ductal saturation > 85% (beyond 2 hours of life)

Clinicians should consider switching the mode of ventilation to HFOV for CDH patients that cannot achieve target PCO_2 on conventional ventilation with PIP < or equal to 28 (weak recommendation, low quality of evidence). Once on HFOV, increase MAP (max of 17) and Delta P as required to achieve goal parameters.

Table 15-12. HFOV Settings

- MAP: 13 (or 2 above that on conventional ventilator)
- iT :0.3
- Hz: 10
- DeltaP: sufficient to produce perceptible chest 'jiggle'

Table 15-13. Initial Ventilator Settings

- PEEP: 5-6 mmHg
- TV: 4-5 ml/kg
- Back-up rate: 40 breaths/minute
- iT: 0.3 seconds
- Pmax: 3-5 above measured PIP, max of 28
- FiO_2: adjust as needed for target pre-ductal saturations of $\geq$ 80%

Table 15-14. Additional Indications for ECMO

- OI > 40 on 2 separate measurements
- PO_2 persistently < 40 mmHg or
- Lactate rising above 3.0
- MAP on HFOV > 17 cm H_2O
- Pre-ductal SpO_2 <85% with pH<7.15

- **Sedation:** Sedation should be used in mechanically ventilated newborns with CDH to facilitate respiratory management and minimize pulmonary hypertension (strong recommendation, low quality of evidence). Facilitate spontaneous breathing and use sedation at the lowest effective dose. Morphine is preferred over fentanyl if infant may require ECMO, due to adherence of fentanyl to pump tubing. Neuromuscular blocking agents should be avoided and used selectively only in infants requiring high ventilatory support (strong recommendation, low quality of evidence). On admission, give morphine 0.05 mg/kg IV bolus followed by a continuous infusion at 0.01 mg/kg/hr. Titrate the continuous infusion by no more than 0.02 mg/kg/hr every 30 minutes, titrate to the lowest effective dose. Consider midazolam 0.05 mg/kg IV every 4 to 6 hours PRN if further sedation is needed. Midazolam continuous infusion at 0.06 mg/kg/hr in term infants can be considered if adequate sedation is unable to be achieved with PRN dosing. Heart rate and blood pressure should be monitored closely as these medications may have a synergistic effect on blood pressure and can result in hypotension. In addition, treatment with these agents may also result in respiratory suppression, requiring changes to ventilator mode/settings to maintain adequate and consistent minute ventilation.
- **Fluids -** Initial fluid intake should be limited to 65 ml/kg/day (strong recommendation, very low quality of evidence). Maintenance fluids should be initially restricted to 40-50 ml/kg/day using concentrated dextrose to obtain an adequate glucose infusion rate. Starter TPN and IL should be utilized as clinically able based on glucose needs.
- **Hemodynamic support -** Circulation should be optimized while avoiding repeated fluid boluses or aggressive volume

resuscitation. Consider vasopressors for hypotension. Hypotension in CDH patients is multifactorial and evaluation for specific etiologies often requires evaluation of effective blood volume status and determination of cardiac positioning, filling and myocardial function by echocardiogram. Low dose dopamine (up to 10 micrograms/kg/min) is recommended for initial pharmacologic management of non-specific hypotension. If hypotension requires dopamine of 10 micrograms/kg/min or more, hydrocortisone (1 mg/kg/dose IV Q8h) should be initiated per consensus guidelines. Dopamine infusion may continue to be titrated up to a maximum of 20 micrograms/kg/min, following which low-dose epinephrine infusion is added. Persistent hypotension requiring increasing pressor support should prompt an evaluation of cardiac function by echocardiography. Addition of special agents such as vasopressin or milrinone should be based upon specific evaluation of cardiac function, blood lactate levels, and other parameters of systemic blood flow and oxygen delivery.

- **Procedures -** Upon admission to the NICU, quickly confirm ET tube and line location by CXR/KUB. Start SpO_2 monitoring (pre and post ductal location). Place umbilical venous catheters, UVC and UAC to maintain reliable central venous access. If correct UVC position cannot be achieved, a temporary low-lying UVC can be temporarily used until a sufficient alternative (e.g double-lumen 2.6 French PICC) is available (strong recommendation, low quality of evidence).
- A STAT head ultrasound should be obtained if concern infant will go on ECMO. An ECHO should be obtained once patient is stable which may be the day after delivery. During transition, attempt to bundle care procedures and minimize handling/noise, as the pulmonary circulation of these patients remains reactive and any manipulations and environmental stimuli may produce significant desaturation events
- **Special considerations -** Current evidence does not support routine surfactant replacement therapy. However, clinicians may consider surfactant replacement in CDH patients treated with Fetal Tracheal Occlusion (FETO) or those delivered at < 37 weeks gestation (strong recommendation, weak quality of evidence). Surfactant should not be used routinely in the non-FETO term CDH patient at birth (strong recommendation, low quality of evidence). Near infrared spectroscopy (NIRS) readings should not be used for patient care management (strong recommendation, low quality of evidence).
- **ECMO -** ECMO should be considered for CDH patients that cannot achieve saturations and/or blood gas targets with maximal HFOV support (weak recommendation, low quality of evidence). The decision to offer ECMO is made by the Congenital Diaphragmatic Program Team (neonatal ECMO clinician and the CDH Pediatric Surgery faculty). Most infants will require CDH repair on ECMO.
- **Repair –** In those patients who do not require ECMO for CDH management, the repair can be considered when physiologically stable: $FiO_2 < 0.5$, pre-ductal SpO_2 85-95%, normal blood pressure for gestation, lactate < 3 mmol/L, urine output $\geq$ 2 ml/kg/hr.
- **Discharge -**All CDH patients should be monitored for pulmonary hypertension. All post-ECMO CDH patients should have a pre-discharge head MRI, a neurodevelopmental evaluation and follow-up, and a hearing assessment. Referral to coordinated pulmonary hypertension and surgery outpatient clinics should be done prior to discharge.

15.13 Neonatal ECMO

Neonatal ECMO improves survival of term or late preterm infants with hypoxic respiratory failure who are failing high levels of conventional ventilator support. The most common underlying conditions for patients needing ECMO at our center include PPHN, meconium aspiration, RDS, sepsis (5%) or other lung malformations (5%) and congenital diaphragmatic hernia (90%). Survival to discharge following ECMO for neonatal respiratory failure currently reported in the large international Extracorporeal Life Support Organization (ELSO) data base is ~75%. Mortality risk is greatest among infants with CDH and acquired pneumonia.

ECLS is an important modality for infants and children with cardiorespiratory failure due to reversible causes. Formerly referred to as extracorporeal membrane oxygenation (ECMO), ECLS not only provides for delivery of O_2, but also eliminates CO_2, and supports myocardial failure.

ECLS Circuit

The circuit basically functions as a pump to add O_2, eliminate CO_2 and warm blood before returning it to the patient. The circuit is comprised of several components.

Cannulae

Venoarterial (most common) - venous inserted through right internal jugular vein with tip of cannula situated within the right atrium, arterial cannula into right common carotid artery with tip residing in aortic arch.

Venovenous - single, dual-lumen catheter inserted through right internal jugular vein with the tip of the catheter in right atrium

Physiology of ECLS

Venoarterial

O_2 delivery is dependent on extracorporeal flow, native cardiac output, O_2 uptake by extracorporeal membrane, and O_2 uptake by native lungs. If the native lungs are not exchanging gas, as occurs in early stages of ECLS, the oxygen-rich blood from ECLS circuit mixes with blood ejected from the left ventricle to determine the patients PaO_2. Increasing PaO_2 may result from increasing extracorporeal flow (decreasing the blood flow through the native lung or the shunt fraction), a reduced cardiac output (also decreases the shunt), and improved native lung function. Reduced cardiac output may be associated with pericardial effusion causing tamponade, hemothorax or pneumothorax, or cardiac failure. Reduced PaO_2 results from increased native cardiac output or decreased extracorporeal flow. CO_2 elimination is dependent upon membrane surface area, sweep gas flow and CO_2 content. Slow flow through the membrane will effectively eliminate all CO_2. The perfusion in neonates on venoarterial ECLS is nonpulsatile; therefore, increased extracorporeal flow will lower systolic blood pressure but maintain the mean arterial blood pressure.

Venovenous

O_2 delivery is dependent on native cardiac output, O_2 uptake by the extracorporeal membrane, and O_2 uptake by native lungs. The degree of recirculation (determined by extracorporeal flow) at the atrial level determines PaO_2 in the right atrium which traverses the lungs to the left heart. Delivery of this oxygenated blood is determined by native cardiac output. During venovenous ECLS the O_2 saturation is seldom greater than 95%. In contrast to venoarterial ECLS, PaO_2 levels in the 40 to50 range are to be expected during venovenous ECLS. Increased PaO_2 results from improved native lung function and less atrial recirculation. Decreasing PaO_2 is generally from increased atrial recirculation. This can be improved by gentle manipulation of the cannula to direct returning blood through the tricuspid valve. Cannula repositioning can be guided by transthoracic ECHO to optimize the flow dynamics within the right atrium (i.e., prevent recirculation). The CO_2 elimination is the same as venoarterial ECLS. Increasing extracorporeal flow rates on venovenous ECLS also may increase recirculation at the atrial level thus reducing O_2 delivery. Hemodynamically, blood flow is pulsatile, and extracorporeal flow has no effect on the arterial waveform.

Hypoxic Respiratory Failure

Respiratory failure indices associated with mortality risk of 80% or greater include:

- OI > 35-60 for 0.5-6 hrs
- $AaDO_2$ > 605-620 mmHg for 4-12 hrs
- PaO_2 < 35-60 mmHg for 2-12 hrs

**These have not been validated for CDH patients

General Inclusion Criteria for ECMO in the NICU

- Gestational age ≥ 34 weeks, weight ≥ 2 kg, age less than one month (**)
- No significant coagulopathy or uncontrolled bleeding
- No major intracranial hemorrhage
- Reversible lung disease with mechanical ventilation < 10-14 days duration
- No uncorrectable congenital heart defect
- No lethal congenital anomalies
- No evidence of irreversible brain damage

**Selection criteria must be individualized for certain preterm infants, fetal tracheal occlusion patients, severe air leak syndromes and viral pneumonia. On rare occasion, patients may exhibit HIE and hypoxic respiratory failure requiring both active body cooling and ECMO.

Baylor/TCH Primary Indications

ECMO should be considered for eligible infants with severe hypoxic respiratory failure after medical management has been optimized (100% FiO_2, iNO, vent settings of PIP 28 cm H_2O or greater and MAP 17 cm H_2O or greater on HFOV).

Additional indications include:

- OI > 40 on 2 separate serial measurements
- PO_2 persistently < 40 mmHg or lactate > 3.0

Infants may benefit from surfactant replacement prior to consideration for ECMO – however, efficacy of surfactant replacement has not been demonstrated in infants with CDH. Clinicians may consider surfactant replacement in CDH patients treated with Fetal Tracheal Occlusion (FETO) or those delivered at < 37 weeks gestation (strong recommendation, weak quality of evidence).

ECMO Mode

Neonatal ECMO may be conducted as VenoArterial (VA) or VenoVenous (VV) bypass support. Use of VV ECMO is preferred whenever possible. VA ECMO is reserved for select patients requiring circulatory support or those too small for VV cannulation. Circulatory dysfunction does not preclude a trial of VV ECMO because function frequently improves after initiation of VV support. Pulmonary Hypertension team should be consulted if infant requiring ECMO due to pulmonary hypertension.

Preparation for Bypass

A detailed Neonatal ECMO Order Set exists in the EMR for ordering lab work and appropriate blood products and medications, as well as the process of initial circuit priming and preparation. ECLS specialist will obtain ECMO medication tray which contains medications needed to prime circuit. K+ and ionized Ca++ of prime blood is checked prior to initiation of bypass. If ionized Ca++ is very low, 1-3 doses of Ca gluconate or Ca chloride may be given just before initiation of ECMO.

Initiation of Bypass

Following cannulation, circuit flow is gradually increased over 15-30 minutes to a test flow rate of 100-125 ml/kg/min. This flow usually provides adequate O_2 delivery on VA ECMO. Pump flow above 125-140 ml/kg on VV ECMO may result in deterioration of systemic oxygenation due to recirculation. If pump flow cannot be increased or pump cutout occurs - infuse volume expanders in 10-15 ml/kg increments. Blood volume expansion is often necessary following the initiation of ECMO. If pump cutout continues – evaluate cannula position. Subsequent flow adjustments are made per individual patient needs.

Adequate ECMO flow is indicated by:

- SaO_2 ≥ 90% (pre-ductal)
- SvO_2 -65-75% (not accurate during VV ECMO)
- Arterial lactate ≤ 3.0
- Capillary refill < 3 seconds

Anticoagulation

The ECMO circuit induces ongoing procoagulant activation necessitating continuous anticoagulation with heparin. A consult to Transfusion Medicine should be placed on all ECMO patients. At the time of cannulation 50 units/kg of heparin are given, followed by continuous infusion of 25 units/kg/hour. Subsequent infusion rate is determined by results of Coagulation Panel (every 6 hours X 48, then every 6hours daily) and ACT (every 1-2 hours) values.

Target values during ECMO (may vary based on parameters set forth by Transfusion Medicine):

- Anti-Factor Xa assay ("heparin level") = 0.2-0.5 (accuracy reduced if TSB > 10 or plasma free Hgb > 200)

- Platelets ≥ 100,000
- Fibrinogen > 200mg/dl
- PT ≤ 17 sec
- PTT = 70-100 sec
- PTT Hepzyme ≤ 37 sec
- D-dimer = none
- Antithrombin > 80 - 100%
- ACT = 160-200**

(**has poor correlation with Anti-Factor Xa activity**)

ACT, PTT and Anti-Xa values are often discordant during monitoring of heparin therapy, since each measures different aspects of the complex coagulation cascade. When discrepancies exist or a complex coagulation issue is present, notify Transfusion Medicine.

Patient Care During ECMO

A complete order set for all phases of ECMO is available in the EMR system.

Respiratory Care

"Lung rest" is a primary goal during ECMO using IMV rate 10-20, PIP 20-22 cm H_2O and PEEP 10 cm H_2O. Nitric oxide should be weaned off during rest settings while infants are on VA ECMO. Nitric should be turned back on during lung recruitment. May consider weaning iNO to off during VV ECMO if infant is a non-responder. Patient oxygen delivery and SpO_2 are maintained by adjustments in pump flow and Hgb concentration (not ventilator parameters). On VA ECMO, target SvO_2 (pre-oxygenator saturation) is 65-75%. Sweep gas flow and oxygen concentration usually should be adjusted to maintain monitored post oxygenator PO_2 (not baby) in 200-250 mmHg range and PCO_2 approximately 35-40 mmHg. Monitor pre-ductal SpO_2 continuously (target 90-95%) with periodic ABG and lactate determinations.

Fluid Management

Fluid administration and slow continuous ultrafiltration (SCUF) are used to minimize adverse effects of positive fluid balance and pulmonary edema. SCUF is a form of continuous renal replacement therapy (CRRT) that utilizes the hydrostatic pressure difference across a semi-permeable membrane to remove plasma water. Some small solutes also are removed by convection. Fluid restriction for patients on ECMO is accomplished by concentrating medications, minimizing flushes and restricting blood products to defined indications only. Restrict primary IV fluids to-50 ml/kg/day on day of life #1. Starter TPN and IL should be considered when initiating fluids if not already on TPN/IL. Within 6-12 hours after the baby is placed on ECMO consider beginning ultrafiltration (background rate-BUFR*) to remove the daily volume of (1) medications, (2) drips and flushes, (3) maintenance infusions for lines. This volume should be calculated prospectively for the next 24 hours and the rate adjusted accordingly. By day of life #2, begin TPN at 50 ml/kg/day and IV lipids at 5 ml/kg/day. If the attending would like to increase the volume of TPN and IL over the 55 ml/kg/day, determine the total volume of TPN and IL over the 55 ml/kg/day and remove this extra volume by UF (alimentation rate—AUFR**). This rate should be adjusted prospectively as one increases the total amount of TPN and IL administered. The use of UF allows you to increase the TPN and IL as needed to attain good nutrition (90 -100 Kcal/k/day—3 -4 grams/kg/day of protein, 15 ml/kg/day of lipid, 10-16 grams/k/day of carbohydrate). Daily volume of blood components given for replacement of hemoglobin and coagulation factors also should be removed by UF (a 'Blood Products Neutral' strategy). However, blood products given for blood volume expansion should not be removed by UF. **Thus, each day's target ultrafiltration rate is determined by calculating the projected next day's BUFR +AUFR in discussion with the CDH program team.** However, body fluid removal by UF may be associated with blood volume depletion. As a result, periodic blood volume replacement will be necessary during UF to maintain adequate pre-load and circulatory function. Kidney function (BUN/Creatinine, UOP) should be monitored closely while on UF.

This requires frequent re-evaluation of the status of the vascular pre-load and circulatory sufficiency. The ideal ultrafiltration rate may not be achievable in some patients.

***BUFR**—add daily volume of medications, drips and flushes and maintenance fluids for lines and divide by 24 = X ml/hour

****AUFR**—[Total desired volume of TPN (X ml/kg) + IL (X ml/kg) for next 24 hours] MINUS [baseline 50/kg TPN + IL 5ml/kg] ml = XX volume divide by 24 hours = X ml per hour

EXAMPLE:
Desired TPN (100 ml/kg) +IL (15/kg) = volume (115 ml) X birth weight (3 kg) = 345 ml per day

Baseline TPN (50 ml/kg) + IL (5 ml/kg) = volume (55ml) X birth weight (3 kg) = 165 ml per day

Desired 345 ml MINUS baseline 165 ml = 180 ml Divided by 24 hours EQUALS 7.5 ml per hour (AUFR)

Total UF in ml/hr = AUFR rate in ml/hr + BUFR rate in ml/hr

Analgesia

Analgesia during ECMO is provided as continuous infusion morphine 0.01 mg/kg/hr or fentanyl 1-2 micrograms/kg/hr. Morphine is preferred because tolerance and signs of dependency develop very rapidly with fentanyl (within 3-5 days with fentanyl compared to 5-7 days with morphine) and due to a greater adhesion loss of fentanyl to the circuit. Initiate morphine infusion at 0.01 mg/kg/hr. If pain/sedation is not adequately controlled, administer a one hour equivalent bolus of the current dose then increase the infusion by 0.01 mg/kg/hr. This can be continued in a stepwise fashion every 30-60 minutes until desired pain score is achieved. Assess pain and sedation effect 30 minutes to one hour after increases in dose. Do not increase continuous infusion by more than 0.01 mg/kg/hr as neonates have decreased elimination and increased CNS sensitivity which can lead to adverse events. If fentanyl is used, initiate infusion at 1 microgram/kg/hr and titrate by 0.5-1 microgram/kg/hr using a strategy similar to that outlined above. High doses of fentanyl (up to 20 micrograms/kg/hr) may be needed by day 6 of ECMO.

Circulation

During VA ECMO, adequate BP and perfusion are usually maintained with typical circuit flow of 100-130 ml/kg/min, allowing pressors to be weaned off or to low level. VV ECMO, however, depends upon the native cardiac output and circulatory

regulation, thus making need for ongoing pressor support more likely. Frequent lab sampling and increased capillary permeability produce depletion of vascular volume throughout the course of ECMO. Periodic transfusions are necessary to maintain HCT $\geq$ 40% and provide adequate blood volume and pre-load. Occasional patients develop hypertension (MBP>65 mm Hg) requiring treatment.

Weaning From ECMO

Recovery of native cardiopulmonary function is indicated by signs of improving oxygenation during reductions in ECMO support. Lung function may be assessed further by a 10-15 min challenge breathing 100% O_2 (hyperoxia test). Increase in PaO_2 to 150-200 mmHg or greater most likely indicates improved V/Q matching and decreasing PVR below systemic levels. When evidence of improvement is present as manifested by ECHO monitoring, pump flow may be incrementally decreased while monitoring PaO_2 and pre-ductal SpO_2 and ECHO indicators. Do not wean flow below 50-60 ml/kg/min or absolute value of 100 ml/min. If the patient tolerates trial reduction in flow with adequate SpO_2 and circulation, a 15 minute "trial off" (VA ECMO) may be attempted with ventilator parameters adjusted to provide increased support. With VV ECMO (which is in series with the native circuit) a "trial off" may be simulated by simply disconnecting the sweep gas from the oxygenator and plugging the connection ports.

Special Considerations

Decisions regarding ECMO must be individualized for certain patients – especially those with CDH infants, premature infants ($\leq$ 34 weeks) or those having complex or multiple anomalies. Such circumstances may require a STAT meeting of medical and surgical members and the Neonatal ECMO Team.

Surgery on ECMO

- 8-12 hours pre-op, obtain confirmation from surgical team for maintaining the following:
  - Fibrinogen > 200
  - Platelets > 150,000
- Order blood products (in addition to emergency blood kept at bedside):
  - 1 unit PRBC's
  - 2 units platelets
  - 1 unit FFP
- Order the following:
  - Pleurovac set up if chest tube to be used.
  - Medications to be available at bedside include extra analgesics/sedation (morphine, fentanyl, midazolam), normal saline, 5% albumin.
- Discuss with Surgery and Anesthesia teams any specific needs for other blood products, medications or special equipment.
- Intra-operative fluids will be administered via the ECMO circuit; however, the anesthesiologist should be provided an IV site for emergency use.
- A peripheral IV will be needed for Amicar® infusion. Amicar® is given directly to the patient and not into the ECMO circuit or a UVC in CDH patients. The surgical team will order specific dosing The Neonatology team will order Amicar® to be ready at bedside for surgery. Typically a bolus of 100 mg/kg will be given 30 minutes before incision and continued as an infusion of 30 mg/kg/hr. Amicar® administration is usually continued for approximately 48 hours, but this is individualized depending upon patient parameters and the surgeon's determination of post-operative status. If renal failure (creatinine > 1.2, urine output < 2 ml/kg/hour), dose should be reduced to 25% of standard dose.
- Target ACT values:

  Usual Ranges for ACT values:

During Surgery	120-140 sec
0-24 Hours Post-Op	130-150 sec
24-48 hours Post-Op	160-180 sec

- The surgical team will provide specific orders for target ACT values after surgery. Amicar® sometimes is stopped before 48 hours. Do not do a "trial off" during Amicar® infusion or for 12 hours after discontinuation. If bleeding complications occur, notify surgery and the Transfusion Medicine team.

Suggested Reading and Resources

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Section 16: Surgery

Editors: Jonathan Davies and Alice King

16.1 Perioperative Management

In emergent cases, initial evaluation is focused on doing a concise history and physical examination concurrent with resuscitation of the infant and preparation for surgical intervention.

Fluid, Electrolytes and Nutrition

Most neonates with an emergent surgical condition will lose fluids by:

- evaporation from exposed bowel
- "third spacing" of fluid in obstructed bowel
- direct loss through emesis or through nasogastric/orogastric tubes

Therefore, fluid restriction following diagnosis is not indicated in these babies. They should be given maintenance fluids with electrolytes as well as replacement fluids. Appropriate intravenous access is necessary to achieve adequate fluid resuscitation. A general rule of thumb is that for every hour with an open abdomen, there are approximately 15 to 20 ml/kg of insensible losses.

If shock is present in a neonate with a surgical problem, it is likely due to hypovolemia unless proven otherwise.

Deficits secondary to intravascular volume depletion can, and should, be corrected prior to surgery with proper fluid resuscitation, including blood products.

In neonates with intestinal obstruction, a large size gastric sump tube should be placed, preferably a Replogle tube, connected to intermittent or low constant suction after hand-aspiration of the stomach. Occluding the gastric decompression tube with a syringe should be avoided because it prevents decompression of the stomach and intestines.

Infants undergoing elective surgery may be given:

- formula up to 6 hours before surgery
- breast milk up to 4 hours before surgery
- clear liquids containing glucose up to 2 hours prior to elective surgery

No infant should remain without fluid intake for longer than 6 hours. If surgery is delayed, IV fluids should be started.

Pre-Operative Evaluation

Initial laboratory evaluation includes blood for type and cross-match, and CBC. In patients with significant fluid losses, serum electrolyte measurements are necessary in order to determine empirical fluid and electrolyte replacement. Baseline and follow-up blood gases are indicated in the evaluation of a severely compromised neonate.

In the pre-operative phase, for major abdominal or thoracic procedures, there should be a type and cross for 20 cc/kilograms of PRBCs. Other blood products should be obtained based on the pre-operative lab parameters or due to underlying medical conditions

Blood Products

The Texas Children's Hospital Blood Bank uses leukocyte-depleted and irradiated blood for neonatal transfusion. Once a unit of blood has been ordered, the blood bank will hold that unit for up to a week for further patient-specific transfusion. Please refer to blood bank protocols for storage time for blood products. For procedures in the NICU, requested blood and blood products should be at the bedside before the procedure starts.

Complications

Anesthesia

Complications are uncommon but can be related to:

- allergies
- side effects and toxicities to the anesthetic and the sedative agents
- administration of fluids and blood products, and
- respiratory/airway

Surgery

Early post-operative complications (< 14 day) are:

- bleeding
- wound infection or dehiscence
- anastomotic leak for a bowel anastomosis (most commonly occurs around post-operative day 4-10)
- abdominal compartment syndrome

Late post-operative complications (> 14 days) are:

- Intestinal adhesion leading to bowel obstruction
- Intestinal fistula formation
- Incisional hernia
- Ostomy complications

Post-Operative Management

Stomas, Intestinal

The long-term success of a stoma depends on the type of stoma created, the segment of bowel brought out and location selected for placement. Careful attention to surgical technique, and the prevention and treatment of common complications help to mitigate the significant morbidity stoma formation. Morbidity from stoma formation remains a significant problem.

When the bowel is divided, the proximal end is brought out as ostomy. These are often used as temporizing maneuvers in emergent situations, such as imminent bowel rupture or to protect a distal anastomosis. Diverting stomas of small bowel may be used in situations such as necrotizing enterocolitis or meconium perforation. These more proximal small bowel ostomies differ from colostomies in that the effluent is more liquid and can be very corrosive to the surrounding skin. Often, more proximal ostomies have a higher volume of stool and can lead to fluid loss and electrolyte derangements.

Surgical management of the distal end of bowel depends on the clinical situation. It can be over sewn and left in the peritoneal cavity or may be brought out to the skin. When it is brought up to the skin, surgery may bring it out as a loop with both proximal and distal ends at the same ostomy site with a shared wall or as a mucous fistula where the proximal and distal ends are no longer in continuity. Bringing the distal end

of bowel up to the skin allows for known or potential distal obstructions to be decompressed, such as with imperforate anus, long segment Hirschsprung disease or strictures from necrotizing enterocolitis. It also permits the option of refeeding effluent from the proximal stoma.

Refeeding may commence after consensus is reached among the surgical, neonatal and intestinal rehabilitation teams. A contrast study may be warranted if anatomy or patency of bowel is in question. The effluent of the more proximal ostomy is collected and refed via a red rubber catheter or Foley catheter inserted 4-5 cm into the mucous fistula. The ostomy output is refed 1:1 continuously via a syringe pump, being sure to protect the skin around the mucous fistula and monitor for significant leakage. The catheter used to refeed is changed every Sunday and more often as needed. For additional information, please refer to 11.2 – Intestinal Failure and Intestinal Rehabilitation.

To prevent skin breakdown, the stoma must be constructed so that it is not flush the skin. This technique allows for a more secure placement of the ostomy bag and prevents skin breakdown. In a tiny premature infant with NEC, the formal maturation of a stoma often is difficult. In these cases, limited fixation of the exteriorized bowel to the skin is sufficient. Ischemia of these fragile stomas is common in the immediate postoperative period. However, as long as the mucosa at the level of the fascia is viable, these stomas usually will heal and function well.

Attention to skin care is essential. Skin around the ostomy site must be kept clean and dry at all times. The ostomy bag may be left in place for 1 to 3 days, but should be changed any time there is leakage and should be emptied when 1/3 full. When changing the bag, all old adhesive must be removed and the site cleaned with soap and water while avoiding excessive scrubbing.

If dermatitis develops, local wound care is analogous to management of diaper rash. The area should be carefully and completely washed and dried. A protective ointment or cream (such as one that contains zinc oxide or petroleum), mechanical skin barriers, or both, should be applied around the stoma before the ostomy bag is placed. Irritation from the corrosive enteric content can also be improved with Stomahesive™ powder, which helps absorb fluid.

Cellulitis should be treated with antibiotics (usually a first generation cephalosporin) and monilial infections with mycostatin powder or ointment. Allergic dermatitis is unusual, but will respond to topical steroid cream therapy.

Other complications of stomas include:

- peristomal hernias
- prolapse
- retraction
- stricture formation at the fascia level

These occur often in newborns requiring stoma creation for treatment of NEC. Dilatation may be successful in treating some strictures, but revision of the ostomy often is required.

16.2 Peripheral and Central Venous Access

Peripheral

Because of the shorter catheter length, peripheral venous access is superior to central venous access for rapid volume infusion.

Sites for peripheral venous access include the veins in:

- hand
- forearm
- lower leg or foot
- scalp

Surgical cutdown or percutaneous central access is indicated after percutaneous attempts at cannulation have failed.

Sites for cutdown or percutaneous central line placement include:

- the saphenous and femoral veins in the lower extremities
- the external jugular
- the internal jugular
- facial veins in the neck

Subclavian veins may be accessed percutaneously, inferior to the clavicle. Vascular cutdown carries a significantly higher risk of infection compared with percutaneous cannulation.

Midline

A midline catheter is inserted peripherally and threaded to an area of greater blood flow in the proximal portion of the extremity. Mid-clavicular tip placement should be avoided as this location is associated with an increased risk of thrombus formation.

Midlines are a valuable alternative for vascular access in select infants due to the potential for extended dwell times and fewer PIV restarts. A midline may be considered in patients who need relatively short term (5-7 days), but stable peripheral access (e.g. patient undergoing tracheostomy and will need drips maintained for several days until airway is stable). Also consider when there is poor access and a central line is contraindicated (e.g. septicemia). A PICC that could not be successfully threaded to central location during insertion may also be secured in place as a midline and safely used.

Midline catheters can be used to infuse antimicrobials, fluid replacement, and other medications well tolerated by peripheral veins. Avoid continuous infusion of vesicants. Extra attention should be given to the catheter site if intermittent infusion of vesicants is needed. A list of vesicants can be found in the Lexicomp formulary.

When compared with central catheters, midlines have higher rates of phlebitis, occlusion, and leaking. Currently, no data exist to support a limit to the dwell time of a properly functioning midline catheter.

Table 16-1. Central line radiographic landmarks

Radiographic Landmark	Major Venous Anatomy in Neonates
T3-5 or 2 vertebral spaces below the level of the carina	Ideal upper body central venous catheter placement: the SVC at RA junction
T1-2	Often associated with right or left innominate venous placement (aka brachiocephalic veins)
Clavicular tip placement	Typically seen with subclavian venous location
Upper portion of an extremity, parallel to the humerus or femur	Ideal midline tip location
T6-7	Right atrial catheter tip placement (consideration should be made for catheter adjustment to SVC)
T8-10	Ideal lower body central venous catheter tip placement (IVC) just above level of the diaphragm
T11-12; L1-3	IVC
L4-5	Iliac venous catheter tip placement
Neck placement, above the level of the clavicle	External jugular tip placement (midline site for scalp placed lines)

Central

Central venous access is indicated when there is need for prolonged access for medications, need for hyperosmolar medications/fluids, TPN, when there is inability to attain peripheral access, and, rarely, for hemodynamic monitoring and access for drawing blood.

Peripherally inserted central catheters (PICCs) have decreased the need for surgically placed central lines. These catheters are placed via a peripheral vein in upper or lower extremity and threaded to a central position. A PICC may last for several weeks or months. Ultrasound use is preferred if available to assess vasculature and ensure catheter to vein ratio is less than 45%.

Non-tunneled (CVC/PERC) catheters can be placed percutaneously into the internal jugular, subclavian, and femoral veins. These are not meant for long term access, but most commonly placed in emergent situations when no other access has been successful. It is recommended to leave in for no longer than 5-7 days given higher risk of complications, especially infection.

Clinical factors may require special consideration in choosing the location of placement of central lines. **(Table 16-2)**

Early complications of central lines include:

- malposition
- pneumothorax
- perforation of a vein or artery with resulting hemothorax and/ or cardiac tamponade, pneumopericardium, infection, and arrhythmias

Placing the catheters under fluoroscopic guidance, obtaining radiographs immediately after placement, or both, will minimize these complications.

Late complications of central lines include:

- breaking or cracking of the line or its constituents
- central line associated blood stream infection (CLABSI)
- tunnel or insertion site infections
- occlusion
- catheter migration
- phlebitis
- bacteremia from accessing the line
- venous thrombosis

Intracatheter thrombosis may be treated by instilling 110% of the internal lumen volume of the catheter of tissue plasminogen activator (TPA; 1mg/ml). If aspiration of the clot is not possible after a 2 hour dwell time, repeat the instillation and attempt aspiration again in 2 hours. TPA doses should be aspirated and discarded when possible. If the catheter remains occluded, a volume of 0.25- 0.5mL of 0.1 N HCl may be used.

Table 16-2. Central line placement location considerations

Clinical Factor	Placement Consideration
Congenital heart disease likely requiring cardiothoracic surgery	Strongly prefer lower extremity PICC placement to avoid catheters in vessels that may be involved during cardiac surgery. Individual vascular anatomy should be taken into account for optimal PICC location.
Possible ECMO candidate (ex: CDH patient)	Prefer lower extremity PICC to avoid interference with ECMO cannulas.
Pre-operative conditions where the lower extremities will be in the surgical field (ex: imperforate anus, sacrococcygeal teratoma)	Prefer upper extremity placement because the lower extremities will be prepped, sterilized and possibly in the field during surgery. Other anatomy and conditions may also need to be taken into account for optimal PICC location.
Renal patients with possible future hemodialysis (including well beyond the neonatal period)	Upper extremity peripheral and central access options should be avoided to preserve for future fistula construction for hemodialysis.
Infants with intestinal failure being discharged to home on long term parenteral nutrition.	Prefer upper extremity “IJ approach” line - tunneled, cuffed, single lumen (inserted either by IR or surgery)

HCl is most useful when occlusion is thought to be secondary to precipitation of total parenteral nutrition.

Tunneled central lines require local and sometimes general anesthesia for removal. The Dacron cuff must be dissected away from the subcutaneous tissue.

Central Line Tip Position

The catheter tip should be placed in the SVC or thoracic IVC. Outside the vena cava, the catheter tip is subjected to smaller diameter vessels, vein curvature, and venous valves that increase the risk of the catheter contacting and damaging the vessel wall. Appropriate SVC placement is described as the T3–T5 level but this depends on infant anatomy and radiographic technique. Appropriate IVC tip placement is not well defined, but we recommend a tip location between the right atrium and the diaphragm, described as T8– T10 based on current evidence.

Placement in the right atrium is not recommended due to risk of arrhythmia and perforation potentially leading to tamponade. Brachiocephalic and subclavian veins have decreased diameter and lack laminar blood flow, and are not considered central.

Additional Information on Peripheral and Central Venous Access

Additional information on peripheral, midline and central lines can be found in the National Association of Neonatal Nurses (NANN) Peripherally Inserted Central Catheters practice guidelines (http://www.nann.org/)

16.3 Specific Surgical Conditions

Thoracic Cavity

Bronchopulmonary Sequestration (BPS)

BPSs are segments of nonfunctioning lung with no connection to the tracheobronchial tree and an anomalous systemic arterial blood supply. Most are unilateral and most often are located in or adjacent to the left lower lobe. Fetal ultrasound shows a homogeneous, hyperechoic mass in the lung; Doppler often demonstrates a blood supply arising from a systemic artery, usually the aorta. It may be difficult to distinguish BPS from CPAM.

A significant arteriovenous shunt can occur through the sequestration and result in:

- high output cardiac failure
- hydrops
- pulmonary hemorrhage

Extralobar sequestration rarely require emergent resection unless a symptomatic shunt exists. Intralobar sequestrations are electively resected because of the risk of infection. These patients should be referred for long term follow up with pediatric surgery.

Congenital Pulmonary Airway Malformation (CPAM)

CPAMs, previously referred to as Congenital Cystic Adenomatoid Malformations (CCAMs), are rare lesions that are almost always unilateral and usually only affect a single lobe. On prenatal ultrasonography they appear as an echolucent cystic mass. Mediastinal shift, polyhydramnios, and hydrops may occur. Doppler studies demonstrate the absence of a systemic vascular supply. There may or may not be associated anomalies. Ultra-fast magnetic resonance imaging (MRI) of the fetus can be useful, especially for differentiating CPAM from other diagnoses such as sequestration. Lesions are most often classified as either macrocystic or microcystic, based on ultrasonographic and pathologic findings. The less common microcystic lesions are generally solid echogenic masses with multiple small cysts and are associated with a worse prognosis.

Fetal CPAMs should be followed with serial ultrasonography. Many will decrease in size or appear to completely resolve before birth; others may increase in size and cause hydrops. The natural history of CPAMs is that they will usually enlarge up to 28 weeks gestation where they will then plateau in their growth curve and often begin to involute. The presence of hydrops is a grave prognostic sign with only isolated cases of survival reported. If the CPAM does not resolve or regress, the severity of presentation relates to the volume of the mass and to the associated findings. Infants with severe pulmonary hypoplasia may have associated pulmonary hypertension. Even if the mass regressed before birth, postnatal CT scans should be performed.

Poor outcomes of infants with hydrops before 32 weeks make the fetus a candidate for prenatal intervention. One prenatal predictor for fetal intervention is the congenital cystic adenomatoid malformation volume ratio (CVR), which is calculated by dividing the CPAM volume by the head circumference. A CVR greater than 2.0 has the highest sensitivity and specificity for predicting development of hydrops and heart failure and the need for fetal intervention.

The fetus with a large CPAM, with or without hydrops, ideally should be delivered at a facility with the capacity for prenatal counseling, including:

- fetal surgery options
- high-frequency ventilation
- ECLS
- emergent pediatric surgical intervention

Once stabilized, early resection of the mass is indicated in all infants with clinical symptoms. Even for children without symptoms, postnatal resection of all CPAMs is recommended because of the possibility of later development of rhabdomyosarcoma arising from within the lesion and difficulty differentiating from pleuropulmonary blastoma.

Congenital Diaphragmatic Hernia (CDH)

Ch 15.12 – Congenital Diaphragmatic Hernia

Congenital Lobar Emphysema (CLE)

CLE, like CPAMs, almost always occur within a single pulmonary lobe. CLE most often present in the left upper lobe.

Identified causes of CLE include:

- intrinsic bronchial abnormalities
- mucus plugs
- extrinsic compression

However, in at least 50% of reported cases, no apparent obstruction can be found. Congenital cardiac or vascular abnormalities are found in approximately 15% of infants with CLE.

Diagnosis is usually made in the postnatal period when an infant has worsening respiratory difficulties. Chest radiograph usually shows an overdistended, emphysematous lobe in one lung.

Preoperative management depends on the severity of symptoms. A relatively asymptomatic infant may be maintained with oxygen. Treatment of the asymptomatic, hyperlucent lobe is controversial. There is no evidence that leaving it impairs development of the remaining lung, but infectious complications often occur and lead many to resect even the clinically asymptomatic CLE. Progressive pulmonary insufficiency from compression of adjacent normal lung requires resection of the involved lung.

Positive pressure ventilation may abruptly exaggerate air trapping and result in sudden cardiopulmonary decompensation. Surgery should be present during induction in the event an urgent thoracotomy is needed.

Esophageal Atresia and Tracheal Fistula

The incidence of esophageal atresia (EA) is 1 in 3000 to 5000 live births. The most common type is EA with a tracheal fistula (TF) to the distal esophageal pouch (86%); others include pure esophageal atresia without a fistula (7%), a fistula without atresia (4%), and, more rarely, fistulas to the proximal or to both the proximal and distal pouches. An infant with EA often presents with excessive secretions, noisy breathing and episodes of choking and cyanosis, which worsen if the child is fed. Diagnosis is confirmed by inability to pass an orogastric tube. There may be abdominal distention secondary to air-trapping within the gastrointestinal tract in cases with a distal TF, especially if bag-mask ventilation was required in the delivery room. Chest and abdominal radiography usually shows that the tip of the orogastric tube is high in a dilated proximal esophageal pouch. The presence of gas within the gastrointestinal tract helps distinguish those with a TF from isolated EA. Contrast swallow fluoroscopy is contraindicated because of the risk of aspiration. Bronchoscopy is useful for detecting an H-type fistula with no associated atresia or a second fistula to the proximal pouch. The presence of other anomalies should be ascertained by careful examination of the patient (e.g., VACTERL).

Preoperative management requires passage of a suction tube (Replogle) into the proximal esophageal pouch. The infant's head should be elevated 30 degrees to minimize risk of aspiration of oral secretions and reflux of gastric secretions via the TF. Total parenteral nutrition should be initiated. It is advisable to avoid heavy sedation and muscle relaxants because spontaneous respiratory effort generates tidal volume with negative rather than positive ventilation decreasing the risk of gastric over distention. Positive pressure ventilation through non-invasive positive pressure and endotracheal intubation should be avoided, if possible.

If intubation is necessary and there is a distal TF, emergent gastrostomy and fistula ligation also may be necessary. Infants should be assessed for associated anomalies. Most immediately necessary is echocardiography to identify the location of the aortic arch and cardiac anomalies, which affect intraoperative management.

A primary repair usually can be accomplished at birth, even in very small infants. Postoperative management should include continuing broad spectrum antibiotics during the perioperative period and decompressing the stomach via continuous drainage of the nasogastric or gastrostomy tube. The nasogastric tube should be left in place until a dye study documents the integrity of the surgical repair (generally obtained at 5 to 7 days postoperatively). If the nasogastric tube becomes dislodged, it should be left out. Suctioning of the oral cavity should be done with a marked suction catheter that will not reach to the anastomotic site. Intubation should be continued until the risk of extubation failure is low. Tracheomalacia is frequent and often responsive to prone positioning, but sometimes requiring reintubation, and very occasionally requiring aortopexy or reconstruction.

Other common complications include:

- anastomotic leak
- gastroesophageal reflux (in approximately 40% of patients)
- anastomotic stricture
- aspiration

GER Treatment in EA

All infants with a history of repaired EA have a significant predisposition for reflux due to an abnormal GE junction related to their primary repair. Studies have reported incidence to be up to 50% in EA patients, with 47% requiring medical management and 33% progressing to fundoplication on long-term follow up. Prolonged acid exposure to the anastomosis can result in stricture formation. This can lead to gastric metaplasia which is noted frequently in EA patients. Limited studies suggest that medical treatment may decrease GI and/or respiratory symptoms in a subset of EA patients, but the benefit to decreasing complications such as anastomotic site stricture have not been proven. However, due to the high prevalence of GER and potential for complications, the ESPGHAN-NASPGHAN recommends that GER be treated with acid suppression using PPIs as first-line therapy in all EA patients in the neonatal period up to the first year of life or longer depending on the persistence of GER (strong recommendation, low quality evidence).

Extracorporeal Life Support (ECLS)

Ch 15.13 – Neonatal ECMO

Abdominal Wall Defects

Gastroschisis

Gastroschisis is a congenital defect of the abdominal wall leading to herniation of abdominal contents. The defect is usually to the right of the umbilical cord. Malrotation is always present and 10% to 15% have associated intestinal atresias. Other associated anomalies are rare. Gastroschisis is associated with increased maternal serum alpha-fetoprotein and can be diagnosed on prenatal ultrasound. Upon delivery, the bowel should be placed in a bowel bag. A Replogle nasogastric tube is placed and put to continuous suction. The infant should be positioned (usually on their side) to prevent kinking of the mesentery and bowel ischemia. Using towels to support the bowel can also be helpful. Systemic intravenous antibiotics

(usually ampicillin and gentamicin) are given to protect the contaminated amnion and viscera. IV access should be obtained, preferably in upper extremity, leaving a site for a PICC line to be placed.

Unlike normal neonates, infants with gastroschisis may require up to 200 to 300 mL/kg in the first 24 hours of life because of third-space losses and evaporation. Fluid administration should be guided by tissue perfusion and urine output. Early intubation should be performed to avoid intestinal distention following prolonged bag-mask ventilation.

The options for surgical treatment include:

- reduction of the bowel and primary closure of the skin and fascia
- placement of a silo constructed in the operating room and sewn to the fascia
- placement of a Silastic™ spring-loaded silo in the NICU

Which treatment is chosen depends on many factors including:

- the size and position of the bowel
- size of the abdomen
- required peak ventilator pressures with reduction
- condition of the baby

No randomized trial has been performed to determine the optimal choice. If a silo is placed, it is gradually decreased in size until the bowel contents are reduced into the abdomen and a delayed primary repair can be performed. A tight abdominal closure can result in respiratory compromise, decrease in venous return, and abdominal compartment syndrome. The infant must be closely monitored after closure. Bowel function may not return for days to weeks following repair and long term TPN is necessary.

Omphalocele

Omphalocele is a persistent opening in the midline abdominal wall that results from incomplete fusion of the cephalic, lateral, and caudal tissue folds, leaving an open umbilical ring and viscera that are covered by a thin sac of amnion and peritoneum. Many omphaloceles are diagnosed on prenatal ultrasound. Maternal alpha-fetoprotein may or may not be elevated.

More than half of infants with omphalocele have associated anomalies and preoperative assessment should be undertaken, including evaluation for other associated anomalies such as congenital heart defects, renal anomalies and chromosomal defects.

A Replogle nasogastric tube should be placed and put to continuous suction. An intact sac should be covered with a moist dressing or intestinal bag. Ruptured sacs are treated like gastroschisis defects.

Surgical treatment depends on the size of the infant's abdomen, the size of the defect, and associated anomalies. The goal of surgical treatment is to close the abdomen without creating abdominal compartment syndrome. Closing fascial defects less than 4 cm usually is easy. Close hemodynamic monitoring for 24 to 48 hours after primary closure is essential, but infants usually can be advanced to full feeds within several days.

If the defect is too large for closure, or if there are severe associated abnormalities, omphaloceles may be allowed to epithelialize with the application of topical agents (e.g., silver sulfadiazine). Epithelialization occurs over several weeks or months and leaves a hernia defect that needs to be repaired at a later date.

Late complications may include:

- gastroesophageal reflux
- volvulus (all infants with omphalocele have non-rotation)
- ventral and inguinal hernias

Outcome depends upon associated congenital anomalies with cardiac anomalies playing the largest determinant of survival.

Abdominal Cavity

Duodenal Atresia

Duodenal atresia occurs in approximately 1 in 5,000 to 10,000 live births and occurs when the duodenum does not recanalize after the seventh week of gestation.

Prenatal diagnosis of duodenal atresia can be made on:

- prenatal ultrasonography in the setting of polyhydramnios
- a dilated stomach and duodenal bulb (i.e., double bubble sign)
- scant meconium in the distal bowel

Neonates present with bilious vomiting (the obstruction is distal to the ampulla of Vater in 85% of cases) and/or feeding difficulties. Physical examination may show a distended abdomen. The classic "double bubble" may be seen on abdominal radiograph. Air in the distal bowel suggests a partial atresia or web. The differential diagnosis of bilious emesis includes: malrotation with volvulus, distal atresias, and Hirschsprung disease. If there is any question, malrotation and volvulus can be ruled out with an upper GI study.

Initial management should involve nasogastric or orogastric decompression, fluid resuscitation and evaluation for associated anomalies. Significant cardiac defects are present in 20% of infants with duodenal atresia, and almost 30% of infants with duodenal atresia have trisomy 21. Duodenoduodenostomy is the preferred treatment, although duodenojejunostomy may be performed instead based on size of the baby and size of the defect.

Survival rates are about 90% with good long-term prognosis. Morbidity and mortality are related to associated anomalies and resulting short gut complications. There's a higher risk of mortality if BW <2kg.

Intestinal Atresia

Small bowel atresia is a congenital occlusion of the intestinal lumen secondary to an intrauterine mesenteric vascular occlusion that causes a complete obstruction. Children with jejunoileal atresia typically have no other associated anomalies. The most common associated conditions are cystic fibrosis, malrotation, gastroschisis, along with low birth weight and multiparity. Intestinal atresia has also been associated with maternal smoking and cocaine use.

Hereditary multiple intestinal atresia (HMIA) is a rare autosomal recessive disorder of multiple intestinal atresias, commonly seen in French Canadians and can be associated with combined immune deficiency.

Diagnosis of intestinal atresia usually is made soon after birth, within the first 1-2 days. Key features are abdominal distension and bilious vomiting, with the majority failing to pass meconium by 48 hours. Prenatal history may include polyhydramnios with dilated, echogenic bowel on prenatal ultrasound. Abdominal radiographs typically show dilated air-filled loops of proximal bowel with no air in the rectum. "Triple-bubble" sign refers to air in the dilated stomach, duodenum and proximal jejunum. Contrast enema may be required to rule out other diagnoses such as meconium plug, meconium ileus, and Hirschsprung disease.

Preoperative preparation includes:

- nasogastric or orogastric decompression
- fluid resuscitation
- broad-spectrum antibiotics

The bowel distal to the atresia is resected and an end-to-end anastomosis is performed. A nasogastric tube is used to decompress the stomach until bowel function returns. Post-op complications include anastomotic leak, stenosis at the site of anastomosis, and short gut syndrome. Mortality is about 10% (90% survival) with prematurity, associated anomalies, infection and short gut syndrome as major contributors to mortality.

Malrotation and Midgut Volvulus

Midgut volvulus is one of the most serious emergencies during the newborn period since a delay in diagnosis and subsequent gangrene of the midgut is almost uniformly fatal. Ninety-five percent of infants with volvulus have bilious vomiting.

Abdominal radiographs may show:

- a normal bowel gas pattern
- a gasless abdomen
- dilated intestine suggesting small bowel obstruction
- duodenal obstruction with a double bubble

Surgical consultation should be immediately obtained when the diagnosis is suspected. Unless immediate surgery is required for signs of peritonitis or deterioration of the child with an acute abdomen, the diagnosis should be rapidly confirmed with an upper GI study. A few hours may be the difference between a totally reversible condition and death (loss of the entire midgut). A nasogastric tube must be placed, IV resuscitation must be started, and the infant must be immediately transported to either the radiology suite or the operating room.

Recurrent volvulus can occur in up to 8% of cases.

Surgical repair via Ladd procedure consists of anticlockwise derotation of volvulus, removal of Ladd's bands, broadening mesenteric root, and placing small bowel on the right and large bowel on the left. The Ladd's procedure may be performed with or without an appendectomy.

Distal Obstructions

Meconium Ileus (MI)

MI accounts for almost 1/3 of all obstructions in the small intestine in newborns, and occurs in about 15% of infants with cystic fibrosis. Over 90% of patients with MI have cystic fibrosis. A family history of cystic fibrosis is common.

Infants with MI usually present with abdominal distention, bilious vomiting, and failure to pass meconium in the first 24 to 48 hours. "Doughy," dilated loops of distended bowel may be palpated on abdominal examination. Radiographs of the abdomen show bowel loops of variable sizes with a soap-bubble appearance of the bowel contents. Contrast enema typically demonstrates a microcolon with inspissated plugs of meconium in the lumen.

Initial treatment begins with a Gastrografin® enema. Under fluoroscopic control, Gastrografin® and water is infused into the rectum and colon. This usually results in a rapid passage of semiliquid meconium that continues for the next 24 to 48 hours. Follow-up radiographs should be obtained. Multiple Gastrografin enemas are often required.

Operative intervention is indicated for MI if:

- the Gastrografin® enema fails to relieve the obstruction
- abdominal calcifications suggest meconium peritonitis
- the diagnosis is not clear
- the infant appears too ill for non-operative treatment

Hirschsprung Disease (HD)

HD (congenital aganglionic megacolon) is the most common cause of intestinal obstruction in newborns, and is more common in boys. HD is familial in 4% to 8% of patients.

Most newborns with HD present with abdominal distension, emesis and failure to pass meconium by 24 hours of age. Physical examination usually shows a distended, soft abdomen. Rectal examination leading to an explosive stool is very suggestive. Abdominal radiographs usually show distended loops of bowel. Contrast enema can show a transition zone, where the rectum has a smaller diameter than the sigmoid colon. However, contrast enema may be inaccurate in up to 20% of newborns. Failure to completely evacuate contrast on a 24-hour follow-up abdominal radiograph also suggests HD. Definitive diagnosis is made by finding aganglionosis and hypertrophied nerve trunks on a suction rectal biopsy.

Initial management should involve nasogastric or orogastric decompression and fluid management. The initial goal of therapy is decompression by either rectal irrigations or colostomy. Rectal irrigations are performed with a red rubber catheter (at least 12 french) and a 60 cc catheter tip syringe. The catheter is gently inserted into the rectum with initial instillation of 10-20 cc of normal saline for a total of 15-20 cc/kg. If the catheter is met with resistance, excess force must be avoided to prevent iatrogenic perforation. In performing a successful irrigation, the total amount of saline instilled, or more, should be returned. The fluid at the conclusion of the irrigation session should be relatively clear. Irrigations should never be performed with water which may result in electrolyte abnormalities.

If a primary pull-through is planned in the immediate postnatal period, irrigations may be performed for a few days or weeks. If the baby has other medical problems, a leveling colostomy is performed by doing serial frozen section biopsies to identify the transition between normal and aganglionic bowel. The definitive pull-through is delayed for 2 to 3 months or until the child reaches 5 to 10 kg.

Hirschsprung-associated enterocolitis (HAEC) can rapidly lead to sepsis and even death. HAEC is characterized by:

- abdominal distention
- constipation OR diarrhea
- explosive, watery, foul-smelling stool on rectal examination.

Enterocolitis can occur either before or after definitive treatment. Parents should be well-educated in its presentation and the need for rapid medical treatment. Repeated episodes warrant investigation to rule out a retained aganglionic segment.

Imperforate Anus (IA)

Diagnosis of IA is almost always made at the time of the first newborn physical examination. The lack of an anal opening usually is fairly obvious, but a midline raphe ribbon of meconium or a vestibular fistula may not become apparent for several hours. The diagnosis of high IA versus low IA may be clarified by performing a delayed (24 to 36 hour) abdominal radiograph in the prone position with a marker on the anal dimple.

IA may comprise part of the VACTERL association. Due to this association, the pre-operative work-up for these patients include a cardiac ECHO, chest and abdominal radiograph, renal ultrasound, and spinal ultrasound (tethered cord).

Initial management should involve nasogastric or orogastric decompression and fluid resuscitation. Perineal fistulas may be dilated or repaired by perineal anoplasty. When possible, primary repair is via primary posterior sagittal anorectoplasty. Intermediate and high imperforate anomalies (distance over 1 cm) require initial colostomy and delayed posterior sagittal anorectoplasty. Recovery after posterior sagittal anorectoplasty is usually rapid. Male patients may require a Foley catheter for 3 to 7 days depending on the complexity of the repair. Anal dilatations with Hegar dilators are begun 2 weeks after surgery. The parents are subsequently required to continue with serially larger dilators until the appropriate size is achieved. Once the desired size is reached, the dilatations are tapered. When this has been completed, a colostomy, if present, can be closed.

Some patients with high anorectal malformations may be initially managed with divided colostomies. The proximal aspects may be pouched in the standard fashion, but should avoid incorporating the distal ostomy. Spillage of stool into the distal colon is unable to be evacuated and can lead to septicemia. When the patient has grown in size, these higher anorectal malformations are repaired.

Sequelae of anorectal malformations can include:

- constipation
- fecal incontinence
- rarely, urinary incontinence

Long-term, well-coordinated bowel management programs are essential to achieve optimal bowel function.

Miscellaneous

Inguinal Hernia

The processus vaginalis is a peritoneal diverticulum that extends through the internal inguinal ring. As the testicle descends during the final trimester from its intra-abdominal position into the scrotum, a portion of the processus surrounding the testes becomes the tunica vaginalis. If the portion of the processus vaginalis in the canal persists, this creates the potential for a hernia. Fluid may be trapped in the portion of the processus surrounding the testis in the scrotum, creating a hydrocele. Almost all pediatric inguinal hernias are indirect (through the inguinal canal). While most infant hydroceles resolve spontaneously within 12 to 18 months, a hernia never spontaneously resolves and requires surgery to prevent incarceration and strangulation of intra-abdominal structures and irreversible damage to the testes. The incidence of inguinal hernia is low in term infants, but increases to 16% to 25% in infants of less than 28 weeks' gestational age. The younger the infant, the higher the risk that the hernia will become incarcerated. Thirty-one percent of incarcerated hernias occur in infants less than 2 months of age.

Risk factors for increased incidence of hernia in infants include:

- chronic respiratory disease
- increased intra-abdominal pressure (ascites, repair of omphalocele or gastroschisis, ventriculoperitoneal shunts, and peritoneal dialysis)
- exstrophy of the bladder
- connective tissue disorders

Hernias often present as a smooth, firm mass lateral to the pubic tubercle in the inguinal canal. The mass may extend into the scrotum and will enlarge with increased intra-abdominal pressure (crying or straining).

Symptoms suggesting an incarcerated hernia include:

- pain
- emesis
- irritability

The mass usually is well defined and does not reduce spontaneously or with attempts at manual reduction. Incarcerated hernias in children can rapidly evolve into strangulation and gangrene of hernia contents. Surgical consultation should be obtained immediately.

Cloacal Malformations and Cloacal Exstrophy

The incidence of cloacal anomalies is 1 in 20,000 live births. They occur exclusively in females and are the most complex of anorectal malformations.

A persistent cloaca (Latin for "sewer") is the confluence of the rectum, vagina, and urethra into one common channel. A persistent cloaca can be diagnosed on physical examination that shows a single perineal orifice. An abdominal mass, representing a distended vagina (hydrocolpos), may be present.

The goals of early management are to:

- detect associated anomalies
- achieve satisfactory diversion of the gastrointestinal tract
- manage a distended vagina
- divert the urinary tract when indicated

A colostomy with mucous fistula should be performed since total diversion of the fecal stream is necessary to prevent urosepsis.

Diagnosing a persistent cloaca correctly is vital because 50% of infants have hydrocolpos and 90% of babies have associated urological problems. Infants should be evaluated with abdominal and pelvic ultrasonography. Both pediatric surgery and urology services should be consulted. If an obstructive uropathy is missed, it may lead to urosepsis and renal failure.

Spinal ultrasonography should be performed during the first 3 months of life since 40% of infants may also have a tethered cord, which may result in urinary and bowel dysfunction and disturbances of motor and sensory function of the lower extremities.

Definitive repair of a persistent cloaca is a serious technical challenge and should be performed in specialized centers by pediatric surgeons and urologists.

- bowel control
- urinary control
- normal sexual and reproductive function

Significant urologic and anorectal issues may involve:

- sex assignment
- surgical treatment
- long-term follow-up

Cloacal exstrophy - the most severe cloacal anomaly, involves an anterior abdominal wall defect in which 2 hemibladders are visible, separated by a midline intestinal plate, an omphalocele, and an imperforate anus.

Initial surgical treatment during the newborn period involves:

- closing the omphalocele
- repairing the bladder
- creating a vesicostomy
- performing a colostomy for fecal diversion

Sacrococcygeal Teratomas

Sacrococcygeal teratomas (SCT) represent the most common neonatal tumor with an incidence of 1 in every 35,000-40,000 live births. There is an unexplained female predisposition with a 3:1 female to male ratio. In the era of increased use of routine prenatal imaging, most SCTs are diagnosed in utero with ultrasound. Feta MRI serves as an adjunct imaging modality because it is able to differentiate SCT from other sacral pathologies such as myelomeningoceles.

Sacrococcygeal teratomas are most commonly classified using the Altman classification:

- **Type 1** – is predominantly external
- **Type 2** – is external with an intrapelvic component
- **Type 3** – is primarily intrapelvic and intraabdominal with a small external component
- **Type 4** – is presacral with no external component

Although neonates with SCT usually have good prognosis, fetuses with SCT are at high risk for complications in utero and perinatally, usually due to the size and vascularity of the lesion. Poor outcomes of prenatally diagnosed SCTs have been associated with factors such as increased vascularity, presence of a solid tumor and a tumor volume to fetal weight ratio (TFR) greater than 1.2. Large, highly vascular SCTs are associated with high mortality and morbidity usually due to polyhydramnios causing premature labor and birth and high-output cardiac failure leading to placentomegaly or hydrops. Repeated ultrasound assessment of prenatally diagnosed SCT is therefore important to evaluate any increase in the size of the tumor.

Factors such as fetal hydrops and premature labor may necessitate fetal intervention including open fetal excision/debulking and intrauterine endoscopic laser ablation. In the immediate neonatal period, neonates with SCTS may require management in the intensive care unit if they have complications such as prematurity, high-output cardiac failure, disseminated intravascular coagulation and rupture or bleeding for the tumor. An uncommon but highly lethal scenario is bleeding from a large SCT tumor. In this situation, placement of a temporary tourniquet around the base of the tumor may be a lifesaving intervention that allows the child to make it to the operating room.

SCTs are otherwise managed postnatally with surgical resection, once the infant is stable. The prognosis is dependent on presence of malignancy and the ability to completely resect the tumor. Most SCT recurrences occur within 3 years of resection therefore all patients should be monitored with physical examination and lab studies including AFP and CA 125 every three months for at least 3 years.

Suggested Reading

Peripheral and Central Venous Access

1. Pettit J, Wyckoff MM. Peripherally inserted central catheters. Guideline for Practice. 2nd ed. National Association of Neonatal Nurses; 2007.

Specific Surgical Conditions

1. Catania VD, Lauriti G, Pierro A et al. Pediatr Surg Int (2016) 32: 1157. doi:10.1007/s00383-016-3974-2
2. Morris G, Kennedy A & Cochran W Curr Gastroenterol Rep (2016) 18: 16. doi:10.1007/s11894-016-0490-4
3. Zani A, Yeh, JP B, King, SK et al. Pediatr Surg Int (2017) 33: 245. doi:10.1007/s00383-016-4016-9
4. Krishnan U, Mousa H, Dall'Oglio L, et al. J Pediatr Gastroenterol Nutr 2016 Nov;63(5):550-570. DOI: 10.1097/MPG.0000000000001401.

Section 17: Overview of Nursery Routines

Editors: Lakshmi Katakam and Lisa Owens

17.1 Daily Routines

Charting

Weight Charts and Weekly Patient FOCs and Lengths

Daily weights should be ordered as well as weekly FOC and lengths (usually measured using length boards). These are recorded in the EMR and are plotted on growth charts. This information is extremely helpful in assessing the nutritional status and progress of our patients. The most current information should be available for rounds with our nutrition team.

Communicating with Parents

Physicians and nurse practitioners are expected to updated parents on a regular basis and document the frequency of updates and nature of important conversations, preferences and special circumstances in the progress note as they see fit.

Child Life

Child Life services is devoted to the psychosocial needs of hospitalized children and their families. In the nurseries, Child Life focuses on developmental needs of newborns, parent support, parent education, and sibling support and preparation. Specifically, Child Life can provide developmental support for infants identified to be at high risk for developmental delays and can offer hospitalized infants a variety of sensory and motor experiences that may facilitate development. Since infants view Child Life Specialists as safe, they can provide infants with noninvasive tactile stimulation and cuddling.

Child Life offers play and development classes for the parents of healthy infants to promote parental involvement and strong parent-infant bonding.

Individual support and education can be offered to parents who may have a difficult time attaching to their infant or who seem very scared and uncomfortable about touching and holding their infant. A photo book has been compiled to show to parents before they visit the NICU and to prepare them for what they will encounter. Child Life also can work with siblings who might be concerned about the baby who remains hospitalized. When a death occurs, either stillborn or neonatal, Child Life offers support and resources to the parents and family.

Occupational and Physical Therapy

Situations in which an OT-PT consult may be helpful include neurologic and musculoskeletal abnormalities, peripheral nerve injuries, chromosomal and non-chromosomal syndromes, feeding, and long-term respiratory problems.

Infection Control

Ch 8.1-Infection Control and Prevention.

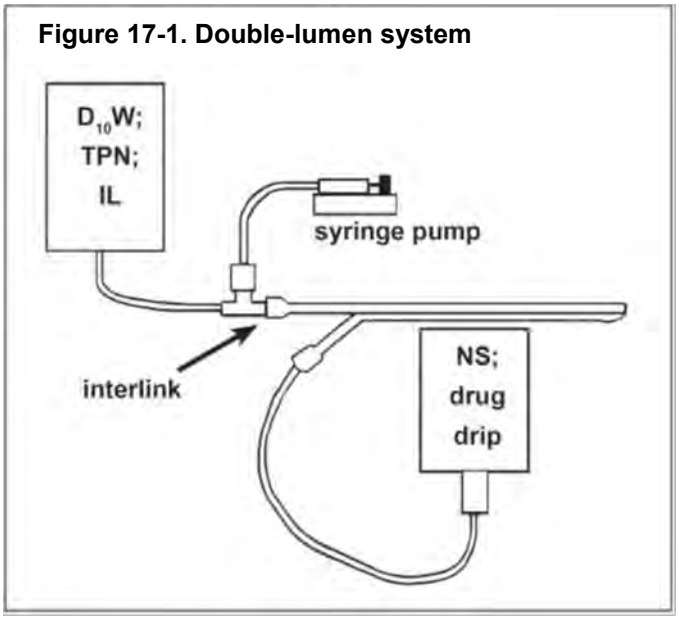
Nutrition Support after Discharge

Ch 13.6-Discharge Nutrition Preparation.

Parent Support Groups

A parent support group meets regularly at Texas Children's Hospital and meetings of parents can be arranged at Ben Taub. Parents should be encouraged to take advantage of these services, especially if the infant has chronic problems.

Figure 17-1. Double-lumen system



ROP Screening

Sec 1–Care of Preterm Infant and Ch 1.1-General Care (Babies < 1500 g)

Neurodevelopment Screening

A neurodevelopmental consult is required for all infants less than 1000 g birth weight and all infants treated with extracorporeal membrane oxygenation (ECMO). Requests for consults on infants who do not meet these criteria, but are considered high risk for neurodevelopmental problems by the attending physician, are done on an ad hoc basis. The request for consultation should be initiated at least two weeks prior to discharge, if feasible.

17.2 Umbilical Catheters

Background

Although umbilical artery and vein catheters are widely used, the potential for serious complications is significant. Reported complications requiring catheter removal range from 5.5-32% for UACs and 10-50% for UVCs. CLABSI is a complication of umbilical catheterization and indwelling vascular catheters account for a major proportion of hospital acquired infections.

Severe complications of UVC placement (excluding CLABSI) include: vena cava or right atrial thrombosis, portal vein thrombosis, hepatic vein thrombosis, hepatic hematoma or infarct. Pericardial effusion and tamponade also occur. Duration of catheterization and catheter position are the most commonly associated risk factors. The appropriate central position is achieved in 30 -73% of attempts. One prospective observation study of 100 neonates using serial ultrasound demonstrated: 64% - satisfactory position, 12% in liver, 15% below liver and 8% in a portal vein or branch. "Silent" portal vein thrombosis was detected in 43%, with significant increase in risk after 6 days duration. Portal vein thrombosis in considered a severe complication of UVC use because of its association with long term portal hypertension. Severe complications do occur in infants with appropriate catheter position. However, any position other than the ideal central location is accompanied by significantly increased risk of serious events or adverse long-term outcome.

Risks of UAC placement include vasospasm, thrombosis, systemic embolization, organ ischemia or injury to a lower extremity. "High" position (T6-T9) UACs are associated with lower risk of vascular complications compared to the low lying position.

Common Indications for UVC

- < 1250 g BW
- > 4 PIV attempts
- Hypoglycemia
- Need for high osmolar infusion (Ca, Mg or >12.5% glucose) or certain vasoactive drugs
- Need for PGE infusion
- Resuscitation
- Exchange transfusion or partial exchange
- Potential ECMO (especially CDH)
- Patients with severe cardiopulmonary compromise- as individually selected

Potential Indications for Double Lumen UVC

- < 1000 g BW
- PGE
- ECMO likely

Common Indications for UAC

- < 1000 g or < 26 weeks
- Cardiopulmonary compromise requiring frequent blood gas or BP monitoring
- CHD requiring specific care or interventions
- Potential ECMO
- Respiratory distress following resuscitation

Contraindications for Umbilical Catheterization

- Patient has active infection (positive blood cultures, specific signs of systemic infection)
- Abnormal or distorted anatomy that produces catheter malposition (relative)
- Abdominal wall defects: omphalocele, gastroschisis
- NEC
- Vascular compromise of lower extremities or target organs.
- Thrombosis of target vessel

Catheter Size

- 3.5 Fr. for < 1500 g
- 3.5 - 5 Fr for > 1500 g
- 8 Fr – a specially designed catheter for exchange transfusion in term sized infants

UVC Catheter Placement Position

Optimal catheter position is junction of IVC and right atrium. This corresponds to a position just above the diaphragm or between the T9-10 vertebrae. There are several published formulae and graphs to estimate the required depth of placement of UVCs, none of which is perfectly predictive. Based on consensus, the Baylor Neonatology Division recommends the modified Shukla formula:

$$\text{Insertion depth} = \frac{3 \times \text{BW in kg} + 9 \text{ cm}}{2}$$

This formula reduces the incidence of over insertion without increasing that of under insertion. In a recent RCT the authors reported a low rate of correctly positioned UVC catheters but no difference between use of this formula and that of classic graphs derived from body surface measurements (31% vs 28%).

If a suboptimal catheter position must be used for initial stabilization, obtain alternate access as soon as possible. If UVC catheter is in liver, pull back to low position if catheter must be used temporarily to achieve stabilization. Avoid infusion of medications or hyperosmolar solutions if not in central position.

A low-lying UVC should only be used for temporary vascular access when suitable alternative access is not available or patient condition is critical and unstable. In these circumstances the catheter should be replaced as soon as possible by either an optimally placed UVC (second attempt at UVC placement), a PICC or peripheral IV. UAC Catheter Position

Optimal catheter tip position is above the diaphragm between T6-T9. This is the "high" position recommended in most publications. A Cochrane database systematic review concluded the "high" position resulted in fewer vasospastic, ischemic and thrombotic complications as compared to low lying catheters.

There are several published formulae and graphs to estimate the required depth of placement of UACs, none of which is perfectly predictive. By consensus, the Baylor Neonatology Division recommends use of the weight based formula of Shukla and Ferrara:

Depth of insertion = (3 x BW in kg) + 9 cm.

A recent RCT comparing use of the Shukla weight based formula to use of graphs derived from body surface measurements reported a significantly higher rate of correct UAC positioning using the weight based formula (91% vs 50%, p=0.001)

Duration of Catheterization

Umbilical catheters should be removed as soon as possible.

Recommended maximum duration of use:

- UAC < 5 days
- UVC < 7 days

Any special circumstance necessitating prolonged duration should be documented in the medical record

"Second Attempt" at Catheter Placement

A second attempt at successful catheter placement is not precluded but should be restricted to the time frame of the original procedure. An exception is that of catheter placement for exchange transfusion or partial exchange, as these procedures may occur later in the clinical course. We do not recommend the "2 catheter" technique for repeat attempts.

Indications for Umbilical Catheter Removal

CLABSI

If essential for medications, remove as soon as medications completed or alternative route established

Do not keep for blood sampling only unless frequent sampling is essential and alternate access not feasible.

NEC

UAC –Vascular thrombosis or persistent vasospasm or ischemia of lower extremity (not promptly improved by warming contralateral extremity)

Confirmation by Imaging and Documentation in the Medical Record

Because estimation of catheter position by formulae or graphs often leads to excessively high or low placement of the catheter tip, radiographic confirmation is essential. Insertion to correct estimated depth does not guarantee proper position of catheter tip. Radiographic (or occasionally US) confirmation of position should be obtained after catheter placement or re-positioning. The procedure of umbilical catheter placement is not complete until there is clear radiographic documentation of optimal catheter position.

The EMR procedure note should document: (a) if the initial radiograph reveals the catheter to be too high, the extent by which the catheter was pulled back prior to obtaining the follow up radiograph; (b) the final depth of placement of the catheter; (c) reasons for leaving a sub-optimally placed catheter in place if this is necessary.

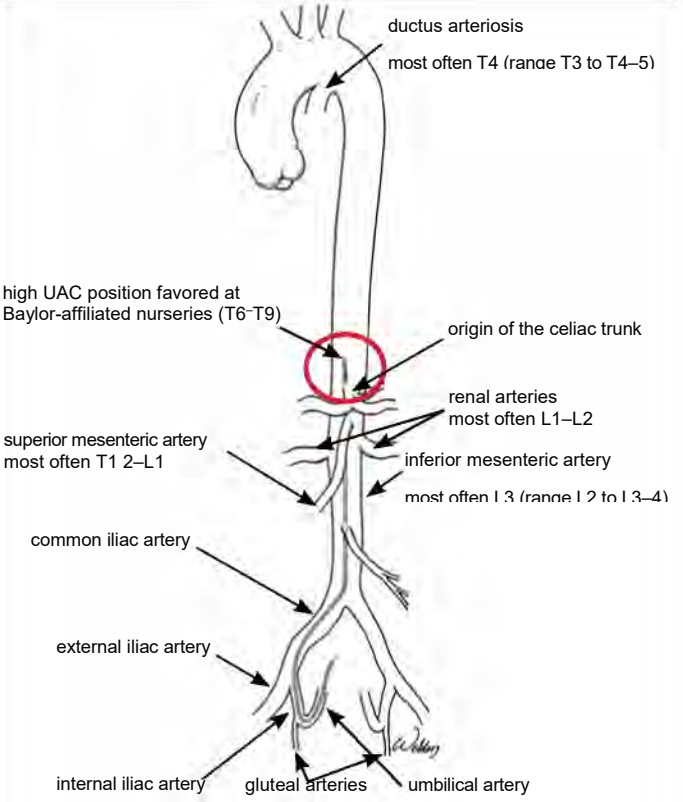
Maintenance of Umbilical Catheters in an Optimal Position

Umbilical catheters, even if optimally placed, may become displaced if patient is moved, the abdomen becomes distended or if they are not secured well. They are also at risk of accidental dislodgement with serious consequences, bleeding. The depth of insertion of the catheter should be documented by the bedside nurse each shift and should be reviewed by the clinical team as part of daily patient rounds and the continued need should be documented in the medical record. If the depth of insertion is found to be different from the original depth, or if there is suspicion of displacement or misplacement, a radiograph or ultrasound study should be obtained.

Figure 17-2. Suggested catheter tip placement; anatomy of the great arteries and veins

Position must be confirmed by x-ray and catheter repositioned if necessary.

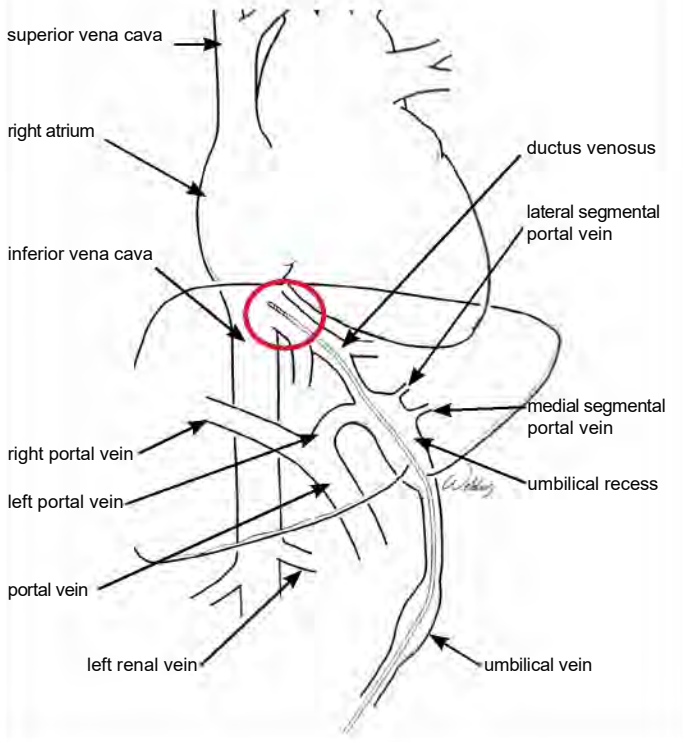
UAC: T6-T9



UVC: juncture of the IVC and the right atrium

Placement within the right atrium may cause dysrhythmia or intimal damage.

UVC ≅ shoulder umbilical length x 0.75



Possible Variances

At TCH, the Vascular Access Team (VAT) is available 24/7 to assist with alternative central access. However, availability of PICC placement is limited in many other Baylor affiliated nurseries. For this reason, guidelines for catheter use/placement in those hospitals with limited vascular access placement teams should be reviewed. In addition, a small proportion of patients have complex clinical circumstances that may necessitate longer than recommended duration of an umbilical catheter, short term use of a low lying UVC or insertion of a double lumen UVC in infants >1250 g BW.

Such instances must be individualized and the attending physician must determine and document the risk versus benefit evaluation. The medical record note should document reasons for the alternate care strategy employed and more desirable options sought as soon as possible.

Potential variances include:

- Critical CDH patients
- 23-24 week ELGAN
- Persistent hypoglycemia
- Long term PGE
- Need for frequent lab work
- Limited availability of alternative vascular access
- Available resources at the Baylor affiliated nurseries

Miscellaneous

- Do not infuse medications or TPN through UAC
- Presence of an umbilical catheter does not preclude trophic feeds.
- Avoid air in catheter set up – many neonates still have anatomic R-L shunts.

17.3 General Guidelines– Ben Taub General Hospital

Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS)

TeamSTEPPS is our patient safety and team work framework at Ben Taub Women's Services (3rd floor). This includes multidisciplinary team huddles every morning and evening.

"I need clarification" is our STOP the LINE safety phrase for BTGH. If you hear this phrase please notify your next in line supervisor right away to join the discussion.

Triage of Admissions

Newborn Nursery Transition Area

The normal newborn transition is with mother in L & D. More complex infants are transitioned in the Level 2 nursery or NICU. **(Table 17–1)**

Daily Activities

Rounds

Rounds are made daily during morning hours. In NICU we wear blue gloves in addition to hand hygiene for all patient contact.

Neo Rapid Response Team

(Neonatology Fellow, Upper level resident, Neo Charge Nurse, Neo Respiratory Therapist, and intern) Labor and delivery has 12 LDRP's (labor, delivery, recover, and post-partum) for low risk patients and 2 operative suites for cesarean sections and the delivery of high risk patients (Rooms 14 and 15). The need for our Neo RRT to attend a delivery is activated through designated pagers provided by the hospital. The pager will display the room number that the mother is delivering. This pager will also serve as a notice to respond to a code situation in other areas of the 3rd floor such

Table 17-1. Triaging Babies for Transitioning

	Level 1	Level 2	Level 3
Gestation Age by Mother's Dates	≥ 36 weeks	32-35 weeks	< 32 weeks
Weight	≥ 2250 grams	1801-2249 grams	≤ 1800 grams
5-minute Apgar	≥ 7	4-6	0-3
Meconium	Asymptomatic baby with or without meconium below the cords		Symptomatic with meconium below the cords
Respiratory distress		Pedi Evaluation No oxygen requirement – High Risk	Pedi Evaluation All babies requiring oxygen or greater support
Sepsis risk factors	Maternal fever or PROM > 24 hours without chorioamnionitis and asymptomatic baby	Chorioamnionitis or Pedi Evaluation – baby with mild symptoms	Pedi Evaluation Baby with significant symptoms
Diabetic mother	All classifications	Symptomatic	High GIR need requiring central access
Congenital anomalies	Minor that are non-life threatening e.g. club foot, renal pyelectasis, DDH, ear tags	Intermediate anomalies e.g. cleft lip with cleft palate	Major anomalies e.g. gastroschesis, myelomeningocele
In-utero exposure	Alcohol, tobacco, illicit and/or prescribed medications at risk for withdrawal HIV positive HSV without active lesions PPD positive without active TB	Substance exposure requiring extended monitoring or medication treatment for withdrawal Active maternal HSV lesions at delivery	Active maternal TB, or maternal varicella
Deal, Gannon, Garcia-Prats Oct 2020			

as 3B (3112), 3C (3113), Level 2 (3114) and 5555 for the first floor Emergency Room. In room stabilization is our practice with criteria in place for dealing with low risk and high-risk delivery situations (This will be included as part of your unit orientation). A five-person limit has been agreed upon for attendance in LDRPs.

Since there has been a great emphasis on reduction of wound infections on OB patients, all physicians are required to use BTGH laundered scrubs. Ensure you have access to the scrub Pyxis located in L & D on your first day of the rotation.

When entering the room, identify yourself and the team to the family and the delivering physician/midwife. After the delivery, please take the time to speak to the parents and the delivering physician/midwife regarding the status of their baby and the disposition of their baby after stabilization (e.g., "your infant is fine and should be able to transition with you" or "your baby will need antibiotics for a few days since you have an infection.")

Scheduled Lectures

Neonatology lectures at Ben Taub are scheduled on a variety of topics Monday through Thursday at 8:30 am in the Neo Library for the NICU team, and Monday – Friday at 12 noon in the 3-D classroom (or by Zoom link) which all residents and students on the nursery rotations should plan to attend. If needed, rounds will be interrupted to assure participation by residents.

Pediatric Grand Rounds each Friday from 8:30 to 9:30 am at Texas Children's Hospital can be seen by videoconference in the 3-D classroom (or by Zoom link) at Ben Taub.

Ordering Routine Studies

Routine Scheduled Labs, X rays, etc.

Schedule lab work, X rays, ultrasound exams, etc. for routine times unless a true emergency exists. Nurses draw the labs in each unit at 5 am for routine morning labs. I Stat (POC) is available for blood gas analysis, glucose, and a basic metabolic panel in both level 3 and level 2 nurseries.

Ordering TPN, Other Fluids, and Feeds

At Ben Taub, TPN must be reordered daily. The order must be placed by 2 pm to be processed by the pharmacy to be started at 9 pm. If the fluids must be changed urgently due to metabolic instability when appropriate, simple IV fluids should be ordered. Please remember, there is no such order as a STAT TPN. All TPN orders are routine. Batch TPN in a D_5W formulation is available in the Pyxis in the NICU at all times. Donor milk is available for babies with a birth weight < 1800 grams or twins (and higher order multiples) of a baby who qualifies. HMF is used as our routine fortifier for preterm babies. We now have available Prolacta® cream and liquid protein supplement for babies under specific circumstances. These should be ordered in collaboration with our Neonatal Dietician on rounds only.

Consultations

Cardiology

Currently, TCH pediatric cardiology provides limited services to our patients here at BTGH. Routine cardiac ECHO's are available on a weekday 8 am-3 pm by ordering an ECHO (#93303), filling out a request form, and calling our BT Pedi/Neo sonographer at Cisco 3-9404/pager 281-952-0223. An "urgent ECHO" can be arranged for infants with hemodynamic instability, severe cyanosis, and cardiac compromise 24/7 by NICU faculty consult with the TCH Outreach Cardiology faculty (832-733-5887 or via TCH page operator 873-824-1000) prior to ordering the study. Questions about follow-up after routine ECHO's can be discussed with the Outreach Cardiologist as needed. **See Pediatric Resident or Fellow Reference Binder** for necessary forms and complete process.

ECG's and Holter scans are performed on the nursery service and sent digitally to the TCH electrophysiology lab. Turn-around time for the ECG reports is usually 24 hours, and 48-72 hours for the Holter scans.

Ophthalmology

For ROP screening guidelines, refer to **Ch 1.1-General Care (Babies <1500 g)**

Notify Pediatric Ophthalmology upon the patient's initial admission to the NICU by ordering the consult in EPIC. A book is kept once referral faxed with date of anticipated first exam, which are generally performed on Tuesdays.

Other Consultations

Other consultations are called through TCH page operator.

Neurodevelopmental

Neurodevelopmental follow up is available when needed for Harris Health patients at Pasadena Clinic or through direct referral into the Desmond Neonatal High-Risk Follow Up Clinic at TCH depending upon parental preference.

Transfer and Off-Service Notes

Every infant must have an off-service note or transfer note completed by the house officer at the appropriate times. When transferring a baby to TCH, please be sure to write the transfer note on a discharge note template in EPIC so it is recognized by Health Information Management.

Discharge Planning

Texas Health Steps (THS) Newborn Follow up Clinic-Ben Taub

Criteria for patients referred to THS for early follow up:

- All normal newborn (Level 1) infants should be encouraged to have their first early follow up appointment with Texas Health Steps (THS) clinic unless parents are unable to travel to Ben Taub. Ben Taub is now Baby Friendly, and all mothers could really benefit from a post discharge lactation follow up at the breastfeeding clinic. Note that most other clinics do not have lactation consultants on site. Additionally, parking will be validated for the first clinic visit. The two week appointment can also be scheduled here, unless their medical home is Legacy, or mom has a two week appointment herself at one of the Harris Health clinics; then mom and baby will be seen together. All newborns with an elevated initial direct bilirubin (0.8 or greater) are to follow up with Newborn Texas Health Steps Clinic for the initial early follow up visit and the two week visit for a repeat of the direct bilirubin to assist in data collection. If the initial direct bilirubin is less than or equal to 0.7, the baby does not need a repeat direct bilirubin at Health Steps clinic at the two week visit despite the value of any repeat direct bilirubin values (per Dr. Harpavat, GI).

- Normal newborns in CPS care or in the process of foster care or screened for neonatal abstinence syndrome
- Intermediate Care Nursery Patients-Level II – meeting the following diagnostic criteria may be referred to the Newborn Texas Health Steps Clinic for their hospital discharge follow-up and/or 2 week well childcare visit.

Criteria:

- Term infants (GA at birth) after management for maternal chorioamnionitis
- Term infants (GA at birth) after assessment and treatment for hypoglycemia
- Term infants (GA at birth) after assessment and treatment for hyperbilirubinemia requiring phototherapy
- Late preterm infants of 35-36 weeks (GA at birth) who have had an uncomplicated hospital course for prematurity
- Term infant with a brief stay in Level III (< 24 hours) for CPAP/RDS that then transitioned

Babies not appropriate for Texas Health Steps Clinic:

- Infants < 35 0/7 weeks gestation at birth
- Discharged home on oxygen or NG/GT feeds
- Complex diagnoses
- Most infants discharged from Level III
- Infants for whom the NBS #2 has been drawn and who have no specific issue in need of follow up

All these infants really do need a medical home from the beginning and will need direct physician care.

Please remind parents:

- ✓ Parking is free and validated for them.
- ✓ Mom will receive up to 45 minutes with the nurse to ask questions at initial visit.
- ✓ Mom will receive breastfeeding help with the lactation consultants.

Outpatient ECHO's are now available as needed through THS.

If infant needs referral to another service for follow up after discharge, the referral and appointment must be made prior to discharge.

For discharges that require Consultative Clinic follow-up, the discharge summary must be sent by fax to the follow-up physician(s). The discharge summary should include a problem list, relevant clinical information, list of medications, as well as condition and the plan of care at the time of discharge.

17.4 General Guidelines– TCH, WT and PFW NICUs

Triage of Admissions

The normal newborn transition is with mother in the Mother-Baby Unit (MBU). More complex infants are transitioned in the NICU. **(Table 17–2)**

Transfers from NICU to MBU

For anticipated transfers to MBU, the resident is responsible for completing the following tasks (even if transfer is expected to occur after 5pm):

- Mother is an inpatient in the MBU or L&D and her discharge is not planned for the day of infant's transfer.
- Identify the accepting MBU pediatrician
  - ➢ Options: Baylor newborn hospitalist, Kelsey-Seybold, or Private pediatrician
  - ➢ If unknown, ask the parents about follow-up pediatrician.
- Contact the accepting pediatrician to provide hand-off
  - ➢ Baylor: During daytime hours, use Voalte ("Pedi 1" or "Pedi 2"). After 4:30pm, page via SPOK ("PFW-Mother/Baby Units (NEO) on-call")
  - ➢ Kelsey-Seybold: page the hospitalist 713-558-7645
  - ➢ Private pediatrician: contact their office
- Follow up any pending results (laboratory, radiology) and order AM labs if necessary.
- Complete Transfer note and include name of accepting physician
- Enter transfer orders in EPIC

Table 17-2. Admission criteria for Pavilion for Women MBU and NICU

	MBU	NICU
Gestation Age by Mother's Dates	≥ 35 weeks	< 35 weeks
Weight	≥ 2000 grams	< 2000 grams
5-minute Apgar	≥ 7	< 7
Respiratory distress	First 6 hours: suspected delayed transitioning without oxygen requirement, significant distress, hypoglycemia, or sepsis risk factors	Failed transition, significant distress, and/or oxygen requirement
Suspected Sepsis	Chorioamnionitis and asymptomatic infant requiring empiric antibiotics	Symptomatic infant
Neonatal Withdrawal Syndrome		Neonatal abstinence scoring
Congenital anomalies	Comfort care patients Minor anomalies that are non-life threatening (e.g. club foot, renal pyelectasis, DDH, ear tags)	Major anomalies

Transfer and Off-Service Notes

Every infant must have an off-service note or transfer note completed by the house officer at the appropriate times.

Neurodevelopmental Follow-up

High-Risk Developmental Follow-up Clinic

This multidisciplinary clinic provides longitudinal neurodevelopmental assessment of infants who weigh less than 1000 g at birth and all infants treated with extra-corporeal membrane oxygenation (ECMO). Clinic staff includes social work, PT/OT, neuropsychology, and neonatology. The timing of a clinic appointment is determined by the Developmental Care team and is based on risk factors for poor neurodevelopmental outcome.

17.5 General Guidelines– TCH Woodlands

In general, TCH-Woodland follows all Texas Children's Hospital guidelines but some workflows differ.

- Morning report is M-W-F at 8 am in the second floor conference center and is hospital-wide. All services are expected to attend.
- Sign out between Neonatologists generally occurs immediately before or immediately afterward of the morning report.
- Evening sign out is at 5 pm and includes the on-call neonatologist and NNP.
- In place of daily teaching bedside rounds, multidisciplinary rounds on all babies occur on Mondays and Thursdays at 11 am in the NICU conference room. All services are represented and each patient's plan of care is reviewed.
- All Medical Center campus neonatology conferences and meetings are broadcast either by video or phone. Pediatric Grand rounds from 8.30 to 9.30 am is also broadcast on Friday.
- The Neonatologist and NNP are members of the house-wide code team and respond to all emergencies in the facility.
- TCH Woodlands has access to most subspecialists on campus. They can be reached via Spok. Unavailable is cardiac surgery, ECMO and neurosurgery.
- ROP screening exams are performed on Monday by the Ophthalmology team and the list is maintained and tracked in a process similar to TCH Main campus.
- There is a multispecialty developmental clinic on the outpatient campus. Disciplines participating in the clinic are nutrition, PO, OT, pulmonary and developmental pediatrics. A consult should be ordered prior to discharge to facilitate an initial developmental exam and introduction to the clinic. Follow up appointment to the clinic will be made at the time of discharge.

17. 6 Transfer Guidelines for the Community Initiative (CI)

Baylor Neonatology currently staffs multiple NICUs in the greater Houston area and surrounding communities. The purpose of this chapter is to assist the Neonatologists in the community with decision making regarding transfer of infants who require a higher level of care. The intent is to encourage conversations with the main campus for support and assistance in management of conditions that are time sensitive and may exceed the capability of referring units.

Infants with Moderate or Severe HIE (Passive Cooling in Community NICUs)

Initiation of therapeutic hypothermia (TH) is time sensitive. Early initiation of TH has shown to improve outcomes. In order to reach the target temperature early without overcooling, we recommend the following:

Time to initiate Passive Cooling

After initial resuscitation and stabilization in the delivery room, referral centers should perform through evaluation of infants at risk for HIE. If an infant meets the criteria for TH (refer section 9), passive cooling could be initiated. Infants with moderate or severe encephalopathy using 'Modified NICHD Sarnat criteria' (refer section 9) are routinely considered candidates for cooling. Infants who do not meet criteria based on age, gestational and severity of encephalopathy can be discussed with the medical director on a case by case basis if clinical impression warrants reconsideration or if eligibility is unclear.

Passive Cooling Steps:

1. After an infant is evaluated for perinatal HIE and determined to be a candidate for TH, Turn OFF Radiant Warmer or other sources of supplemental heat.
2. Obtain core (rectal) temperature and follow temperatures frequently. Pass lubricated rectal probe (up to ~ 5-6 cm). If rectal probe not available, may use axillary temperature**.**
3. Turn OFF the temperature in the transportation incubator prior to transport if this determination is made in the delivery room.
4. On arrival to NICU, Place infant under the Radiant Warmer/ open incubator and obtain rectal or axillary temperature.
5. **Temperature Monitoring**
   - Place a skin temperature probe for continuous monitoring. The servo temperature can be set at 34.0°C. Alternatively turn OFF the heater output to zero.
   - Continuous or intermittent q15 mins rectal temperature monitoring is the best way to monitor core temperature. If rectal probe not available, axillary temperature q15 minutes should be used. Please note, axillary temperature is not a reliable indicator of core temperature and skin temperature should not be used to make decisions.
6. RN to attempt peripheral IV (avoid scalp IVs) on arrival to NICU while the team sets up for umbilical lines. Insert UVC Double Lumen and single lumen UAC.

7. **Measures to avoid overcooling:**
   - If rectal or axillary temperature:
     a. Decreases to < 33.5˚C (92.3˚F), turn ON heater output to 10-25%. May consider maintaining at low heater output (~10%) until temperature reaches 34˚C.
     b. Decreases to < 33˚C, use a warmed blanket over infant's trunk until rectal temperature reaches 33˚C along with heater output of ~25%.
     c. Remove the warm blanket once temperature reaches 33 and may adjust the heater output to ~10-25%.
     d. Turn OFF Heater output at 34 ˚C.
8. Call TCH Transport center 832-824-5550 to initiate transport.

Laboratory studies

1. Request cord gas at delivery. Postnatal blood gas with lactate within one hour of delivery.
2. Obtain: CBC, Blood culture, comprehensive metabolic panel (CMP), ionized calcium, bedside glucose.

Fluid and Electrolytes

1. NPO and Total fluid goal (including medication and flushes) approximately 40ml/kg/day
2. IV Fluids with dextrose concentration appropriate to avoid hypoglycemia.
3. Maintain GIR at least ~4mg/kg/min.

Medications

1. Antibiotics: Start Ampicillin and Aminoglycoside therapy.
2. Sedation: Prevent any shivering. Use morphine 0.1mg/kg or consider morphine drip (load with 0.1mg/kg and begin at 0.01mg/kg/hour).
3. Antiepileptics: If evidence of clinical seizures, consider Phenobarbital Loading dose of 20 mg/kg IV; And discuss with neurology

Monitoring and Documentation Until Infant Transported

1. MD to document neurology exam hourly till time of transfer.
2. Document Sarnat exam
3. RN to document rectal/axillary temperature and vital signs q 15mins.
4. Time of passive cooling initiation and time to reach target temperature to be documented.

Family Update

- Ensure mother and family are updated, supported and reason for transfer clearly communicated.

Neonates with Mild HIE at Referring NICU

In certain instances, early abnormal neurologic exams rapidly improve and hence may not require transfer for TH. As initiation of TH is time sensitive, physicians at referring hospitals, managing infants with mild HIE should consider the system related factors (distance of the referring hospital, transport time, transport team availability) when planning to observe infants at their facility.

If mild HIE symptoms persist at 2-3 hrs of life, with no signs of improvement or deteriorating biochemical markers, referring physicians should call TCH neonatologist via transport center and discuss the optimal place of observation (referring facility vs TCH). This approach can avoid delayed initiation of active TH or a missed opportunity to start effective TH within the therapeutic window.

Infants with Hemolytic Jaundice

Severe hyperbilirubinemia near or at exchange transfusion levels is a medical emergency. The time needed for preparation for exchange transfusion (ET) especially the blood bank procedures involved to prepare and supply blood, almost always requires 4-6 hours and must be factored in to the decision-making process. Several factors play a role in transferring infants for ET: the transfer time, serum bilirubin level (TSB), risk of neurotoxicity and the underlying disease process. Referring facilities should consider the following criteria for calling and informing TCH about a potential transfer for ET.

Criteria for calling and discussing with TCH neonatologist (one or more of the criteria below)

1. Severe hemolysis defined by a TSB ≥ 17 mg/dL accompanied by a hematocrit <35%.
2. TSB levels near exchange level (within 2-3 mg/dL) despite intensive phototherapy for 4-6 hours and intravenous immunoglobulin **(Ch 7.5- Fig 7-4 for Exchange Transfusion threshold).**
3. Serum bilirubin rising more than 0.5-1 mg/dL per hour despite intensive phototherapy
   1. B/A ratio

Table 17-3. B/A ratio

Risk Category	B/A ratio at which call to inform TCH for potential exchange transfusion
Infants ≥ 38 0/7 wk	6.5
Infants 35– 36 6/7 and well or ≥ 38 0/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	6
Infants 35–36 6/7 if higher risk or isoimmune hemolytic disease or G6PD deficiency	5.5

Criteria for Transfer to TCH for Exchange Transfusion **(Ch 7.5-Management of Neonatal Jaundice)**

Infants with Hypoxic Respiratory Failure

Infants born with hypoxic respiratory failure (HRF) are initially managed with treatment of the underlying cause, optimizing ventilator support, stabilizing hemodynamic status and use of sedation with analgesia as needed. Many term and late-preterm infants with HRF are initially managed in level 2

or level 3 centers where inhaled nitric oxide (iNO) or Extracorporeal Membrane Oxygenation (ECMO) may not be available. To optimize patient outcomes, it is important that infants with escalating needs are identified early and transferred to a higher level of care in a timely manner. Early transfer of infants who are potential ECMO candidates can help minimize delays and risk of instability during transport. Consider the following criteria in the decision making process. **(Ch 15.13-Neonatal ECMO for general inclusion criteria for ECMO)**

Criteria for calling and discussing with TCH neonatologist and/or ECMO physician (one or more criteria below)

1. Oxygenation index of $\geq$ 15
2. Alveolar-arterial pO_2 gradient of $\geq$ 400 mmHg
3. $FiO_2 \geq 60 – 80\%$
4. Conversion from conventional to high frequency ventilation
5. Initiation of iNO
6. Hypotension requiring vasopressor support
7. Consideration of congenital cyanotic heart disease as a cause of hypoxia

Criteria for transfer to TCH NICU (one or more criteria below)

1. Oxygenation index of $\geq$ 20
2. Alveolar-arterial pO_2 gradient of $\geq$ 600 mmHg
3. $FiO_2 \geq 80 – 100\%$
4. Intravenous Dopamine infusion $\geq$ 15 mcg/kg/min or Epinephrine infusion $\geq$ 0.2 mcg/kg/min or addition of a second vasopressor
5. Inability to perform an echocardiogram to exclude congenital heart disease
6. Lack of response to iNO or increasing OI after initial response to iNO

Infants with Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) continues to be one of the most common surgical emergencies in the newborn period. Options for surgical intervention include exploratory laparotomy and placement of a peritoneal drain. Many studies have attempted to develop clinical criteria or identify biomarkers to predict surgical NEC, however, the presence of pneumoperitoneum remains the only absolute criteria for operative intervention. Clinical deterioration is a relative indication that requires clinicians to consider if the potential benefit is greater than the risk of operative intervention. While the majority of babies diagnosed with NEC improve with bowel rest, decompression of the GI tract and parenteral antibiotic therapy, it is important to identify infants at highest risk for progression to surgical NEC to minimize delays in transport to a surgical center. Consider the following criteria while determining when to initiate transfer.

Criteria for calling TCH neonatologist to discuss infants at risk for surgical NEC (one or more criteria below)

1. Presence of a fixed and dilated loop or pneumatosis on serial abdominal radiographs
2. Presence of portal venous gas on abdominal radiograph
3. Presence of a fixed abdominal mass or abdominal wall discoloration
4. Focal fluid collection on ultrasound imaging
5. Hypotension with or without need for vasopressor
6. Positive blood culture with GI pathogen
7. Decreasing platelet count or persistent thrombocytopenia $< 100 \times 10^3$/uL or absolute neutrophil count <2000 cells/uL
8. Blood gas pH $\leq$ 7.25 or persistently elevated lactate $\geq$ 1.5
9. Persistently elevated or rising CRP

Suggested Reading

1. Barbara J. Stoll, Nellie I. Hansen, Edward F. Bell, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039-1051.
2. K Crawford, SZ, Kamupira, S Morley, AW Kelsall. G36(P) Outcomes of infants transferred from the neonatal intensive care to the paediatric ward and paediatric intensive care after 44 weeks corrected gestational age. Archives of Disease in Childhood 2018;103:A14.
3. Kieran EA, Laffan EE, O'Donnell CP. Estimating umbilical catheter insertion depth in newborns using weight or body measurement: a randomised trial. Arch Dis Child Fetal Neonatal Ed. 2016 Jan;101(1):F10-5. PMID: 26265678.

Section 18: Medications

Editors: Caraciolo Fernandes and Mohan Pammi

18.1 Medication Dosing

Usual dosing ranges of medications for newborns are detailed in **Tables 18–1, 18-2, 18-3.**

18.2 Managing Intravenous Infiltrations

(See Management of Drug Extravasations – Lexicomp)

Infiltration of intravenous (IV) fluids and medications can be associated with damage to the skin and underlying tissue. Hypertonic solutions, pressors, calcium-containing solutions, and blood may be especially caustic.

- Regular, close observation of the site by the staff helps identify this problem before it becomes serious.
- Secure peripheral IV lines with transparent tape or transparent polyurethane dressing so the insertion site is readily visible.
- Monitor peripheral IV sites for any of the following: redness, blanching, edema, capillary refill greater than 3 seconds at the site, or difficulty irrigating the IV.
- Stop the infusion and disconnect IV tubing. Do not flush the line prior to removal.
- Do not remove the needle/catheter if aspiration or antidote is indicated. Discontinue needle/catheter promptly if no aspiration or antidote is indicated.
- Nurse to notify the physician after discontinuation of the peripheral IV if the site remains edematous, red, blanched, or dark in color.
- Elevate the involved extremity. If the site is on the scalp, elevate the head of the bed.
- If indicated in extravasation guidelines under the individual agent that has infiltrated, apply dry, cold or warm compresses as indicated. Do not apply heat, especially moist heat, to any IV fluid extravasation.
- Continued close assessment with frequent vital signs may be important.
- Plastic Surgery consultation may be indicated.

Hyaluronidase

Hyaluronidase is used to treat IV infiltration resulting from hypertonic solutions. It should not be used to treat extravasations secondary to dopamine, dobutamine, epinephrine or norepinephrine. After skin preparation with povidone-iodine and allowing the skin to dry for 1 minute, inject 0.2 mL of 20 units/mL solution, subcutaneously or intradermally, into the leading edge of 5 separate extravasation sites with a 25-, 27-, or 30-gauge needle. Needle should be changed before each entry into skin to prevent bacterial contamination and minimize pain. Best results can be obtained if used within 1 hour of extravasation injury.

18.3 Common Antibiotics

Renal clearance in newborns is closely related to gestational age. Thus, elimination of antibiotics that are cleared by the kidney, as indicated by trough serum levels, is also related to postmenstrual age (PMA = gestational plus postnatal age). The recommendations in **Table 18–1** provide general guidelines for selection of initial antibiotic doses and intervals based upon categories of postmenstrual age, day of life, and body weight. Initial selected dose is designed to achieve serum levels effective against the spectrum of anticipated organisms. Interval of administration is intended to minimize risk of drug accumulation with possible toxicity. Antibiotic doses should be adjusted for weight gain on a weekly basis. Consult a pharmacist for assistance in patients with renal dysfunction.

Serum Antibiotic Levels

Measurement of serum levels is necessary when treatment is anticipated for longer than 48 hours or if renal dysfunction is present. Aminoglycoside peak and trough levels should be drawn before and after the third dose and a minimum of once weekly during therapy. Peak levels are obtained 30 minutes after the IV infusion is complete; a trough level is drawn immediately before the next dose. Both levels are necessary to determine safety and efficacy. Because aminoglycosides have potential for renal toxicity, measurement of BUN and creatinine is recommended. For complicated or severe infections, a Pediatric Infectious Disease consultation is recommended.

There is a correlation between vancomycin serum trough levels and efficacy. Trough levels should be maintained between 5 and 20 mcg/mL depending on organism, MIC, source of infection, and other patient factors. For pediatric patients, vancomycin at an appropriate dose is not nephrotoxic when used alone. Vancomycin serum levels should be performed if one of the following criteria is met:

- Known or suspected renal dysfunction
- Patients in whom treatment is unsuccessful
- At the request of the Infectious Disease, Renal Service, or Clinical Pharmacy Specialist

18.4 Analgesia

Morphine and fentanyl are the two most common analgesic agents used in the neonatal intensive care unit. The starting dose for morphine is 0.01 mg/kg/hour and fentanyl is 0.5 to 1 mcg/kg/hour. If pain/sedation is not adequately controlled, administer a one hour equivalent bolus of the current dose then increase the infusion by no more than 0.01-0.02 mg/kg/hr for morphine or 1 mcg/kg/hr fentanyl. This can be continued in a stepwise fashion every 30-60 minutes until desired pain score is achieved. Assess pain and sedation effect 30-60 minutes after each increase in continuous infusion rate. Tolerance to fentanyl doses commonly occurs within 3-5 days and within 5-7 day for morphine. Doses may require adjustment if the patient is continued on a continuous infusion past these timeframes.

For post-surgical pain, addition of scheduled acetaminophen via the enteral, rectal, or intravenous route can be considered to reduce opioid requirements. Continuation of acetaminophen for post-surgical pain should be re-assessed by the team every 48 hours.

Table 18–1. Guidelines for initial antimicrobial doses and intervals

Amikacin

General dosing, susceptible infection: IV
GA < 30 weeks:
PNA ≤ 14 days: 15 mg/kg every 48 hours
PNA > 14 days: 15 mg/kg every 24 hours
GA 30-34 weeks:
PNA ≤ 60 days: 15 mg/kg every 24 hours
GA 35-43 weeks:
PNA ≤ 7 days: 15 mg/kg every 24 hours
PNA > 7 days: 17.5 mg/kg every 24 hours
GA ≥ 44 weeks: 5-7.5 mg/kg every 8 hours

Amoxicillin

UTI prophylaxis (hydronephrosis, vesicoureteral reflux):
PO**:** 10 mg/kg every 24 hours
Asplenia prophylaxis: PO:
10 mg/kg every 12 hours

Ampicillin

Neonatal early onset sepsis: IM, IV:
100 mg/kg every 8 hours

General dosing, susceptible infection, non-CNS involvement: IM, IV:
GA ≤ 34 weeks:
PNA ≤ 7 days: 50 mg/kg every 12 hours
PNA >7 days: 75 mg/kg every 12 hours
GA 35-43 weeks:
All: 50 mg/kg every 8 hours
GA ≥ 44 weeks:
Mild/moderate infection: 12.5-50 mg/kg every 6 hours
Severe infection: 50-67 mg/kg every 4 hours

Meningitis including Group B streptococcal, empiric therapy or treatment: IV:
PNA ≤ 7 days: 100 mg/kg every 8 hours
PNA > 7 days: 75 mg/kg every 6 hours

Prophylaxis for patients with asplenia: IV:
50 mg/kg every 12 hours

UTI prophylaxis (hydronephrosis, vesicoureteral reflux): IV:
25 mg/kg every 24 hours

Ceftazidime

General dosing, susceptible infection: IM, IV
Body weight < 1 kg:
PNA ≤ 14 days: 50 mg/kg every 12 hours
PNA > 14 days: 50 mg/kg every 8 hours
Body weight 1-2 kg:
PNA ≤ 7 days: 50 mg/kg every 12 hours
PNA > 7 days: 50 mg/kg every 8-12 hours
Body weight > 2 kg:
PNA ≤7 days: 50 mg/kg every 12 hours
PNA 8-60 days: 50 mg/kg every 8 hours

Meningitis: IV
PNA ≤ 7 days: 50 mg/kg every 8-12 hours
PNA > 7 days: 50 mg/kg every 8 hours

Clindamycin

General dosing, susceptible infection: IM, IV
Body weight < 1 kg:
PNA ≤ 14 days: 5 mg/kg every 12 hours
PNA > 14 days: 5 mg/kg every 8 hours
Body weight 1-2 kg:
PNA ≤ 7 days: 5 mg/kg every 12 hours
PNA > 7 days: 5 mg/kg every 8 hours
Body weight > 2 kg:
PNA ≤ 7 days: 5 mg/kg every 8 hours
PNA 8-28 days: 5 mg/kg every 6 hours

Gentamicin

General dosing, susceptible infection: IV
GA < 30 weeks:
PNA ≤ 14 days: 5 mg/kg every 48 hours
PNA > 14 days 5 mg/kg every 36 hours
GA 30-34 weeks:
PNA ≤ 14 days: 5 mg/kg every 36 hours
PNA > 14 days: 5 mg/kg every 24 hours
GA 35-43 weeks:
PNA ≤ 7 days: 4 mg/kg every 24 hours
PNA > 7 days: 5 mg/kg every 24 hours
GA ≥ 44 weeks:
All: 2.5 mg/kg every 8 hours

Nafcillin

General dosing, susceptible infection (non-CNS): IV
GA ≤ 34 weeks:
PNA ≤ 7 days: 25 mg/kg every 12 hours
PNA > 7 days: 25 mg/kg every 8 hours
GA 35-43 weeks:
PNA ≤ 7 days: 25 mg/kg every 8 hours
PNA > 7 days: 25 mg/kg every 6 hours
GA ≥ 44 weeks:
All: 25-50 mg/kg every 6 hours

Meningitis: IV
GA < 44 weeks:
PNA ≤ 7 days: 25 mg/kg every 8 hours
PNA > 7 days: 25-37.5 mg/kg every 6 hours
GA ≥ 44 weeks:
All: 50 mg/kg every 6 hours

Penicillin G

General dosing, susceptible infection (non-CNS, non-GBS): IM, IV
PNA ≤ 7 days: 50,000 units/kg every 12 hours
PNA 8-28 days: 50,000 units/kg every 8 hours
GBS (non-CNS): IV
PNA ≤ 7 days: 50,000 units/kg every 12 hours
PNA 8-28 days: 50,000 units/kg every 8 hours
PNA 29-60 days: 50,0000 units/kg every 6 hours
Meningitis, Group B streptococcus: IV
PNA 0-7 days: 84,000-150,000 units/kg every 8 hours
PNA 8-28 days: 100,000-125,000 units/kg every 6 hours
PNA 29-60 days: 100,000 units/kg every 6 hours
Meningitis, other susceptible organisms: IV
PNA 0-7 days: 50,000 units/kg every 8 hours
PNA 8-28 days: 50,000 units/kg every 6 hours

Vancomycin

General dosing, susceptible infection: IV
Body weight < 1.2 kg:
PNA ≤ 28 days: 15 mg/kg every 18-24 hours
Body weight 1.2-2 kg:
PNA < 7 days: 15 mg/kg every 12-18 hours
PNA ≥ 7 days: 15 mg/kg every 8-12 hours
Body weight > 2 kg:
PNA < 7 days: 15 mg/kg every 8-12 hours
PNA ≥ 7 days: 15 mg/kg every 6-8 hours

Zidovudine

Low risk infants: PO
GA < 30 weeks: 2 mg/kg every 12 hours through 4-6 weeks of age
GA 30-34 weeks:
PNA ≤ 14 days: 2 mg/kg every 12 hours
PNA > 14 day: 3 mg/kg every 12 hours through 4-6 weeks of age
GA ≥ 35 weeks: 4 mg/kg every 12 hours through 4-6 weeks of age

Table 18-2 Medication administration chart			
Drug	**Dose**	**Administration**	**Comments**
Emergency Medications			
Adenosine (3 mg/mL)	**IV:** Initial: 0.1 mg/kg If not effective within 2 min, give 0.2 mg/kg	Rapid IV push over 1-2 seconds; flush with saline before and after	• Administer in a central catheter or at a peripheral IV site as proximal to trunk as possible (i.e. not in lower arm, hand, lower leg, or foot).
Albumin 5%	**IV:** 10-20 mL/kg/DOSE	Over 2-4 hours	• For volume repletion only. • For albumin replacement, use albumin 25%.
Calcium chloride10% (100 mg/mL)	**IV:** 20 mg/kg/DOSE	Give as IV push over 3-5 minutes	• Hyperkalemia, cardiac arrest with hypocalcemia • Do not give in line with phosphate-containing fluids
Calcium gluconate (100 mg/mL)	**IV:** 100 mg/kg/DOSE	Give as slow IV push over 5-10 minutes	• Do not give through line with phosphate-containing fluids.
Cardioversion (synchronized)	0.5 to 1 J/kg initially; If not effective, increase to 2		• Sedate if possible, but do not delay cardioversion.
Dextrose 10%	**IV:** Hypoglycemia: 2 mL/kg per dose Hyperkalemia: 4 mL/kg with 0.1 units/kg regular insulin	1 mL/min	• For hypoglycemia and hyperkalemia
Epinephrine (0.1 mg/mL)	**IV:** 0.01-0.03 mg/kg/DOSE (0.1-0.3 mL/kg) **ET:** 0.05-0.1 mg/kg/DOSE (0.5 to 1 mL/kg)	IV push Follow with 5 manual breaths for ET admin	• Maximum 0.1 mg (1 mL). Repeat every 3-5 minutes for pulseless arrest, PEA, asystole, bradycardia.
Lidocaine (10 mg/mL)	**IV:** 1 mg/kg/DOSE **ET:** 2 mg/kg/DOSE	IV push over 1 min Follow with 5 manual breaths for ET admin	• Consider for pulseless VT/VF. Not for SVT.
Naloxone (0.4 mg/mL)	**IV, IM:** 0.1 mg/kg/DOSE; repeat every 2-3 minutes, if needed **ET:** 0.2 mg/kg/DOSE	IV push over 30 seconds Follow with 5 manual breaths for ET admin	• All pain relief will also be reversed. • May precipitate withdrawal.
Sodium bicarbonate 4.2% (0.5 mEq/mL)	**IV:** 2 mEq/kg/DOSE	IV push over 2 minutes	• Use in code situations is discouraged. • May lead to IVH and worsen intracellular acidosis.
Intubation Medications			
Atropine (0.1 mg/mL)	**IV:** 0.02 mg/kg/DOSE	Rapid IV push	• No minimum dose.
Fentanyl (5 mcg/mL)	**IV:** 1-2 mcg/kg/DOSE **Intranasal:** 1.5-2 mcg/kg/DOSE	Administer over 5 minutes if no paralytic is used	• Analgesia should be used prior to intubation. • To make fentanyl 5 mcg/mL concentration: Draw 1 mL fentanyl 50 mcg/mL and dilute with 9 mL NS. • For intranasal: NO atomizer is used, give half of total dose in each nostril. Use 50 mcg/mL concentration.
Vecuronium (1 mg/mL)	**IV:** 0.08-0.1 mg/kg/DOSE	Rapid IV push	• **Preparation:** 10 mL saline added to 10 mg vial to make 1 mg/mL

Continuous Infusions		
Alprostadil (5 mcg/mL)	**IV continuous infusion:** 0.0125-0.1 mcg/kg/min	Titrate to effect
Dopamine (1.6 mg/mL)	**IV continuous infusion:** 2.5-20 mcg/kg/min	**Preparation:** Dilute to 5 mL of 3.2 mg/mL concentration dopamine in 5 mL of D5W
Epinephrine (0.05 mg/mL)	**IV continuous infusion:** 0.01-1 mcg/kg/min	**Preparation:** Dilute 0.5 mL of 1 mg/mL epinephrine in 10 mL of D5W
Phenylephrine (0.1 mg/mL)	**IV continuous infusion:** 0.1-0.5 mcg/kg/min	**Preparation:** Dilute 0.1 mL of 10 mg/mL phenylephrine in 9.9 mL NS

Table 18-3. Medication administration chart (continued)

Drug	Dose	Infusion	Comments
Sedation/Pain			
Fentanyl	**IV:** 1-2 mcg/kg/DOSE **IV continuous infusion:** Initial IV bolus: 1-2 mcg/kg, then start at 0.5-1 mcg/kg/hr; titrate by 1 mcg/kg/hr	Run bolus on pump over 5 minutes	• Tolerance may occur within 3-5 days. • More sedative properties than morphine. • Preferred opioid in patients with renal dysfunction. • Rapid bolus faster than 5 minutes may increase chest wall rigidity
Lorazepam	**IV, anxiety and sedation:** 0.05 mg/kg/DOSE (range 0.02-0.1 mg/kg) every 4-8 hrs **IV, status epilepticus:** 0.1 mg/kg/DOSE; may repeat in 10-15 min.		• Injection contains 2% benzyl alcohol, polyethelyne glycol, and propylene glycol, which may be toxic to newborns in high doses. • Avoid benzodiazepine use in patients < 44 weeks PMA due to neurodegenerative properties.
Midazolam	**IV:** 0.05-0.15 mg/kg/DOSE every 2-4 hours **IV continuous infusion:** ≤32 weeks PMA: 0.03 mg/kg/hr > 32 wees PMA: 0.06 mg/kg/hr Titrate by 0.01 mg/kg/hr	Run bolus on pump over 5 minutes	• Avoid benzodiazepine use in patients < 44 weeks PMA due to neurodegenerative properties.
Morphine	**IV/IM/SQ:** 0.05-0.1 mg/kg/DOSE every 4-8 hrs **IV continuous infusion:** Initial IV bolus: 0.05-0.1 mg/kg, then start 0.01 mg/kg/hr, titrate by 0.01 mg/kg/h		• Tolerance may occur within 5-7 days. • Avoid in patients with renal dysfunction.
Other Medications			
Cosyntropin Low Dose Stim Test	**IV:** 1 mcg once	IV push	• Check cortisol levels before the dose and at 30 minutes and 60 minutes after the dose.
Ibuprofen lysine	**IV:** 10 mg/kg once, then 5 mg/kg q 24 for 2 doses (Base doses on birth weight)	Infuse on pump over 15 minutes	• For treatment of PDA. • Preferred over indomethacin due to lower incidence of nephrotoxicity.
Indomethacin	**IV:** 0.1 mg/kg every 24 hours for 3 doses (Base doses on birth weight).		• For IVH prophylaxis in neonates ≤ 26 6/7 weeks gestation or <800 grams birth weight. • Start within 12 hours of birth.
Levetiracetam	**IV, loading dose:** 20–40 mg/kg given intravenously at a rate of 2–5 mg/kg/minute **IV, PO, initial maintenance dose:** 3 mg/kg every 8 hours		• See neurology chapter for more details on levetiracetam use in status epilepticus.
Milrinone	**IV:** 0.375-0.75 mcg/kg/min as a continuous infusion; titrate dose to effect.		• Loading doses may cause significant hypotension. • Avoid in severe obstructive aortic or pulmonic valvular disease.
Phenobarbital	**IV**, **loading dose**: 20 mg/kg loading dose, then 10 mg/kg at 20-minute intervals until the seizure is controlled or a total dose of 40 mg/kg is reached. **IV, PO, initial maintenance dose**: 3-4 mg/kg once daily; increase to 5 mg/kg, if needed (usually by second week of therapy)		• Assess serum concentrations. • Goal trough maintenance level 20-40 mcg/mL.
Ursodiol	**PO:** 15-22.5 mg/k every 12 hours **OR** 10-15 mg/kg every 8 hours		• For use in cholestasis. • Suspension is compounded. Please allow time for outpatient prescription planning before discharge.
Vecuronium	**IV:** 0.1 mg/kg/DOSE every 1-2 hours as needed; maintenance: 0.03-0.15 mg/kg/DOSE **IV, continuous infusion**: 0.06-0.09 mg/kg/hour		• Half-life prolonged in hepatic disease. • Caution should be used as duration of effect may be prolonged in these patients.

Tables

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