Guidelines for Acute Care of the Neonate

Edition 24, 2016–2017

Updated: July 2016

Arnold J. Rudolph, MMBCh (1918 - 1995)

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Baylor College of Medicine

Texas Children's Hospital®

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Preface

Purpose

The purpose of these guidelines is to help neonatology fellows, pediatric house officers, and others with the usual routines followed in caring for common problems encountered in acute care of the neonate. These guidelines were designed by the Section of Neonatology, Baylor College of Medicine (BCM). Where appropriate, national guidelines or reference to peer-reviewed scientific investigations are cited to help in the decision-making process. Also, regional traits unique to the southeast Texas patient population are considered when appropriate. The guidelines are reviewed and revised annually (or more frequently as necessary) as new evidence and recommendations for clinical care become available. Users should refer to the most recent edition of these guidelines.

Dedication

These guidelines are dedicated to Dr. Arnold J. Rudolph (1918–1993), who taught the art of neonatology and whose life continues to touch us in innumerable ways.

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 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.

Summary of Major Changes, 24th Edition

Minor changes were made in addition to the major content changes detailed below.

Cardiopulmonary

- Care of the Infant on ECMO
- Analgesia for ECMO
- Postnatal Corticosteroids for Treatment of BPD
- Management of the CDH Patient
- Use of HHHFNC

Environment

- Updates to Thermal Regulation

Medication

- New Gentamicin Dosage Schedules

Metabolic/Endocrine

- Work Up and Management of Persistent Hypoglycemia

Nutrition

- Guidelines for Feeding Babies 1250-2000g
- Use of IV Lipid in ELBW Babies

Contents

Chapter 7. Hematology

Chapter 8. Infectious Diseases

Chapter 9. Medications

Chapter 10. Metabolic Management

Chapter 11. Neurology

Chapter 12. Normal Newborn

Chapter 13. Nutrition Support

Chapter 14. Surgery

Chapter 15. Palliative Care, Pain/Symptom Management, the End of Life and Hospice

Appendix. Overview of Nursery Routines

Care of Very Low Birth Weight Babies

1

General Care (Babies < 1500 grams)

Example of Admission Orders

Each infant's problems will be unique. Appropriate routines will 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/radiant warmer is preferred for infants with BW < 1250 grams or < 32 weeks. If servo- control mode of warmer or incubator is used, indicate servo skin temperature set point (usually set at 36.5°C). Always use radiant warmer in servo-control mode.
- Use plastic wrap blanket to reduce evaporative water loss if on a radiant warmer for babies who weigh 1250 grams or less.

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 (VS) and blood pressure (BP) 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.

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, and level of end expiratory pressure

SIMV – rate, PIP, Ti, PEEP

A/C – PIP, Ti, PEEP, Back Up Rate

VG – Target Vt, Pmax (instead of PIP)

FiO_2 – as needed to maintain target saturations

Diagnostic Imaging

- Order appropriate radiographic studies.
- Order cranial US 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) **(see Cardiopulmonary chapter).**
- **antibiotics** – if infant is considered to be at risk for sepsis **(see Infectious Diseases chapter).**
- **caffeine citrate (for infants BW 1250 grams or less)** – 20 mg/kg loading dose followed by 5 mg/kg/day given once daily. Initiate therapy within first 10 days of life.
- **Vitamin A (for infants BW 1000 grams 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.
- 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,

Table 1–1. Admission labs

CBC, platelets	at admission
Blood culture, ABG	at admission, if appropriate
Glucose screening	at 30 minutes 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)

  - » 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. **See 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 **(Pediatrics 2013; 131:189-195).** 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 1501 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 placing them at high risk will be scheduled on an individual basis. Clinic appointments are made through the Neonatology office.

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.

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.

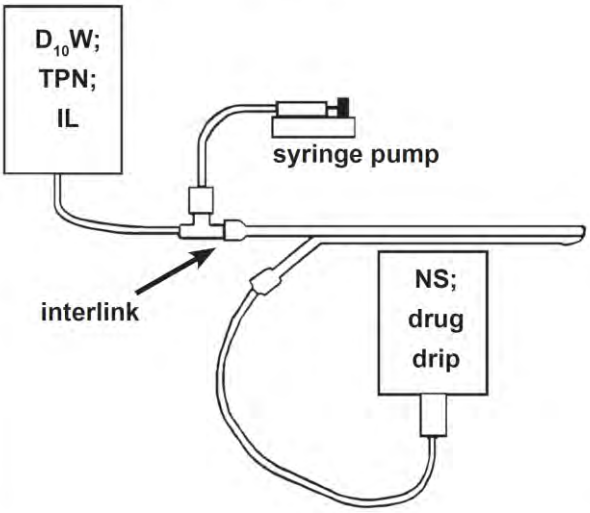
Volume Expansion

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). **(See Chapter 2-Cardiopulmonary Care).** 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).

Figure 1–1. Double-lumen system



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). A major benefit of the Volume Guarantee ventilator mode is the "self-weaning" function it provides. 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

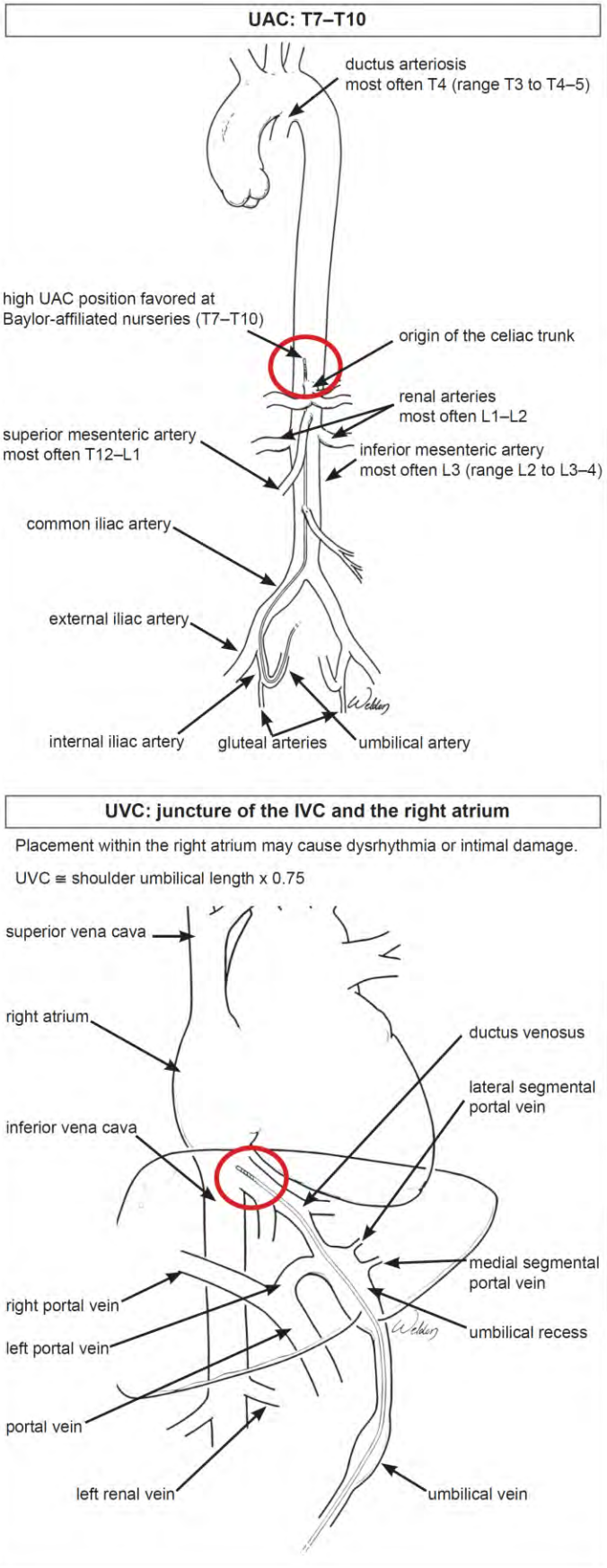
Evidence indicates that caffeine citrate started during the first 10 days of life in infants with BW 1250 grams or less decreases the rate of bronchopulmonary dysplasia without short term adverse effects and improves neurodevelopmental outcome at 18 months. All infants with a BW 1250 grams or less (whether 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

Figure 1–2. Suggested catheter tip placement; anatomy of the great arteries and veins

Position must be confirmed by X ray and catheter repositioned if necessary.



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.
- 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 reduced evaporative water and heat loss.

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 **(Kim 2001)** 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 **(1.3% - Schwartz 1997, 2.8 % - Haase 2011, 42% Kim 2001, and 46% - Morag 2006).** 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 **(Simmons 1978, Cochrane Review 2004).**

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

- < 1000g or < 26 weeks
- Cardiopulmonary compromise requiring frequent blood gas or BP monitoring
- CHD requiring specific care or interventions
- Potential ECMO
- Respiratory distress following resuscitation
- Select patients requiring exchange transfusion

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 **(Verheij, 2013).** 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:

$$\text{Insertion depth} = \frac{3 \times \text{BWkg} + 9\ \text{cm}}{2}$$

This formula reduces the incidence of over insertion without increasing that of under insertion **(Verheij 2013).** In a recent RCT **(Keiran 2015)** the authors reported a low rate of correctly positioned UVC catheters but no difference between use of this formula and that of classic graphs **(Dunn 1966)** 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 BWkg) + 9cm.

A recent RCT **(Kieran 2015)** comparing use of the Shukla weight based formula to use of graphs derived from body surface measurements **(Dunn 1966)** reported a significantly higher rate of correct UAC positioning using the weight based formula (91% vs 50%, p=0.001)

Duration of Catherization

Umbilical catheters should be removed as soon as possible.

Recommended maximum duration of use:

- UAC < 5 days (CDC rec)
- UVC < 7 days (modified from CDC rec and CLABSI guidelines)

Any special circumstance necessitating prolonged duration should be documented in the medical record

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.

"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. 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. 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.

Possible Variances

A small proportion of patients have complex clinical circumstances that may necessitate longer than recommended duration of an umbilical catheter or short term use of a low lying UVC. 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:

1. Critical CDH patients
2. 23-24 week ELGAN
3. Persistent hypoglycemia
4. Long term PgE
5. Need for frequent lab work
6. Limited availability of alternative vascular access

Miscellaneous

1. Do not infuse medications through UAC
2. Presence of an umbilical catheter does not preclude trophic feeds.
3. Avoid air in catheter set up – many neonates still have anatomic R-L shunts.

Summary

A sizable proportion of umbilical catheters placed are in suboptimal position. Catheter position and duration of use are major risk factors for serious complications. Although complications may occur with optimal catheter position, suboptimal positioning is associated with significantly increased risk of adverse events.

Complications can be minimized by ensuring that they are (1) placed only when indicated; (2) of appropriate size (3) placed in the optimal location and maintained there until remove; (4) accessed and used properly while in place; and (5) removed as soon as possible.

Multi-lumen UVCs

Catheters with multiple lumens are used exclusively for umbilical vein cannulation. Double lumen UVCs should be reserved for critically ill neonates requiring simultaneous multiple infusions **(Georgiadis, 2007).** Number of luminae should be kept to a minimum to limit the number of sites available for possible contamination. Multi-lumen catheters provide a route for continuous or multiple drug infusions without the need to start numerous peripheral IVs. They come in several brands, most of which are 3.5, 4, or 5 French size. Each type has a central lumen (usually 18 to 20 gauge) and one or two side ports (usually 21 to 23 gauge). With a double-lumen catheter, the central lumen is used to infuse the regular mainstream fluid (usually DW or TPN). The side port lumen can be used to administer intermittent medications and blood products (via the usual sterile interface system) or for continuous infusion of drugs. When a side port is not being used, administer a continuous infusion of heparinized NS through the side port at a rate of 0.5 mL per hour to maintain patency. Double-lumen 3.5 F catheters are used for many infants with BW less than 1500 grams.

Resuscitation and Stabilization

Recommendations for neonatal resuscitation and process algorithms are available at:

1. Circulation 2015;132 (suppl 1): S204-S241
2. www.aap.org/nrp

Circulatory Disorders

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 placenta is the organ of respiration in the fetus **(see Figure 2–1);** the lung receives only a small amount of blood flow since it does not oxygenate the blood in utero. The fetal circulation diverts oxygenated blood from the placenta away from the right heart and distributes it to the left heart via the foramen ovale (between the right and left atria). The left heart, in turn, distributes this oxygenated blood to the brain and peripheral circulation. The right heart receives deoxygenated blood from the fetal veins and diverts it from pulmonary artery to aorta via the ductus arteriosus. This blood then is distributed via the aorta and umbilical arteries to the placenta for oxygenation. This type of circulation is termed "a circulation in parallel" because both the right and left ventricles ultimately eject blood to the aorta and systemic circulation.

Postnatal (Adult) Circulation

This circulatory pattern **(Figure 2-2)** is termed "a circulation in series." Venous return from all parts of the body converges in the right heart. The right heart ejects blood, via the pulmonary artery, to the lung for oxygenation. Oxygenated blood subsequently returns to the left heart where it is ejected to the systemic circulation for distribution to peripheral organs.

Transitional Circulation

This circulatory pattern (**Figure 2–3)** combines features of the fetal and adult circulation. Usually it functions for 10 to 15 hours after birth, but in 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 exists for abnormal mixing of blood between the systemic (oxygenated) and pulmonary (deoxygenated) circulations. Under such circumstances blood may flow either along the pulmonary-to-systemic circuit (right-to-left shunt) with resulting hypoxemia or along the systemic-to-pulmonary circuit (left-to-right shunt) with resulting pulmonary congestion. The primary determinant of the direction of shunting through the fetal circulatory pathways is the relationship between systemic and pulmonary vascular resistance. The main determinants of resistance to blood flow in the pulmonary circuit are alveolar hypoxia, sensitization of the pulmonary vascular bed by sustained hypoxia, and reduced total pulmonary vascular bed such as that seen in hypoplastic lungs.

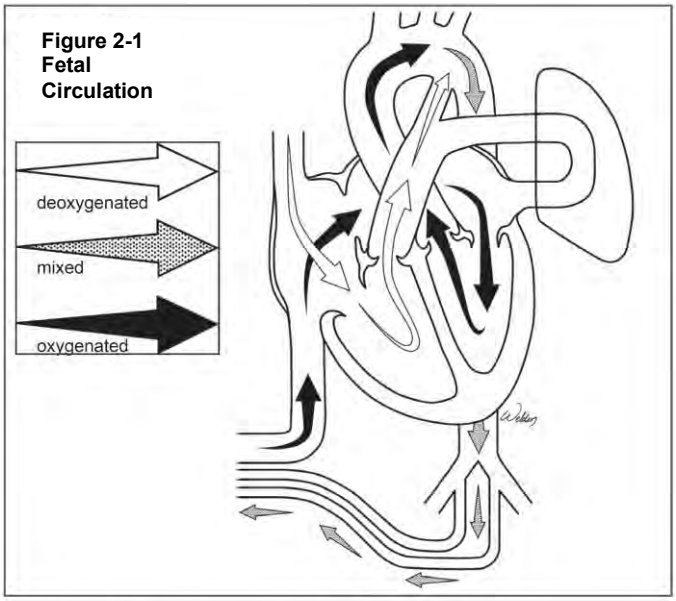


Figure 2-1
Fetal Circulation

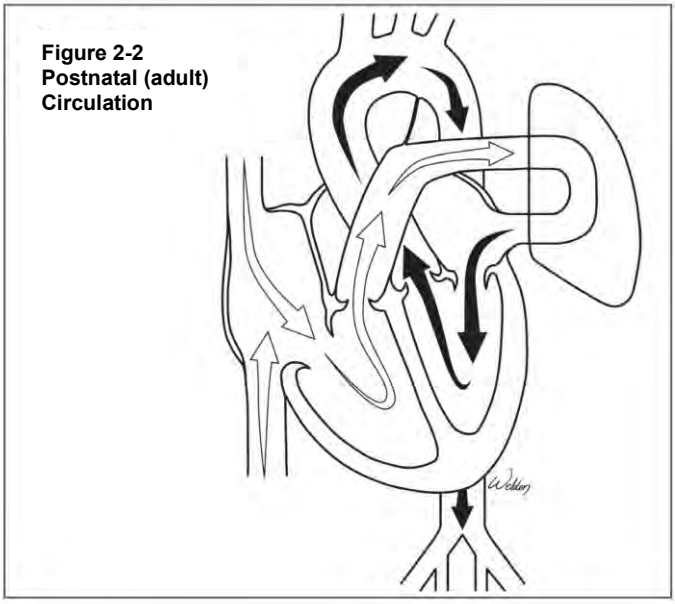


Figure 2-2
Postnatal (adult) Circulation

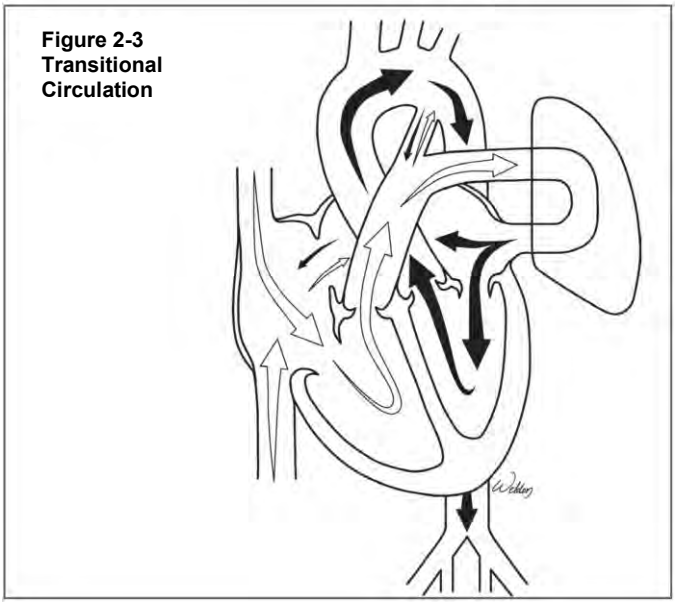


Figure 2-3
Transitional Circulation

Disturbances of the Transitional Circulation

Parenchymal Pulmonary Disease

Pneumonia, respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), meconium aspiration, or other pulmonary disorders may have either left-to-right or right-to-left shunt via the persistent fetal pathways.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

PPHN is associated with underdevelopment, maldevelopment, or abnormal adaptation of the pulmonary vascular bed. This results in delayed fall in postnatal pulmonary vascular resistance and right-to-left shunting through persistent fetal pathways and intrapulmonary channels, which produces severe arterial hypoxemia.

Congenital Heart Disease

In structural malformations of the heart, the fetal circulatory channels (particularly the ductus arteriosus) may function as alternative pathways to maintain blood flow to the lungs (e.g., tricuspid atresia or transposition of the great arteries) or the systemic circulation (e.g., hypoplastic left heart). Postnatal closure of these fetal circulatory pathways may lead to abrupt deterioration of a previously asymptomatic infant.

Patent Ductus Arteriosus (PDA)

Persistent PDA in small premature infants may cause increasing left-to-right shunting, progressive pulmonary edema, and deterioration of respiratory function.

Circulatory Insufficiency

Adequate circulatory function requires three components:

- preload (blood volume and venous capacitance),
- pump function (heart rate and myocardial contractility), and
- afterload (peripheral vascular resistance and hematocrit).

The intact circulation delivers oxygen to tissues at a rate that meets metabolic needs. Failure to do so is circulatory insufficiency. Although hypotension may be part of the clinical syndrome, it is a variable accompaniment. Range of normal mean aortic blood pressures in the first day of life is depicted in **Figure 2–4.** Shock is best defined as circulatory dysfunction that produces inadequate tissue perfusion. Parameters suggesting inadequate tissue perfusion include:

- low mean arterial blood pressure,
- reduced urine flow (less than 1 mL/kg per hour),
- urine specific gravity greater than 1.020,
- poor capillary filling, peripheral pallor, or cyanosis,
- lactic acidosis, and
- increased arterial-venous O_2 content difference.

Nonspecific Hypotension

Nonspecific hypotension is the most common NICU circulatory problem. It often is associated with respiratory distress and is particularly common in (~50%) babies less than 28 weeks' gestation. Proposed etiologies include down-regulation of catecholamine receptors and relative adrenal insufficiency but actual etiology in most infants remains undetermined. A large PDA may be a contributing factor in VLBW infants.

The most common definitions of "hypotension" in the NICU setting are:

- MAP < 30 mm Hg or
- MAP < GA in weeks

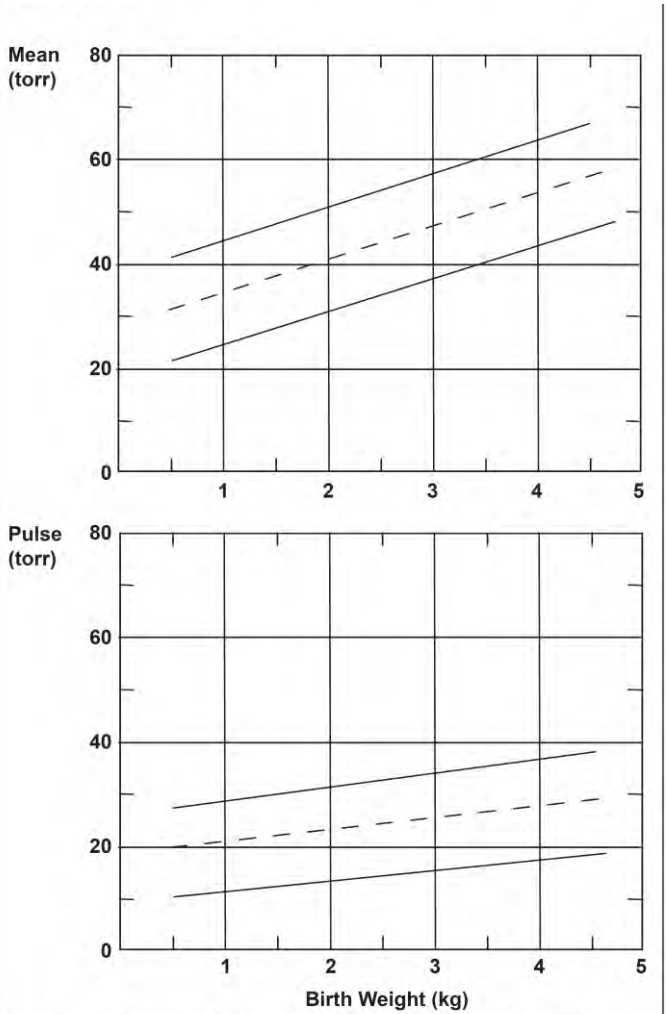
These definitions mostly relate to VLBW infants in the first 3-5 days of life and cannot directly identify the presence of inadequate systemic blood flow. In addition, evidence of benefit of treating values below these thresholds is lacking.

Although BP is an easily measured circulatory parameter, it is an insensitive indicator of organ blood or tissue oxygen delivery. Other indicators of circulatory status must be evaluated. These include presence of oliguria (urine output < 1 ml/kg/hr), poor capillary refill (> 3 sec.), elevated blood lactate level (> 3.0) and low systemic oxygen saturation. Emerging technology such as NIRS and echocardiographic measurement of SVC flow velocity may provide additional information regarding adequacy of the circulation.

Treatment

Treatment of hypotension always should be directed toward specific etiology if one can be determined. In many cases, however, no specific etiology is apparent and treatment is purely

Figure 2-4. Mean aortic blood pressure during the first 12 hours of life.



Linear regression (broken lines) and 95% confidence limits (solid lines) of mean pressure (top) and pulse pressure (systolic-diastolic pressure amplitude) (bottom) on birth weight in 61 healthy newborn infants during the first 12 hours after birth. For mean pressure, $y = 5.16x + 29.80$; n = 443; $r = 0.80$. For pulse pressure, $y = 2.31x + 18.27$; n = 413; $r = 0.45$, $P < 0.001$.

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symptomatic. It is important to recognize that evidence of benefit (or safety) of treatment of neonatal hypotension is lacking.

Volume expanders - Bolus infusions of blood 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.

Dopamine – Initial treatment of choice in non-specific hypotension (dose 2.5 to 20 mcg/kg per minute). A Cochrane meta-analysis found dopamine superior to dobutamine in raising BP in hypotensive premature infants. No evidence exists that combining dopamine and dobutamine (or dopamine plus other pressors) increases efficacy in management of non-specific hypotension. However, certain infants with cardiac disorders may benefit from combinations of low dose pressor agents. Approximately 60% of hypotensive premature infants initially respond to dopamine.

Systemic corticosteroids - produces short term improvement in mean blood pressure in most pressor-resistant, hypotensive neonates. 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.

If pressor resistant hypotension persists with other evidence of circulatory insufficiency or impaired systemic oxygen delivery we recommend staged intervention with hydrocortisone.

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

(2) If hypotension and circulatory dysfunction persists or recurs over next 4-6 hours, continue treatment with 1 mg/kg/dose every 8 hours for 24-48 hours, then taper off steroids by day 5 (**RCT – Ng, Pediatrics 2006;117:367**). As BP improves, attempt to wean off pressor agents.

Hydrocortisone use in this setting is symptomatic, not physiologic, treatment that should be employed only when the practitioner feels hypotension is producing compromise of organ blood flow or tissue oxygenation. Neither safety nor long-term benefit of short-course therapy for hypotension has been established. 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. We do not recommend concurrent administration of hydrocortisone and indomethacin. Hyperglycemia and impaired bone mineralization also are associated with corticosteroid use.

Vasopressin - Vasopressin has minimal to no inotropic or chronotropic effects. It induces vasoconstriction via multiple mechanisms, and its effects on the cardiovascular system are not fully understood. Vasopressin's vasoconstrictive effects are preserved during hypoxia and severe acidosis, as are often encountered in critically ill preterm neonates. Its use has been documented in a small pilot trial and case reports and retrospective reviews. In the pilot trial **(Rios, 2015)** hypotensive ELBW infants response to vasopressin infusion was similar to that of dopamine. No short term adverse effects were observed. A potential complication of its use is hyponatremia. Current evidence is insufficient to recommend routine use of vasopressin. However, selective indications for use in neonates may include: (1) cardiac patients (2) infants with CDH or other forms of PPHN and refractory hypotension (3) infants with hypotension and evidence of low systemic flow who are resistant to pressors and pulse steroids or (34) severe circulatory insufficiency requiring immediate intervention to raise BP.

Medication Resistant Hypotension - infants with poor response to the agents above should receive further evaluation including echocardiogram to evaluate for structural heart disease, myocardial dysfunction or a large PDA. Monitoring with blood lactate determinations and possible NIRS may be appropriate.

Other Medications - under select circumstances agents such as milrinone, sildenafil or concurrent infusion of low dose epinephrine may be appropriate. Specific evaluation (as discussed above) and possible consultation with Cardiology or Pulmonology are appropriate in these circumstances.

Combination Medications - in complex circumstances involving myocardial dysfunction combinations of medications (such as dopamine plus epinephrine) in low doses might be chosen. In hypotensive infants with CDH or other forms of PPHN, addition of vasopressin when dopamine dose exceeds 10 micrograms/kg/min might be appropriate.

Hypovolemic Shock

Etiologies

Common etiologies of hypovolemia in the first 24 hours of life:

- 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.
- Abruptio placentae.
- 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.
- Infants with RDS do not have reduced blood volume unless associated with some other factor.

In general, the central venous hematocrit correlates well with RBC volume during the first 24 hours of life. Afterward this becomes unreliable. Mean hematocrit values for various groups of infants are small for gestational age (SGA) 53%, premature appropriate for gestational age (AGA) 46%, and term AGA 55%.

Treatment

Treat initially with infusion of 10 to 15 mL/kg normal saline until whole blood or packed red blood cells (PRBCs) are available or parameters of tissue perfusion are improved. Use of 5% albumin infusions is not recommended. Initial hematocrit may be useful in estimating the magnitude of volume replacement but subsequent hematocrit values cannot be used as

a sole guide to adequacy of volume replacement. Estimated deficit and adequacy of tissue perfusion are other important parameters. It is possible to raise the hematocrit into the normal range with PRBCs while a significant blood volume deficit still exists. If PRBCs are used, central venous hematocrit should not be raised above 55%.

Cardiogenic Shock

Cardiogenic shock is not a common condition in neonates during the first few days of after birth. When it occurs, inadequate tissue perfusion usually is related to 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, or
- circulatory collapse related to supraventricular tachycardia (SVT), or after cardiac surgery or ECMO.

Symptoms

Chief manifestations of cardiogenic shock are pulmonary and hepatic congestion with respiratory distress and peripheral circulatory failure. Poor pulses and capillary filling, cardiomegaly, hepatomegaly, and gallop rhythm may be present.

Treatment

Treatment approaches to cardiogenic shock fall into three major areas:

- **Fluid restriction and diuretics** - Main effects are related to reduction of circulating blood volume with reduction of venous return to the heart. This reduces cardiac filling pressures and relieves pulmonary edema and circulatory congestion. Furosemide may be given at a dose of 1 mg/kg, IV, twice daily. However, caution is necessary to avoid reducing pre-load to a level that further impairs cardiac output.
- **Augmentation of myocardial contractility** - Dopamine may be effective at doses of 2.5-10 micrograms/kg/min but higher doses may raise afterload and impair cardiac output. Other side effects are increased myocardial oxygen consumption and redistribution of circulating blood volume. Dobutamine may be used if purely inotropic effects are desired. In some circumstances use of low dose combinations of two drugs may be appropriate (e.g. low dose dopamine + epinephrine)
- **Milrinone -** is an inotropic drug that increases cAMP levels through direct inhibition of phosphodiesterase, preventing the hydrolysis of cAMP. It has an inotropic effect on the heart and a dilating effect on veins and arterioles, effects that do not depend on neurotransmitter stores or receptors. It simultaneously can raise cardiac output and lower PVR, without a significant increase in myocardial oxygen demand. Toxicities include arrhythmias, tremor, thrombocytopenia, and vomiting. Milrinone is of benefit in right ventricular failure and in weaning cardiac surgery patients from cardiopulmonary bypass. It is routinely used in neonates with low cardiac output associated with congenital heart disease or myocardial dysfunction. Its role in management of PPHN is under investigation.
- **Afterload reduction and vasodilators** -This therapy is used to reduce cardiac workload by reducing peripheral vascular resistance and myocardial afterload. Although evidence in neonates is limited, milrinone is most commonly chosen in this setting. Vasodilators therapy should be guided by recommendations from the Pediatric Cardiology Service.

Septic Shock

Clinically, septic shock represents the collective effects of circulating bacterial toxins on systemic and pulmonary capillary beds, leading to multiorgan hypoperfusion and cellular anoxia. Little is known about septic shock in neonates, but the pathophysiology seen in adults is assumed to apply to neonates.

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 **(American College of Critical Care Medicine-2007)** during this process.

Effects of vasoactive substances on the lung include a rise in pulmonary artery pressure, increase in pulmonary capillary pressure, and increase in fluid filtration from microvasculature in the lung leading to pulmonary interstitial edema. This leads to progressive compromise of pulmonary function with resultant hypoxemia.

Such effects on the systemic and pulmonary circulation soon lead to profound tissue anoxia and progress to irreversible shock. Early stages of septic shock manifest by an intense peripheral vasoconstriction with maintenance of normal or elevated arterial pressure. Progressive fall in urine output may occur. As vascular pooling progresses, hypotension and metabolic (lactic) acidosis occur.

Treatment

Although the influence of treatment on the outcome of septic shock is difficult to evaluate, such therapy should be applied aggressively during the early vasoconstrictive phase and may be categorized as:

- **Blood volume expansion** - increases effective blood volume, enhances venous return to the heart, and improves cardiac output. Although volume expansion is the mainstay therapy of septic shock, it may be accompanied by

pulmonary congestion and exacerbation of respiratory dysfunction. The accompanying pulmonary edema often requires use of CPAP or mechanical ventilation. Give normal saline initially in 10 to 15 mL/kg increments. Transfusion of whole blood or packed red blood cells may be necessary up to a central hematocrit of 55%. Monitoring arterial pressure, body weight, serum sodium, and urine output is essential. Measurement of central venous pressure and assessment of cardiac size on x-ray may be helpful.

- **Inotropic and pressor agents** - Use of these agents in septic shock is complex, and the agent selected depends on clinical circumstances. Dopamine (dose 2.5 to 20 mcg/kg per minute) is the initial agent of choice in attempt to augment cardiac output, raise blood pressure and enhance renal blood flow with minimal increase in cardiac afterload. If echocardiogram demonstrates significant reduction in myocardial function, dobutamine may be preferable to provide inotropic effects without changes in peripheral vascular resistance. In severe septic shock that is refractory to volume expansion and other pressors, epinephrine may improve circulatory function by reducing pooling in capacitance vessels.
- **Corticosteroids** - Theoretically, corticosteroids block the effects of endotoxin and inflammatory mediators on vascular tone and the integrity of the capillary membrane. They also increase response of receptors to endogenous and exogenous catecholamines. Evidence of efficacy in newborns is lacking, but some infants who are refractory to the above measures may exhibit an increase in blood pressure in association with short-term administration of systemic steroids.

Cardiovascular Physiology in the Newborn

After birth, closure of the foramen ovale and ductus arteriosus creates separation of the systemic and pulmonary circulations, allowing the entire blood volume to enter and exit each ventricle in series.

Systemic cardiac output (CO) is the volume of blood ejected from the left ventricle each minute. It is the product of the heart rate (HR) and stroke volume (SV), which is defined as 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 -** the end-diastolic volume (EDV), or volume in the ventricle after filling. Preload increases with increased circulating blood volume, venous tone, ventricular compliance, and atrial contractility, and 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.
2. **Afterload -** the force that resists myocardial fiber contraction during systole, and 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.
3. **Contractility -** the force and velocity of a contraction. Increased contractility leads to an increase in stroke volume.

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

The Qp:Qs ratio can be altered by changes in systemic and peripheral vascular resistance (SVR, PVR), as shown in **Table 2-1**.

Table 2-1. Interventions to alter SVR and PVR

Factors that Increase SVR	Factors that Decrease SVR
Hypothermia Oxygen Agitation/crying Knee-chest position Meds: Dopamine, Epinephrine, Norepinephrine	Hyperthermia Metabolic acidosis Meds: PGE (↓), Nitroprusside
Factors that Increase PVR	**Factors that Decrease PVR**
Hypercarbia, respiratory acidosis Metabolic acidosis Low FiO2 – subambient FiO2, alveolar hypoxemia Pulmonary vascular under- or maldevelopment Meds: Catecholamines	Hypocarbia, respiratory alkalosis Supplemental oxygen Meds: iNO, PGE (↓↓)

Congenital Heart Disease

Congenital heart disease typically presents in the newborn period and up to the first year of life. Most serious life threatening lesions that require urgent medical or surgical intervention usually present within the first several days of life. Timing and mode of presentation depend upon the cardiac lesion or combination of lesions, timing of ductus arteriosus closure, and fall in pulmonary vascular resistance. A differential for congenital heart diseases based on symptoms is presented in **Table 2-2.**

Other differential diagnoses to consider when working up a patient for congenital heart disease include bacterial sepsis, primary pulmonary disease, anemia, and metabolic disease.

Workup of Suspected Cardiac Disease

Vital Signs

Pulse Oximetry: Pulse oximetry 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. Infants with left heart defects may be missed

by pulse oximetry. All infants are now screened with pulse oximetry in the newborn period. 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.

Table 2-2. 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)
Severe cyanosis caused by restricted pulmonary blood flow (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 from Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant, 9th edition with permission.**
*** May present with left-to-right shunt and congestive heart failure**

Blood Pressure - Blood pressure (BP) 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 measurement in a conscious infant is associated with distress and agitation, and may give erroneous readings. A normal newborn may have up to a 15mmHg gradient between upper and lower extremities. Non-invasive BP measurements are better for monitoring hemodynamic changes than for making diagnoses.

Physical Examination

Pulses and Perfusion - Systemic hypoperfusion characterized by weak central and peripheral pulses, delayed capillary refill time, and hypotension is common in cardiac lesions with ductal-dependent systemic 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.

Cyanosis - Central cyanosis is a manifestation of arterial oxygen desaturation. The degree of cyanosis depends on the concentration of desaturated hemoglobin ($\geq$ 5 g/dl). Polycythemic infants 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, which is not indicative of arterial oxygen desaturation.

Respiratory distress - 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 and murmurs - Auscultation of heart sounds and murmurs is rarely diagnostic in newborns. The second heart sound (S2) is important in diagnosing cardiac disease but takes great practice to develop the skill. Single S2 is associated with significant pulmonary hypertension, TGA, and pulmonary atresia. The characteristic "to-and-fro" sytolic-diastolic murmur is heard in absent pulmonary valve syndrome and truncus arteriosus with truncal stenosis and regurgitation. Heart murmurs may be absent in severe heart disease; hence, a high index of suspicion should be maintained based on other findings.

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

Hyperoxia Test

The hyperoxia test is a useful tool to help differentiate primary pulmonary from cardiac causes for 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. In pulmonary disease, 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. Infants with fixed right to left cardiac shunts (no increase in Qp or in mixing of systemic and pulmonary venous returns) will demonstrate 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 (TAPVC without obstruction). Additionally, PaO_2 <100 mmHg does not rule out persistent pulmonary hypertension.

Investigations

Laboratory Tests - Basic lab tests such as CBC, ABG with lactate and Chem10 may be obtained. 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 determined by comparing the width of the cardiothymic silhouette to the width of the chest wall. This ratio should not be >0.65. Degree of pulmonary vascularity (normal, increased or decreased) may indicate the type of cardiac lesion.

EKG/ECHO - Aside from arrhythmias, EKG is relatively non-diagnostic for cardiac diseases. 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.

Basic Physiology & Management of Neonatal Cardiac Disease

Acyanotic Congenital Heart Disease (Large L→R 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. Saturations are usually normal. Examples of diseases in this category include VSD, ASD, endocardial cushion defects, PDA, and AP window. ASDs are typically not symptomatic in the first year of life; an infant with a symptomatic ASD should be worked up for left-sided obstructive lesion(s) as a cause of augmented left to right shunting.

Medical therapy for infants who show signs of pulmonary over circulation includes diuretics (furosemide) 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, which is typically performed outside of the neonatal period.

Cyanotic Congenital Heart Disease

Right-sided obstructive lesions (Large R→L shunt) - Lesions involving an anatomic obstruction to pulmonary blood flow include critical pulmonary stenosis, pulmonary atresia, tricuspid atresia, and Ebstein's anomaly. Tetralogy of Fallot is also included in this category, although varying degrees of pulmonary outflow tract obstruction may exist. These defects are characterized by 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 is required to maintain ductal patency. Interventions that increase pulmonary blood flow by altering PVR may be helpful. Palliation with a BT shunt may be needed in the neonatal period prior to surgical repair. Pulmonary atresia with intact ventricular septum, critical PS, tricuspid atresia, and Ebstein's anomaly typically follow single ventricle physiology and are managed surgically with univentricular repair (staged pathway).

Complete mixing with normal or increased pulmonary blood flow - In total anomalous pulmonary venous connection and truncus arteriosus, there is complete mixing of pulmonary and systemic blood flow, and pulmonary blood flow may be increased at the expense of the systemic circulation. In TAPVC, mixing occurs as pulmonary venous return joins systemic venous return at the level of the SVC, right atrium, coronary sinus, or IVC. 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. Surgical repair is emergent and may be complicated by postoperative pulmonary artery hypertension.

In truncus arteriosus, there is complete mixing of the circulations in the 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 around 85% (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, resulting in poor coronary and systemic perfusion. Close attention should be given to ST segments as an indicator of myocardial ischemia. Workup should include evaluation of 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 not helpful and may lead to worsened systemic perfusion.

Separate circulations with poor mixing - In D-TGA, the aorta leaves the right ventricle and supplies 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 (R→L) increases LA pressure and further improves atrial-level mixing. Management in the neonatal period includes PGE, as well as an atrial septostomy if needed. Surgical repair, the arterial switch procedure, is performed in the first 2 weeks of life in infants with an intact ventricular septum and later in those with a VSD. Double-outlet right ventricle (DORV) with subpulmonic VSD has similar circulation to D-TGA with a VSD and also requires an arterial switch procedure for repair.

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 saturations in the ventricle and aorta depend on the relative systemic and pulmonary blood flow. Therefore, if

pulmonary blood flow is unrestricted, a decrease in PVR may lead to increased pulmonary blood flow and decreased systemic blood flow. 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 **(see section on HLHS below).**

Left-Sided Obstructive Lesions Leading to Systemic Hypoperfusion

Defects in this category include hypoplastic left heart syndrome (HLHS), critical aortic stenosis (AS), critical coarctation of the aorta, and interrupted aortic arch (IAA). In these lesions, the PDA is essential to maintain systemic blood flow. At the time of ductal closure, these infants present with signs of poor systemic perfusion including weak or absent peripheral pulses, metabolic acidosis, and shock.

Coarctation and IAA result in increased afterload to the LV, leading to LV hypertrophy and systemic hypertension. Management includes PGE in the neonatal period if CHF and/or poor systemic perfusion are present, with repair in early infancy if hypertension or ventricular dysfunction is present. In females with coarctation, Turner syndrome should be considered.

Critical AS presents in a similar fashion to HLHS. Moderate to severe AS requires balloon or surgical valvulotomy if ventricular dysfunction develops. A Norwood approach may be needed if there is marked annular hypoplasia, unicuspid aortic valve, ventricular hypoplasia/dysfunction, or associated subaortic obstruction.

HLHS involves varying degrees of left-sided valvular stenosis with LV and/or aortic hypoplasia. Management in the preoperative period is characterized by PGE administration and careful prevention of excessive pulmonary blood flow and pulmonary hypertension. Surgical repair involves three stages: (1) Norwood procedure in the neonatal period, characterized by creation of a "neoaorta" to provide systemic blood flow and an aortopulmonary shunt (typically BT shunt) to provide pulmonary blood flow, with excision of the atrial septum, (2) Bidirectional Glenn procedure at 2-6 months of age, which involves ligation of the previous aortopulmonary shunt and connection of SVC to the right pulmonary artery, and finally (3) Fontan procedure at 1-3yr of age, defined by anastomosis of the IVC to the right pulmonary artery, effectively separating the pulmonary and systemic circulations.

Table 2-3. Principles for understanding and interpreting NIRS

Oxygen transport balance – The Fick Principle

$VO_2 = CO \times (CaO_2\text{-}CvO_2)$

$(SaO_2\text{-}SvO_2)/SaO_2 = VO_2/DO_2$ = oxygen transport balance

Oxygen extraction ratio (OER) = $(SaO_2\text{-}SvO_2)/SaO_2$

*NIRS-derived rSO_2 may be substituted for SvO_2 to calculate OER at bedside

Interpretation of oxygen extraction ratio (OER)

25-30% Normal
30-40% Elevated
40-50% Impending shock
>50-60% Onset of shock, tissue hypoxia, lactate begins to accumulate

Elevated OER may be due to:

↑ Qp:Qs (Large L→R shunt or single ventricle physiology)
Poor contractility
Low preload states
Arrhythmia
Outflow obstruction (AS, aortic hypoplasia)
Significant hypoxemia

Considerations for improving oxygen transport balance:

Minimize oxygen demand
Ensure normothermia
Treat agitation and pain
Provide respiratory support
Treat arrhythmia

Improve cardiac output
Correct acidosis
Provide assisted ventilation
Administer volume
Provide inotropic support
Improve balance SVR:PVR to favor systemic blood flow if ↑ Qp:Qs
Administer PGE if outflow obstruction

Increase oxygen content
Administer RBC transfusion
Address hypoxemia (D-TGA/PA/PS – PGE or septostomy to increase mixing or improve PBF)

Abbreviations: VO_2, oxygen consumption; DO_2, oxygen delivery; CO, cardiac output; CaO_2, arterial oxygen content; CvO_2, venous oxygen content; SaO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation; rSO2, regional oxygen saturation

General Care of Neonates with Congenital Heart Disease

Care of all neonates with cardiac disease within the NICU, which includes those with congenital heart defects, myocardial functional impairment, and arrhythmias, should reflect the standard principles of management for the general NICU population. However, this population requires an approach that incorporates appreciation of the natural history of the disease and the associated morbidities. In contrast to the well preterm infant, for neonates with cardiac disease, the common course is to become more symptomatic over time and remain at risk for decompensation.

Environment of Care

Maintaining an environment with appropriate neurodevelopmental stimuli remains essential for the care of these neonates. Attention to pain, discomfort, and agitation are important aspects of developmental care, but are vitally important 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 employed as appropriate. 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 ensuring 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 frequent vital sign measurement, continuous pulse oximetry and regular physical assessment by nurses and practitioners. 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 at least every 4-6 hrs. Four-extremity blood pressure monitoring should be performed upon admission for all patients and regularly in those with suspicion for aortic arch hypoplasia, often while awaiting closure of the ductus arteriosus. Multi-site (cerebral, renal) near-infrared spectroscopy (NIRS) should be initiated at admission **(see Table 2-3)**. Laboratory investigations may include regular monitoring of blood gas and lactate levels, particularly when there is concern for adequacy for systemic blood flow or cardiac output. Optimal measurement of lactate is obtained by arterial puncture or indwelling line; however, certain cardiac patients will undergo regular monitoring of capillary lactate specimens as part of their care. Capillary lactate specimens may be used as a method for trending lactate levels in these instances, 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.

References

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Vascular Access

For those with uncertain 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. As for all neonates, central catheters should be removed when no longer necessary; however, the need for maintaining peripheral vascular access should be considered. Despite clinical stability, the potential for decompensation requiring urgent therapy (PGE, adenosine, vasoactive medications and volume resuscitation) exists for many neonates with cardiac disease.

Nutrition

Nutritional support remains of critical importance for this group of neonates. Many may 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 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. For others, use of TPN should be considered if the infant is not anticipated to receive enteral feeds within 2-3 days. If enteral feeding is provided, consideration of adequacy of mesenteric blood flow must be considered. If there is risk for mesenteric hypoperfusion, slow progression of feeding may be indicated. Safe enteral feeding has been documented during PGE infusion. 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 literature to support this belief.

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, but 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 decrease in LV afterload, but may impair systemic venous return and decreased 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.

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.

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.

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.

Supraventricular Tachycardia (SVT)

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

Atrioventricular Reentrant Tachycardia (AVRT)

In neonates with WPW, a delta wave or pre-excitation 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 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 pathway. 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 critically ill 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 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 or digoxin may be used as alternatives. 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 0.1mg/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. Despite extensive experience with adenosine, adverse effects have been noted, including the generation of wide complex tachyarrhythmias.

Propranolol - This enteral β-blocker is first line therapy for uncomplicated SVT or atrial tachycardia in neonates and infants. It is commercially available in 2 concentrations (4 mg/mL and 8 mg/mL). Propranolol, in particular, has been associated with hypoglycemia.

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.

Amiodarone - For patients who are unresponsive to β-blockade, a class III antiarrhythmic may be successful in terminating SVT. Many adverse effects are associated with amiodarone therapy, including pulmonary fibrosis, thyroid toxicity, corneal deposits,

hepatotoxicity, decreased growth, developmental delay, dermatologic hypersensitivity, and proarrhythmia (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, and co-administration with calcium chloride may be warranted. 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 should be avoided.

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. In general, the more severe the cyanosis or the systemic hypoperfusion, the more urgent the administration of PGE_1. If there is doubt regarding diagnosis and the infant is symptomatic, it is reasonable to begin treatment with PGE_1 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 physiology.

The response of the ductus arteriosus to PGE_1 is related to the time since spontaneous closure. Cyanosis in newborn infants is usually recognized shortly after ductal closure; therefore, the infants respond well to PGE_1. Those with cyanosis beginning at several weeks of age should not be assumed to be unresponsive to PGE_1. If the ductus arteriosus had recently closed, it may still respond.

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_1, they have the highest likelihood of not responding and of needing urgent surgery.

Long-term infusion of PGE_1 does permit a period for maturation of the lungs and nutrition and, for many premature infants, is preferable to open heart surgery in those weighing less than 1800g. The risk that pulmonary vascular disease will develop within several months, even in an infant with truncus arteriosus or transposition of the great arteries, is small. Therapeutic response is indicated by increased pH in those with acidosis or by an increase in oxygenation (PO_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 the start of PGE_1. Using the lowest effective dose can decrease the risk of apnea.

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 for acute decompensated heart failure. If diuresis with loop diuretic is inadequate, addition of a thiazide diuretic may be considered. Oral bioavailability of furosemide is poor. Consider using a 1:2 conversion factor when transitioning from IV to PO furosemide if the same pharmacologic effect is desired.

ACE Inhibitors

By inhibiting the production of angiotensin II and aldosterone, treatment with ACE inhibitors leads to vasodilation resulting in a reduction in systemic vascular resistance and afterload and an increase in cardiac output. In addition, ACE inhibition attenuates cardiac remodeling that contributes to heart failure progression. Captopril was the first ACE inhibitor studied in infants and children. 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 enalapril at and can be administered once to twice daily. Due to lack of data comparing ACE inhibitors, the selection of ACE inhibitor agent is generally based on ease of dosing, individual patient response and tolerability. The use of ACE inhibitors in preterm infants has been associated with a high incidence of acute kidney injury. Adverse effects of ACE inhibitors include hypotension, hyperkalemia, increased blood urea nitrogen (BUN), increased serum creatinine, anuria, acute kidney injury, and rare angioedema.

β-blockers

In adults, β-blockers have been shown to decrease mortality and morbidity through reversal of adrenergically mediated myocardial dysfunction, reduced activation of neurohormonal systems, antiarrhythmic effects and negative chronotropic effects. It is unclear if beta blockers exert the same effects and benefits on pediatric heart failure patients.

Propranolol is the most commonly used β-blocker in infants for hypertension and arrhythmias. Carvedilol, a non-selective β-adrenoreceptor 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 symptomatic hypotension and mild worsening of heart failure symptoms, especially at onset of treatment. Initiation 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.

Management of Neonatal Respiratory Distress

The primary lung diseases producing respiratory symptoms and respiratory failure in newborns are Respiratory Distress Syndrome (RDS), retained fetal lung fluid (transient tachypnea of the newborn, TTN), pneumonia, meconium aspiration, and pulmonary edema (usually associated with severe cardiac anomalies). Any of these may behave functionally similar to RDS. Surfactant replacement has been effective in many such circumstances (RDS, pneumonia and meconium aspiration) and other strategies of respiratory management are similar.

Basic Strategy of Respiratory Management

- "CPAP first"
- Lung protective mechanical ventilation
- SpO2 target 90-95% for most infants
- Permissive hypercapnia (PCO2 35-55 mmHg, pH $\geq$7.20) for most patients

"CPAP First" Strategy

Current evidence indicates that early CPAP is an effective strategy for support of ELBW infants, even the most immature. CPAP initiated immediately after birth, with subsequent selective use of surfactant, is at least as safe and effective as intubation and routine prophylactic surfactant - including the INSURE technique. **(CURPAP Study 2010, Support Trial 2010, Dunn 2011)**. Preterm infants treated with early CPAP alone are not at increased risk of adverse outcome and the need for subsequent surfactant treatment or mechanical ventilation is reduced **(AAP-2014).** Recent meta-analysis demonstrates that early CPAP combined with selective surfactant use results in lower rates of death or BPD as compared to routine prophylactic or early replacement surfactant **(Fischer 2013, Cochrane Review 2012)** and this strategy recently has been endorsed by the AAP **(Pediatrics 2014;133:171).**

Infants 30 0/7 Weeks' PMA or Less

The goal of early care of these infants is prevention of lung derecruitment, preservation of the surfactant monolayer and avoidance of the cycle of volutrauma-atelectatrauma. Infants who exhibit good respiratory effort at birth should be placed on CPAP immediately. Administer caffeine to babies 1250 grams or less. (**See Chapter 1 - Care of Very Low Birth Weight Babies)** If respiratory distress subsequently persists with O_2 requirement of 30-40% or greater, the baby should be intubated and receive early rescue surfactant (within the first 2 hours of life). Extubation to NCPAP is desirable following surfactant treatment but this decision must be individualized. Rapid extubation may not be possible (or desirable) for some very immature or critically ill infants. Additional doses of surfactant should be administered if the baby exhibits a persistent oxygen requirement above 30%.

Prevention of progressive atelectasis and maintenance of adequate lung inflation from birth by the above interventions is essential in this patient population.

If a baby requires mechanical ventilation from birth and has a persistent oxygen requirement of >30%, surfactant should be administered.

Rapid improvement following surfactant administration necessitates close monitoring and reduction in ventilator PIP (or Vt), Fio2, and possibly rate (SIMV). Initial reduction in ventilator settings after surfactant should be determined by clinical assessment (e.g., adequacy of chest rise). Monitor clinical signs closely and obtain blood gases within 30 minutes or less of dosing and frequently thereafter. Volume Guarantee (VG) mode may be combined with A/C or SIMV- in attempt to prevent over-distension of lungs as compliance improves rapidly after surfactant treatment. When ventilator support has been weaned to minimal levels and the infant has good respiratory effort, extubate and place infant on nasal CPAP.

Minimal support includes:

- SIMV rate < 25/min (not applicable to A/C with VG)
- $FiO_2 \leq 30\%$
- Vt 4-4.5 ml/kg (VG) or PIP $\leq$ 20 cm
- PEEP = 5-6 cm

Infants More Than 30 0/7 Weeks' PMA

If no specific intervention is required at birth but an infant subsequently exhibits respiratory distress, the following graded strategy is recommended.

Oxygen - spontaneously breathing infants in this category with respiratory distress may be managed initially with warm, humidified oxygen. Try to keep PaO_2 50 to 80 mmHg or SpO_2 within defined target range discussed below.

- Early nasal CPAP–If infant exhibits persistent respiratory distress and requires 30-40% oxygen or more (or 1/2-3/4 LPM of 100% O2 by NC), place infant on 5 to 6 cm H2O NCPAP and adjust as needed.
- Rescue surfactant–If oxygen requirement remains at or above 30-40% despite nasal CPAP at 6-8 cm- intubate and give rescue surfactant.

If a baby in this category already requires mechanical ventilation and has a persistent oxygen requirement greater than 30%, administer rescue surfactant. (**See Exogenous Surfactant section.)**

Oxygen

Goals of acute and chronic administration of oxygen are to avoid potential hazards of hypoxemia and hyperoxemia, especially in premature infants. No clear relationship has been established between specific arterial PO_2 values and adequacy of tissue oxygenation. This depends on complex factors, especially adequacy of the circulation. PaO_2 in a newborn is not constant; it varies widely throughout the day, especially in mechanically ventilated infants or those with chronic lung disease (CLD).

In emergency situations, administer oxygen in amounts sufficient to abolish cyanosis. As soon as this immediate goal is achieved, initiate SpO_2 monitoring to evaluate adequacy of oxygenation and determine further needs. An oxygen blender and pulse oximeter should be available at the delivery of all infants. Initiate emergency resuscitation with 40% O_2 for premature infants and room air for term infants. Adjust subsequent FIO_2 based upon pulse oximetry values.

Table 2–4a. 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.

Source: 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. Used with permission from AAP.

Short term oxygen administration is often provided via low flow (0.025-2 LPM) NC. The relationship between NC flow and delivered FiO_2 is described in **Tables 2-4a and 2-4b.**

Monitoring

Oxygen administration to neonates is most commonly monitored today with pulse oximetry. Oxygen therapy targeted to maintain a defined range of oxygen saturation values decreases need for supplemental oxygen, reduces duration of oxygen use, reduces risk of severe ROP and decreases episodes of pulmonary deterioration in infants with BPD.

FiO_2

Periodically, monitor inspired oxygen concentration and determine arterial oxygen tension or saturation when oxygen is administered. Frequency and type of monitoring depends on the nature and severity of the disease process as well as birth weight and gestational age. Patients receiving supplemental oxygen should have continuous monitoring with pulse oximetry.

Administration of oxygen via NC is a particularly difficult issue because of imprecise measurements and poor control of delivered FiO_2. A multicenter study found 27% of babies on NC were receiving less than 23% effective Fio_2 and 9% were receiving room air. The inspired oxygen concentration achieved by use of NC oxygen administration can be estimated using **Table 2-4a and Table 2-4b.**

Arterial Blood Gas Measurements

Arterial oxygen tension (PaO_2) measured under steady state conditions is the classic technique for determining the efficiency of gas exchange between the lungs and pulmonary capillary blood. Most sources consider 50 to 80 mmHg to be the usual range for newborn PaO_2. However, in a controlled NICU environment, PaO_2 in the range of 40 to 50 mmHg may be acceptable. In such circumstances, evaluate circulatory status and hemoglobin concentration.

Table 2–4b. 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 ref 1 (of the source publication).
Source: 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. Used with permission from AAP.

Pulse Oximetry

Pulse oximetry is the current standard for monitoring trends in central oxygenation in the NICU. Movement artifacts and low pulse pressure may impair the efficacy of this technique. Artifacts of saturation measurement also may occur in the presence of high-intensity light, greater than 50% Hgb F, and some radiant warmers.

Capillary Blood Gas Determination

This technique tends to underestimate PaO_2 and is unreliable for oxygen monitoring. Capillary sampling may be useful for determining pH and PCO_2, but should not be used as a tool for oxygen monitoring. Pulse oximetry measures O_2 saturation of hemoglobin, not the PaO_2; thus, at saturation ranges above 95% it is insensitive in detecting hyperoxemia. This shortcoming is of particular importance when oxygen is administered to small premature infants less than 1500 grams. A strategy of targeted oxygen saturation is used for oxygen administration with or without positive pressure support. In premature infants, or term infants with acute respiratory distress, adjust oxygen administration to maintain SpO_2 in the 90-95% range (alarm limits 88-96%). For infants with congenital heart disease, pulmonary hypertension or BPD (especially if term or beyond), oxygen delivery and targeted oxygen saturation **must be individualized**.

Nasal CPAP

Nasal constant positive airway pressure (NCPAP) is effective in managing apnea of prematurity, as a tool to maintain lung recruitment in small premature infants, and as early intervention in acute respiratory distress syndrome (RDS).

Continuous flow CPAP is the mode delivered by most neonatal ventilator systems. **Bubble CPAP** is a specific type of continuous flow CPAP that appears superior for support of preterm infants. Observational studies report enhanced gas exchange with bubble CPAP as compared to conventional delivery systems. A recent RCT reported reduced post extubation failure with bubble CPAP as compared to a variable flow CPAP system. Data regarding impact on work of breathing is limited but other types of continuous flow CPAP usually increase work of breathing. **A bubble CPAP delivery system is currently the method of choice in the Baylor nurseries.** 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 occasionally needed.

Indications for Nasal CPAP

Apnea of Prematurity

Nasal 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 to 32 weeks. Nasal CPAP for apnea is used in conjunction with administration of caffeine.

Maintenance of Lung Recruitment

Nasal CPAP is used in this setting to oppose high chest wall compliance and low lung volume in VLBW infants. Inborn infants $\leq$30 weeks' gestation are placed on nasal CPAP at birth to maintain lung recruitment. Larger infants also may be candidates if they appear immature, have early RDS or are at risk for postnatal chest wall dysfunction or apnea. Nasal CPAP also is useful to maintain lung recruitment post extubation in select infants.

Acute Lung Disease

We recommend nasal CPAP for all 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. Optimal effects occur between 6 to 8 cm H_2O but in some patients, lung over distension may occur at these levels. Inadequate response to nasal CPAP include persistent O_2 requirement above 40 %, severe apnea or severe hypercapnia.

Heated Humidified High Flow Nasal Cannula

High flow respiratory therapy involves delivery of inspiratory gas flows significantly exceeding those of normal spontaneous breathing. It is important that gas delivery with any HFNC device be heated and humidified (HHHFNC) to prevent mucosal injury from cold dry gas delivery. Two primary mechanisms of action for HFNC therapy have been described and differences are significant.

CPAP Effect

Pharyngeal end expiratory pressure during HHHFNC is dependent upon gas flow and level 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 at gas flows above 1-2 LPM. These variances make attempts to produce CPAP effects with HHFNC's problematic, since pharyngeal distending pressures are not monitored. Evidence regarding effects of HHHFNC on work of breathing in neonates is inconclusive **(Courtney 2001, Saslow 2006 and Brenne 2015)** and data are limited regarding effect on lung volume and recruitment.

Enhanced Dead Space Ventilation (Pharyngeal Washout) Effect

A different effect of HHHFNC is that of NC flow rates that exceed the patient's spontaneous inspiratory flow (> 2 LPM for neonates) and minimize entrainment of room air. Clinical and fluidic 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. Available evidence suggests this effect may be the primary mechanism for reported benefits of HHHFNC therapy in adults and older pediatric patients. In this application, HHHFNC must be used as an "open" system that maximizes nasopharyngeal purging with flow of 3-8 LPM and 40-50% NC leak, using each vendor's specifically recommended NC sizes. Evidence in neonates regarding this mechanism is limited.

Use in Neonates

Use of HHHFNC in the NICU environment has increased but the primary mechanism of action in neonates has not been identified. Most studies in infants have compared HHHNC therapy to various forms of conventional CPAP in premature infants.

A meta-analysis of 15 studies (**Cochrane Review 2016**) noted that most current evidence involved use of HHHFNC post extubation. When used for post extubation support (6 studies) there was no difference in rate of treatment failure, need for re-intubation, death or BPD. However, several of these studies allowed "rescue" with NCPAP or NIPPV for patients failing HHHFNC, resulting in reduced need for re-intubation. Incidence of nasal trauma was significantly reduced. Subgroup analysis of one of these trials **(Manley 2013)** revealed superiority of NCPAP for babies < 28 weeks gestation **(Manley 2016).** Thus HHHFNC seems to be a valid alternative to NCPAP for post extubation support in larger, more mature infants. Current evidence suggests NCPAP is superior for post extubation support of babies $\leq$ 26 weeks.

Meta-analysis of HHHFNC compared to CPAP for primary support of early neonatal respiratory disorders found no difference in primary outcome of death or BPD **(Cochrane Review 2016)** or incidence of treatment failure or pneumothorax **(Manley 2016).** HFNC resulted in longer duration of respiratory support. However, the number of infants randomized to the HFNC strategy in these trials was small and most excluded extremely preterm infants. Preliminary results from a larger multicenter RCT **(Roberts 2016)** demonstrate a significantly higher number of infants meeting study failure criteria among those randomized to HFNC for early support of RDS. At present we do not recommend HHHFNC for acute management of RDS or initial support of preterm infants following birth. Recent AAP guidelines recommend a strategy of early CPAP with selective surfactant administration for preterm infants with RDS **(Pediatrics 2014; 133:171)**. Benefits of NCPAP in these settings are well established. Babies' extubated following surfactant replacement should be placed on NCPAP.

The use of HHHFNC in management of established BPD has not been studied. However, the pharyngeal "washout" associated with this technique might be of value in select patients.

Several commercial vendors now market devices for HHHFNC's. Any device used for this purpose in a neonate should be specifically designed as a HHHFNC device delivering flows in the 3-8 LPM range. The vendor's specifically sized nasal cannulae should be used to allow the recommended 40-50% leak. These devices do not provide for measurement of pharyngeal distending pressure but some include a pressure pop-off valve to prevent delivery of extremely high distending pressures.

Mechanical Ventilation

Premedication for Non-Emergency Intubation

Premedication for **elective** intubation improves physiologic stability, reduces time to intubation and decreases number of intubation attempts. The AAP recommends the following strategy:

1. A narcotic analgesic is recommended (e.g. fentanyl)
2. A vagolytic agent should be considered (e.g. atropine)
3. Use of a muscle relaxant should be considered (e.g. vecuronium or rocuronium) depending upon clinical circumstances

Potential adverse events include:

1. Fentanyl induced chest wall rigidity. Avoid high doses and infuse drug slowly over 2-5 minutes. Have nalloxone, a muscle relaxant and properly sized LMA's immediately available.
2. Failure to intubate after administration of a muscle relaxant. Maintain effective ventilation with mask/bag or LMA. Short acting agents may be reversed with atropine and neostigmine.

Prior to administration of premedication all procedural equipment, suction and the above noted emergency medications should be immediately available.

Endotracheal Tube Positioning

Attempts should be made to position the tip of the ET tube in the mid-trachea. This corresponds to the tip being visible slightly below the level of the clavicles on chest radiograph. All chest x-rays should be obtained with the infants head midline and neither flexed nor extended. Both arms should be positioned at the sides.

Importance of Adequate Lung Recruitment

In order for effective ventilation and pulmonary gas exchange to occur, lung inflation (recruitment) must be optimized. In neonatal mechanical ventilation, this "open lung" strategy is achieved by applying adequate levels of PEEP (or MAP during HFOV). Optimal PEEP must be tailored to the lung compliance of each individual patient. In infants without lung disease, appropriate PEEP may be in the 4 to 5 cm range. For those with poorly compliant or atelectatic lungs, PEEP levels up to 8 cm H_2O or more may be necessary.

Overview of Mechanical Ventilation

Conventional ventilator modes are recommended for initial management of neonates requiring ventilator support. The preferred strategy for most patients is that of patient triggered, volume targeted ventilation with support for each patient breath using the Assist/Control (A/C) mode to minimize work of breathing. Alternatively, Synchronized IMV may be appropriate for certain larger or older infants. HFOV is reserved for rescue of neonates failing conventional ventilation, for certain patients with congenital diaphragmatic hernia (CDH) or for infants with severe pulmonary air leaks **(see High Frequency Oscillatory Ventilation section).** Volume targeted ventilation is based upon monitoring of expired Vt and adjustment of ventilator parameters (either manually or via automated computer control) in attempt to minimize lung injury by providing adequate minute ventilation with the lowest effective PIP and Vt delivered in the most consistent manner.

Acute Ventilation of Preterm and Term Neonates

A/C + PEEP with Volume Guarantee (VG) until extubation

If SIMV is used – SIMV + PEEP (volume targeted - VG preferred)

HFOV is used for rescue of babies with severe, acute lung disease requiring consistent high PIP (28-30 cm or above). Also useful for babies 34 weeks or greater with hypoxic respiratory failure/PPHN at high risk for ECMO, who are unresponsive to conventional ventilation. May be especially useful in management of CDH with severe respiratory failure.

Volume Guarantee (VG)

During conventional time cycled pressure limited neonatal ventilation (TCPL), delivered tidal volume (Vt) is determined by PIP, Tinsp, compliance of the respiratory system and magnitude of ET tube leak. Lung mechanics and leak change throughout the day. As a result Vt varies widely on any fixed combination of ventilator settings. VG mode on the Draeger Babylog and VN500 ventilators maintains a more consistent Vt delivery in the face of these changing conditions. In VG mode, the operator selects a target Vt and a limit (Pmax) to which the inflation pressure can be increased by the ventilator to achieve the targeted volume (Pmax). 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 safety feature during rapid changes following surfactant administration. VG is the most common of several new modes of "volume targeted" ventilation (VTV) in neonates. A recent Cochrane meta-analysis of 12 studies **(2011)** reported significant reductions in death or BPD, as well as severe IVH and air leaks, associated with VTV strategies as compared to traditional TCPL ventilation.

We recommend A/C + VG as primary mode of ventilation for babies ≤ 32 weeks PCA, to continue until extubation or evolution into prolonged ventilator dependency (≥ 4 weeks). This mode can be used for many older, larger infants as well. **As with all modes of mechanical ventilation, blood gases, chest excursion and other indicators of ventilation must be monitored closely to avoid over ventilation and hypocarbia.**

Initial Ventilation

Infants ≤ 32 weeks gestation are ventilated using a volume targeted strategy employing VG.

Mode: A/C + VG + PEEP with Draeger Babylog or VN500 (allows VG control for all breaths)

Vt Target: 4.0-6.0 ml/kg (<1000g=4.5-5.0 ml/kg) and (>1000g=4.0-4.5 ml/kg).Subsequent adjustments in increments of 0.5 ml/kg.

Pmax (PIP limit): Initially set at 25-28 cm H_20. This allows 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 maintain it 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. Thus, it is important, for patient safety, to adjust Pmax downward as lung compliance improves and working PIP decreases ("self-weaning" benefit of VG). Maintain ~ 3-5 cm H_2O difference between Pmax and "working" PIP.

PEEP: ≥5cm

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 ≤ 0.25 sec is used, it may be necessary to decrease slope to 0.02-0.04 sec,

Ventilator Back Up Rate (BUR): 30/min (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 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

During VG ventilation the Vt of each patient triggered breath is the sum of that provided by the ventilator and that of patient effort. As compliance improves, the ventilator will "auto-wean" (thus avoiding over-distension of the lungs) and a greater proportion of the Vt will be supplied by patient effort. Depending on the PCO2, the target Vt may be adjusted in 0.5 ml/kg increments in association with adjustment of the Pmax to remain 5-8 cm above working PIP. If target Vt is too high hypocarbia or diminished spontaneous breathing may occur. If target Vt is set too low there may be tachypnea and increased work of breathing, as infant is forced to contribute an excessive proportion of his own effort to the total Vt. Progressive atelectasis or subsequent extubation failure may occur.

Causes of "Low Tidal Volume" Alarm - Pmax too low, large ET tube leak, ET tube malposition, forced exhalation, abdominal "splinting", deteriorating lung mechanics or inadequate Ti to achieve pressure plateau.

ET Tube Leak - VG usually can be used with up to 45-50% leak (large ET leaks impair delivery of adequate Vt in any ventilator mode). Draeger VN500 provides automatic leak compensation by increases in inspiratory gas flow and wave form pattern and can be used with larger air leaks than the Babylog. If persistent large leaks generate frequent Low Tidal Volume alarms, or impair adequate ventilation, assure proper ET tube position and try changes in patient position. On occasion, persistent large leaks may require re-intubation with larger size tube.

Adjusting Circuit Gas Flow - If there is no pressure plateau during inflation (flow does not fall to 0 by end of inspiration), flow rate or Ti should be increased to overcome reversible ET tube leak. If pressure plateau is longer than needed to complete inflation, consider reducing circuit gas flow or Ti.

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

Infants in ≤ 32 weeks PMA category should remain on VG support until extubation or evolution into prolonged ventilator dependency (≥ 4-6 weeks). VG automatically "weans" the working PIP as lung compliance improves. In A/C the infant controls the ventilator rate. Reducing the BUR has no effect on delivered rate and ventilation unless the infant's spontaneous respiratory rate is very low or absent. Therefore, the main parameters reduced during weaning are FiO_2 and the target Vt. Do not wean target Vt ≤ 3.5 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.

Indications for Potential Extubation to NCPAP

- $FiO_2 \leq 30\%$
- Target Vt is weaned to 4-4.5 ml/kg range and spontaneous breathing is comfortable
- MAP is < 8-10 cm H_20
- Blood gases are satisfactory
- Breathing pattern appears comfortable

Table 2-5. Ventilator manipulations to effect changes in PaO_2 and $PaCO_2$

To increase PaO_2	To decrease PaO_2
• Increase FiO_2	• Decrease FiO_2
• Increase PEEP	• Decrease PIP or Vt
• Increase PIP or Vt	• Decrease PEEP if > 5 cm H_2O
To increase $PaCO_2$	**To decrease $PaCO_2$**
• Decrease PIP or Vt	• Increase SIMV rate
• Decrease SIMV rate if PIP < 18-20	•Increase PIP or Vt

Prolonged Mechanical Ventilation

For VLBW infants who require prolonged mechanical ventilation (> 4-6 weeks), the clinician should review the infant's status and make specific decisions regarding the appropriate mode of on-going ventilator support. This decision may be aided by consultation with the unit Medical Director or one of the Neonatology Section BPD physicians. VG may play a role in prolonged ventilation of some infants but selection of primary mode of ventilation (SIMV, PSV, A/C, etc.) will vary depending on a number of clinical circumstances.

Volume Guarantee References

(Keszler M. NeoReviews Vol.7 No.5 May 2006)
(Klingenberg, et. al. J Perinatol 2011; 31:575-585)

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. Ventilators we use to deliver synchronized breaths detect patient respiratory efforts by:

- measuring ET tube airflow with a hot wire anemometer (Babylog and VN500)
- measuring circuit airflow or pressure change with a pneumotachometer (Servo 300, Puritan-Bennett 840)

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 IMV. 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 at his own spontaneous rate 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 to 40). Between mandatory ventilator breaths additional spontaneous breaths occur without support. The operator sets the ventilator breath rate, PIP (or Vt) and Tinsp

Initial Ventilator Settings – SIMV Mode

Mode	SIMV + PEEP. (VG preferred)
Rate	20 to 40 cycles 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 seconds
System flow	8 to 10 L/min
FiO_2	Adjust for desired saturation

Subsequent Ventilator Adjustments

Oxygenation is a function of FiO_2 and mean airway pressure, which is determined by the PIP, PEEP, and the inspiratory duration. These parameters determine the PaO_2.

Ventilation (minute ventilation) is a function of respiratory rate and tidal volume. These settings determine the $PaCO_2$. In general, moderate hypercarbia (PCO_2 ~ 60 mmHg) is acceptable, but hypocarbia (PCO_2 less than 35 mmHg) should be promptly corrected since it generally indicates over distention of the lung by high-volume ventilator breaths.

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.

As lung compliance improves, wean FiO_2 and PIP (or Vt) followed by ventilator rate. When support has been weaned to FiO_2 less than 40%, PIP 18 to 20 cm H_2O, rate 25 or less, and PEEP 5 cm H_2O, and there is good respiratory effort, the infant may be extubated. Either nasal CPAP or supplemental O_2 may be necessary post extubation depending upon gestation and

clinical status. **(For weaning during use of VG see section on Volume Guarantee.)**

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.

Assist–Control (A/C)

In A/C mode the patient breathes at his own spontaneous rate, but each patient breath triggers a ventilator breath. PIP (or Vt) and inspiratory time are set by the user. 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 (**Abukar and Keszler, J.Perinatol 2005;25:638).** However, no specific long-term benefits have been established for this technique.

A/C mode with VG is recommended for initial ventilation VLBW infants, those with CDH or those with other forms of pulmonary hypoplasia. In hypoplastic lungs, increases in delivered tidal volume–even at high ventilator pressures– is limited by poor compliance and the underlying low maximal lung volume. In such patients, minute ventilation can only be maintained by high breath rates – whether spontaneous or ventilator delivered. A/C is also suitable for improving comfort of many larger infants with acute lung diseases requiring ventilator support.

All modes of synchronized ventilation must provide a backup mandatory ventilation rate in case of apnea. In either of the fast rate synchronized modes, the inspiratory time should be limited to 0.33 seconds or less to avoid breath stacking, since the infant's spontaneous respiratory rate may be high.

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 (usually as a weaning technique) 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 (**Reyes 2004)** 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

The primary decision facing clinicians caring for infants still ventilator dependent beyond 4-6 weeks of life is whether to continue support with a conventional volume targeted ventilator mode or change to a more individualized strategy employing techniques such as PSV, prolonged inspiratory time or manipulation of inspiratory flow patterns. Depending upon individual patient physiology, such a strategy might utilize either volume targeted or pressure limited control.

Small premature infants who do not wean to CPAP by 4-6 weeks –despite closure of a symptomatic PDA and/or control of apnea–usually have evolving bronchopulmonary dysplasia ("New BPD"). (**See the section Bronchopulmonary Dysplasia: classic BPD and the "New" BPD**). These infants may require a more prolonged period of mechanical ventilation. Poor chest cage function with atelectasis and pulmonary interstitial edema producing low lung compliance are dominant abnormalities. As a group such infants have significantly reduced ventilation and effective tidal volumes. Nevertheless most of these infants will become stable and can be progressively weaned from ventilator support. During this period, continuing acute care ventilator strategies such as A/C + VG or SIMV + VG are appropriate for many. Attempts to minimize FiO2 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 **(Keszler-2009, Klingenberg 2011).** Most of these infants progressively improve over a variable period of time. As lung function improves they can be weaned by progressive reductions in PIP and SIMV rate (SIMV mode) or target Vt (VG mode).

However, a small proportion of infants remain ventilator dependent beyond 6-8 weeks of age 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 long term ventilator strategy and SpO2 target range. 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 than those employed for acute care ventilation. 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 hyperinflation of the lung may occur.

Once retinal maturation has occurred, it is recommended to maintain SpO_2 95% or greater. Close monitoring is necessary in attempt to optimize oxygenation and reduce hypoxia time in order to minimize PVR and risks of high RV afterload leading to corpulmonale. Reductions in FiO_2 or ventilator support should be done in small increments with several days' 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.** When FiO_2 required decreases to 40% or less and the infant is comfortable breathing on low (10 cm H_2O) PSV - extubation may be attempted. At this point, many can be successfully extubated despite a ventilator PIP or Vt significantly higher than the target values used during ventilator weaning of acute lung disease.

After weaning from mechanical ventilation, most infants with moderate-severe BPD require supplemental oxygen for additional weeks or months. Close monitoring of SpO_2 and to detect subtle hypoxia time is critical **(see BPD section: Oxygen below)**.The role of CPAP or HHHFNC post extubation in BPD infants is poorly studied. NCPAP devices may produce agitation in older infants. Although the theoretical benefits of enhanced diffusive effects and CO_2 removal reported for HHHFNC systems seem desirable, little objective data exists at present to guide use of this technique in infants with BPD.

High-frequency Oscillatory Ventilation (HFOV)

HFOV is a technique for maintaining effective gas exchange with lower tidal volumes and lower peak airway pressures than those usually employed for conventional mechanical ventilation. This may reduce airway distension during tidal ventilation and potentially reduce airway injury. Basically, HFOV is a CPAP device with enhanced gas mixing and co_2 removal.

Uses of HFOV include ventilatory support of RDS, management of neonates with pulmonary air leak, and ventilation of neonates with respiratory failure who are at risk for requiring ECMO (with and without nitric oxide [NO]). Some centers use HFOV electively as a primary ventilation strategy for RDS. Current evidence does not demonstrate any

Long-term benefits of this strategy as compared to rescue use. Although individual studies have reported a reduction in risk of BPD or long term airway dysfunction this effect was inconsistent. Pulmonary air leaks occurred more frequently in the HFOV group **(Cochrane Review 2015).**

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.

Table 2–6. 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])	$\Delta P = resistance \times (flow)^2$
	$Resistance = 0.32\ density \times L \times (Reynolds\ Number)^{-1/4} / (4 \sim {}^2r^5)$
	$Reynolds\ Number = 2 \times density \times (flow \times \sim r^1 \times viscosity^{-1})$

Indications for Use

Potential candidates for HFOV include:

- **Babies 34 or more weeks' gestation with severe respiratory failure who are at high risk for requiring ECMO.** This includes infants with PPHN, sepsis, pneumonia, RDS, meconium aspiration, CDH or pulmonary hypoplasia. Such babies also may meet criteria for iNO. If a physician chooses HFOV, iNO may be given via the oscillator. One study reported a reduced need for ECMO in patients in these categories treated with HFOV plus iNO as compared to either modality alone.
- **Management of severe, acute lung disease.** HFOV is recommended when conventional ventilator PIP reaches or exceeds 28 cm H_2O or mean airway pressure exceeds the 12- to 14-cm H_2O range (10 cm H_2O in babies < 1000 g). 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.
- **Infants with 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 quite non uniform (e.g., meconium aspiration). It is important to differentiate this before initiating HFOV, just as with conventional ventilation, because 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– each is influenced by specific manipulations.

HFOV 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. Bias flow, piston centering, frequency, and percent inspiratory time are set initially and rarely vary throughout the course.

Initial settings

Bias flow	6 to 8 L/min
Piston centering	centered
Frequency	15 Hz
% Inspiratory time	33%
Paw	1 to 2 cm H_2O higher than the level on prior IPPV
ΔP	just high enough to produce perceptible chest wall motion
Fio_2	1.0

Control of Ventilation (PCO_2)

Manage ventilation by adjusting ΔP. In the Provo Multicenter Trial (surfactant + high volume strategy) average ΔP for initial treatment was 23 cm H_2O. 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 10 Hz 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
- chest X ray estimate of lung volume
- pulse oximetry

Special Considerations

- In non-homogeneous lung diseases such as meconium aspiration, pneumothorax, and pulmonary interstitial emphysema (PIE), emphasize weaning Paw and ΔP, even if higher $PaCO_2$, lower PaO_2, and $FIO_2 \geq 0.7$ must be accepted. These disorders have uneven expiratory time constants and, thus, have an 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.
- Frequent chest X rays are necessary to monitor for hyperinflation. A suggested schedule is:
  - » within 2 to 4 hours of initiating HFOV
  - » every 8 to 12 hours during initial 24 hours of HFOV
  - » then once daily unless additional indications
- On chest X ray, the diaphragms should be at the T8.5 to T9 level, **if lung anatomy is normal. In pulmonary hypoplasia or CDH, these guidelines cannot be used, so do not try to inflate the lungs to these volumes.**
- Maintain an unrestricted airway during HFOV. Limit suctioning to whatever frequency is needed 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 12 hours 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. Under no circumstances should an infant's position not be moved while on HFOV.

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.

Non-Invasive Ventilation (NIPPV)

Systemic review of several small RCT's have reported a reduction in post extubation failure in VLBW infants receiving non-invasive Nasal IPPV as compared to NCPAP **(Cochrane Review 2014)** .However, recent trials comparing NIPPV to NCPAP for management of early RDS demonstrate no difference in need for

mechanical ventilation or survival without BPD **(Meneses 2011, Kipalani 2013)**. This technique may be of value for rescue of select prematures exhibiting frequent apnea/desaturation events or persistent PCO_2>65 mmHg following extubation. Use of synchronization may be an important factor in use of this technique. Currently, ventilators currently available in most Baylor NICU's provide only non-synchronized NIPPV. Thus pressure controlled mandatory IMV is actually being delivered. Reported breath rates utilized have been 12-25/min with initial PIP set at level of ventilator support at time of extubation or 2-4 cm H2O higher.

Surfactant Replacement Therapy

(Also see Chapter 1 - Care of Very Low Birth Weight Babies.) 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. Prophylactic or early rescue surfactant reduces occurrence of air leaks and improves survival without BPD. Recent evidence indicates early NCPAP combined with selective use of surfactant if RDS develops is the optimal strategy to reduced risk of death or BPD **(AAP, Pediatrics 2014;133:171 and Pediatrics 2014;133:156).**

"CPAP First"

CPAP at birth is recommended for preterm infants ≤ 30 0/7 weeks gestation. **(See this chapter: Infants 30 0/7 Weeks PMA or Less and Infants More than 30 0/7 Weeks PMA).** Early implementation of NCPAP is recommended for babies > 30 0/7 weeks with RDS persistently requiring 30-40% supplemental oxygen.

Rescue Treatment

We recommend early surfactant treatment for babies still requiring 30-40% O_2 despite CPAP. 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. However, use of early CPAP may modify the need for rescue treatment in some preterm infants.

Rescue surfactant therapy using either single- or multiple-dose surfactant replacement is accompanied by reduced mortality from RDS as well as reduced occurrence of pneumothorax. Some treated infants may benefit from 2 or more doses. Repeat dosing is recommended for patients with a continued oxygen requirement greater than 30% and MAP greater than 6 to 7 cm H_2O persisting after the last surfactant dose.

- Spontaneously breathing infants with RDS requiring 30-40% oxygen despite nasal CPAP are candidates for endotracheal (ET) intubation, MV and rescue surfactant. 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.
- Outborn infants with RDS who require 30-40% oxygen or greater despite NCPAP should receive surfactant in the rescue mode. Lung mechanics may improve rapidly, requiring rapid weaning of ventilator FiO_2, PIP (or Vt), or rate. When weaned to minimal settings, attempt extubation and place infant on nasal CPAP.
- Outborn infants with RDS already on MV are candidates for rescue surfactant if they exhibit a persistent O_2 requirement of 30% or greater.

Surfactant Product Selection and Administration

Always assure proper ET position clinically prior to dosing to avoid instillation into a main stem bronchus.

Commonly used surfactant products include those of bovine (Survanta®) and porcine (Curosurf®) origin. A recent meta-analysis of 5 RCT's 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. **(Singh, et al, Pediatrics 2011;128;e1588)**

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 of birth weight. Up to 2 subsequent doses of 1.25 ml/kg may be given at 12 hour intervals.

The surfactant may be administered using ventilator settings employed just prior to dosing. Administer Curosurf® using a 5 Fr. Catheter positioned just distal to the tip of the ET tube. Administer each dose in 2 aliquots, with infant positioned on right side for one and left side for the other. Surfactant should be administered rapidly and the catheter removed. The infant should be placed back on the ventilator for approximately one minute. If chest excursion and ventilation remains poor, or SpO_2 falls significantly, a temporary increase in PIP (or VT) or a short period of manual (bag) ventilation may be necessary to clear surfactant from the large airways. If oxygenation deteriorates during dosing, an increase in ventilation usually is necessary (increase the PIP or VT on the ventilator or provide a period of manual ventilation). An increase in FIO_2 alone will not be sufficient. After dosing procedure is completed, and infant is stable resume pre-dose ventilator settings.

During or immediately following the dosing procedure lung compliance may improve rapidly. Continued monitoring of chest excursion is essential to allow rapid reduction in ventilator PIP or Vt as improvement occurs. An ABG should be obtained soon after dosing to avoid hyperventilation or over-distension of the lungs associated with surfactant administration.

Survanta®

Recommended Initial dose is 4 ml/kg divided into 4 aliquots. This may be repeated every 6 hours for up to 4 doses. The surfactant may be administered using ventilator settings employed prior to dosing.

The 4 aliquots should be instilled into the ET tube through a 5 Fr. end-hole catheter. Each aliquot is administered with the infant in a different position:

- head and body inclined 5-10º down, head turned right
- head and body inclined 5-10º down, head turned left
- head and body inclined 5-10º up, head turned right
- head and body inclined 5-10º up, head turned left

After each aliquot, remove the catheter and ventilate the infant for at least 30 seconds or until stable. This may require increasing ventilator PIP or Vt briefly, or manual ventilation. If

desaturation occurs, this implies temporary airway obstruction by surfactant and merely increasing FiO_2 will not be adequate. When dosing is complete and patient stable, resume prior ventilator settings.

Surfactant Replacement for Term Infants with Hypoxic Respiratory Failure

Current evidence indicates surfactant treatment improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO) in term babies with hypoxic respiratory failure associated with RDS, meconium aspiration, pneumonia or sepsis, and some cases of idiopathic PPHN. Benefits are greatest for infants requiring positive pressure ventilation who are treated when the oxygenation index reaches 15 on 2 separate determinations. In this setting, up to 3 doses of surfactant may be necessary. No benefits of surfactant therapy have been identified in infants with CDH **(Van Meurs 2004, Lally 2004, AAP 2014).**

Inhaled Nitric Oxide (iNO)

Mechanism of Action

Nitric oxide produces primary relaxation of vascular smooth muscle. When inhaled, the gas becomes a selective pulmonary vasodilator. It appears to increase PaO_2 by dilating vessels in better-ventilated parts of the lung, thus allowing redistribution of blood flow from regions with low ventilation/perfusion (V/Q) ratios or a reduction in shunting. It combines with hemoglobin and is rapidly converted to methemoglobin and nitrate. As a result, there is no effect on SVR or systemic BP. Approximately 70% of the inhaled dose is excreted in urine as nitrate.

Use in Term and Late Preterm Infants:

Inhaled nitric oxide has been shown to improve oxygenation and reduce the need for ECMO in babies 34 or more weeks' gestation who have disorders that produce acute hypoxic respiratory failure. Those disorders include idiopathic PPHN and pulmonary hypertension secondary to meconium aspiration, neonatal pneumonia or sepsis, or RDS. In patients with PPHN in association with parenchymal lung disease, the combination of iNO plus HFOV has been shown to be more effective in improving oxygenation than either strategy alone. This group of patients also benefited from replacement surfactant before qualifying for iNO.

Initiation of therapy is recommended if a patient 34 or more weeks' gestation on mechanical ventilation has an Oxygen Index (OI*) of at least 25 on two separate measurements.

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

Response to iNO is defined as an increase in $PaO_2 \geq 10$ mm Hg or oxygen saturation $\geq$ 5%.

Use in Preterm Infants

Use of INO in VLBW infants has increased in recent years. However, RCT's and several meta-analyses have failed to establish evidence of specific benefit in this population.

Recent AAP/Committee on Fetus and Newborn guidelines recommend against routine or rescue use of iNO in preterm infants with respiratory failure, as well as use of iNO for prevention or amelioration of BPD **(Pediatrics 2014;133:164).** However, observational studies have reported response to INO among select groups of preterm infants with prolonged rupture of membranes, oligohydramnios, pulmonary hypoplasia and echocardiographic evidence of pulmonary hypertension **(Chock, Am J Perinatol 2009;26:317 and Aikio, J Pediatr 2012;161:397).** A trial of iNO may be appropriate for babies in this select subgroup who exhibit pulmonary hypertension physiology rather than that of parenchymal lung disease **(Pediatric Pulmonary Hypertension Network, 2015)**.

Administration

Optimal lung recruitment is necessary prior to iNO administration.

Inhaled nitric oxide is administered via the ventilator circuit at an initial dose of 20 ppm. Response to therapy is defined as a change from baseline PaO_2 of at least 10 to 20 mmHg. Higher doses confer no additional benefit and should not be used.

Weaning

If there is no response to optimized ventilation plus 20 PPM iNO, wean the iNO every 15 minutes in increments of 20-15-10-5 PPM. At 5 PPM attempt to wean by increments of 1 PPM every hour until discontinued.

In babies responding to iNO who are stable for 4 hours begin to wean FiO_2 by decrements of 2-5%. When FiO2 has decreased to 60% and patient is stable, wean iNO every hour in decrements of 20-10-5 PPM. At 5 PPM attempt to wean by decrements of 1 PPM every 1-2 hours.

Wean with caution below iNO concentrations of 5 PPM because precipitous deterioration in oxygenation has been reported, even in responders, at these low levels. When iNO is discontinued it may be necessary to increase FiO2 as much as 15%.

Monitoring

Before initiating iNO, exclude congenital heart disease. During gas delivery, continuously monitor NO and nitrogen dioxide (NO_2) levels. 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 NO2 concentration is below 3 PPM. If the NO2 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 metHb levels greater than 7% persist despite weaning or discontinuing therapy, the patient can be treated with blood 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.

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 of 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

Prophylactic indomethacin significantly reduces occurrence of symptomatic PDA, PDA ligation and, to a lesser extent, grade IV IVH in ELGAN babies (**Ment 1994, TIPP Study 2006**). However, these short term benefits have not been associated with improvement in survival or reduction in severe neurodevelopmental delay.

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/hg of birth weight
- **Second dose:** (24 hours after first) – 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), platelets fall below 50,000, overt bleeding occurs or infant requires corticoteroids for circulatory support.

Treatment of PDA

Medical or surgical treatment usually is reserved for symptomatic infants with moderate to large PDA with large left to right shunts 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.

Conservative management includes modest restriction of fluid intake, diuretics, avoidance of further decrease in PVR, 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 medical management is inadequate.

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 of ibuprofen.**
- **Surgical ligation of PDA may be considered.**

Indomethacin Treatment

If ibuprofen 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. 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.

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

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.

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.
- 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 **(J Pediatr 2012:160:584, J Pediatr 2007;150:597).** Other surgical morbidities may include vocal cord paralysis and thoracic duct trauma resulting in chylothorax.

The Meconium-Stained Infant

Passage of meconium in utero may be a sign of fetal distress but most often is not. Passage of meconium occurs in about 12% of deliveries. If meconium has been passed into the amniotic fluid, there is a chance of aspiration into the trachea and lungs with resultant meconium aspiration syndrome.

The presence of meconium staining may be associated with PPHN and the physiology of this disorder may dominate the clinical picture **without superimposed aspiration.**

After Delivery

If the infant is vigorous (heart rate greater than 100 bpm; strong respiratory efforts; good muscle tone), despite meconium-stained amniotic fluid, current evidence does not support routine tracheal intubation and direct suctioning.

If the infant is depressed (lack of vigor; see above) with meconium stained amniotic fluid:

- Place infant under a radiant warmer for initial steps in resuscitation
- If no spontaneous breathing or HR < 100/min after initial steps begin positive pressure ventilation
- Routine intubation/suctioning in this setting no longer is recommended **(NRP 2015 – see Circulation 2015; 132 (suppl 2):S543-560).** Select individual patients might require intubation and suctioning if airway is obstructed.

Respiratory Management of Congenital Diaphragmatic Hernia (CDH)

If the CDH is diagnosed before birth, the parents should meet with Neonatology, Maternal-Fetal Medicine, and Fetal/Pediatric Surgery physicians. Fetal ECHO and MRI is usually obtained. Scheduled induction of delivery is often arranged at about 38 weeks to allow for planned stabilization.

Strategy of respiratory management includes:

1. Monitoring pre-ductal oxygen saturation for primary decision making,
2. Allowing spontaneous breathing (avoid sedation or neuromuscular blockade), and
3. Using gentle, low volume ventilation in attempt to minimize trauma to the underdeveloped lungs.

For a known CDH delivery, the on-call neonatal ECMO clinician at TCH should be alerted to the impending delivery, and the presence of a crystalloid primed ECMO circuit in the ECMO storage area should be confirmed. At the TCH Perinatal Center, a neonatology faculty member and pediatric surgeon attend the delivery.

At the time of delivery, immediate intubation should occur to avoid bag-mask ventilation. Maintain the infant with head positioned at the "foot" of the bed. A pre-ductal saturation monitor should be immediately placed (goal saturation $\geq$80% or improving). A replogle tube should be placed and attached to intermittent suction. Gentle ventilation should be initiated with a synchronized mode (A/C + VG is preferred).

Recommended initial ventilator settings are:

- A/C + VG with Ti=-0.3 sec,
- TV 4-5 ml/kg PEEP 5-6 cm H_2O, 100% O_2.
- Initially set Pmax at 25-28 cm H_20.

This allows 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 maintain it 3-5 cm above the "working" PIP.

- If no spontaneous breathing, initiate IMV 40, Ti 0.3 sec., PIP 20 to 25 cm H2O, PEEP 5 cm H2O, 100% O2.
- Quickly place a peripheral IV.
- Monitor cuff blood pressure if no UAC.
- Avoid sedation and musculoskeletal blockade if at all possible.

Initial O_2 saturation target is preductal value > 80%.
If preductal saturation remains less than 80% and/or pH is less than 7.20 (or not slowly improving), increase TV in 0.5 ml/kg increments up to a "working" PIP of 28-30 cm H2O.

Upon admission to the NICU, quickly confirm ET tube and line location by CXR/KUB. Start SpO_2 monitoring (pre and post ductal location). A **temporary** low lying UVC and appropriately positioned UAC should be inserted in all CDH patients requiring central access. A stat HUS and cardiac ECHO should be obtained. However, cardiac ECHO may be unnecessary in infants whose mothers had prenatal studies adequate to rule out major cardiac anomalies. Circulation should be optimized (avoid repeated volume boluses and initiate dopamine as needed). Maintenance fluids should be initially restricted to 40-50 ml/kg/day, using concentrated dextrose to obtain an adequate glucose infusion rate. If a centrally placed UVC cannot be

obtained, consider PICC placement for central access. Transfuse PRBCs if needed to optimize O_2-carrying capacity. During transition, bundle care procedures and minimize handling and noise, as the pulmonary circulation of the CDH patient typically remains very unstable and any manipulations may produce significant desaturation events.

Goals of continued ventilator support:

- pH 7.20 or greater with lactate 3mmol/L or less
- PCO_2 5-70 mmHg
- Pre ductal saturations $\geq$ 80% (first 2 hours of life)
- Pre ductal saturation $\geq$ 85% (beyond 2 hours).

If these targets cannot be maintained with "working" PIP $\leq$ 28cm $H_20$and 100% O_2), initiate HFOV.

A trial of iNO may be initiated but evidence of benefit in CDH is lacking. Current evidence does not support routine surfactant replacement therapy. However, clinicians may consider surfactant replacement in CDH patients treated with Fetal Tracheal Occlusion or those delivered at < 37 weeks gestation.

If MAP on HFOV > 17 cm H_2O, pre ductal SpO_2 <85%, pH<7.15, OI consistently $\geq$40 or lactate $\geq$3 ECMO should be considered and the ECMO clinician contacted.

The decision to offer ECMO to the parents and initiate ECMO is made by the neonatal ECMO clinician and the Pediatric Surgery faculty member jointly. Some infants may require CDH repair on ECMO.

Goals of on-going ventilator support for infants not requiring ECMO:

- pH 7.20 or greater,
- PCO_2 45-65 mmHg, P_aO_2 40-90 mmHg
- Pre-ductal saturations $\geq$ 85%

Most symptomatic CDH patients need continued fluid restriction and diuretic support for a prolonged period of time. CDH 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

In outborn infants or those without a prenatal diagnosis, care should be adjusted to these guidelines as soon as the diagnosis of CDH is made.

All CDH patients should be monitored for on-going pulmonary hypertension. All post-ECMO CDH patients should have a pre-discharge head MRI, a neurodevelopmental evaluation and follow-up, and a hearing assessment.

Management of Hypotension

Hypotension in CDH patients is multifactoral 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 continues (especially in conjunction with ongoing hypoxemia) current evidence suggests addition of vasopressin infusion may effectively raise systemic BP and reduce PVR, resulting in improvement in both circulation and systemic oxygenation in some patients.

If this combination is inadequate hydrocortisone would be the next choice for symptomatic management. Addition of special agents such as milrinone or low dose epinephrine should be based upon specific evaluation of cardiac function, blood lactate levels and other parameters of systemic blood flow and oxygen delivery.

Neonatal ECMO

Neonatal ECMO improves survival of term or near term infants with hypoxic respiratory failure who are failing high levels of conventional ventilator support. Most neonates requiring ECMO for respiratory failure have PPHN (30% of TCH Neo ECMO patients) associated with meconium aspiration, RDS, sepsis or congenital diaphragmatic hernia (63% of Neo ECMO). 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.

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/Exclusion Criteria

- Gestational age $\geq$ 34 weeks, weight $\geq$ 2.0 kg (**)
- No significant coagulopathy or uncontrolled bleeding
- No major intracranial hemorrhage (ICH)
- Reversible lung disease with mechanical ventilation < 10-14 days duration
- No uncorrectable CHD
- No lethal congenital anomalies
- No evidence of irreversible brain damage
- Child less than one month of age (**)

**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 exhibiting persistent hypoxic respiratory failure despite support with 100% O_2 + INO on conventional MV with PIP 30 cm H_2O or greater or HFOV with MAP 17 cm H_2O or greater.

Additional indications include:

- OI > 40 on 2 separate measurements
- PO2 persistently < 40 mmHg or lactate > 3.0

Most of these infants benefit from surfactant replacement prior to consideration for ECMO – however, efficacy of surfactant replacement has not been demonstrated in infants with CDH.

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 today 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.

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. 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 CaCl 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:

- $SaO_2 \geq 90\%$ (pre-ductal)
- SvO_2 -65-75% (not accurate during VV ECMO)
- Arterial lactate ≤ 3.0
- Prompt capillary refill

Anticoagulation

The ECMO circuit induces ongoing procoagulant activation necessitating continuous anticoagulation with heparin. 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 6-12 hours daily) and ACT (every 1-2 hours) values.

Target values during ECMO include:

- Anti-Factor Xa assay ("heparin level") = 0.2-0.5 (accuracy reduced if TSB > 10 or plasma free Hgb > 200)
- Platelets $\geq$ 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 (new methodology)

(**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, immediate consultation with the Coagulation Pathology Team is recommended.

Patient Care During ECMO

A complete order set for all phases of ECMO is maintained 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. Most patients can be progressively weaned off INO – though this must be individualized in CDH infants. Patient oxygen delivery and SpO2 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 restriction and slow continuous ultra filtration (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 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. Within 6-12 hours of initiating ECMO, attempt to begin ultrafiltration (background ultrafiltration rate - BUFR*) calculated to remove daily volume of (1) drips and flushes (2) medications and (3) maintenance infusions for lines. This volume should be calculated prospectively for the next 24 hours and the rate adjusted accordingly. By day # 2 begin TPN 50 ml/kg and IV lipid 5 ml/kg. If the attending wishes to increase the volume of TPN + IL over 55 ml/kg/day, determine the total volume of TPN + IL over 55 ml/kg/day and remove this extra volume by UF (alimentation ultrafiltration rate – AUFR*). This rate should be adjusted prospectively as the provider increases the total amount of TPN + IL administered. The use of UF allows increasing TPN and IL as needed to attain good nutrition (90-100 Kcal/kg/day, 3.5–4 grams/kg/day protein, 15 ml/kg/day of lipid and 10-15 grams/kg/day of carbohydrate).Daily volume of blood components given for replacement of hemoglobin and coagulation factors also should be removed by UF (Blood Products Neutral). However, blood products given for blood volume expansion should not be removed. **Thus each day's target ultra filtration rate is determined by calculating the projected next day BUFR + AUFR.** 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. This requires frequent re-evaluation of the status of vascular pre-load and circulatory sufficiency. The ideal ultrafiltration rate may not be achievable in some patients.

*BUFR - add daily volume of drips and flushes, medications, and maintenance fluids for lines and divide by 24 hours = X ml/hour

** AUFR – [Total desired volume of TPN (ml/kg) + IL (ml/kg) for next 24 hours] MINUS [baseline 50 ml/kg TPN + 5 ml/kg IL] = XX volume divided by 24 hours = X 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/gk/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. Increase in PaO_2 to 150-200 mmHg or greater indicate improved V/Q matching and decreasing PVR below systemic levels. When evidence of improvement is present pump flow may be incrementally decreased while monitoring PaO_2 and pre-ductal SpO_2. 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 **(see Respiratory Management of Congenital Diaphragmatic Hernia)**, infants $\leq$34 weeks or those having complex or multiple anomalies. Such circumstances may require a STAT meeting of medical and surgical members of the Neonatal ECMO Team.

Surgery on ECMO

1. 8-12 hours pre-op, obtain confirmation from surgical team for maintaining the following:
   - Fibrinogen > 200
   - Platelets > 150,000
2. Order blood products (in addition to emergency blood kept at bedside):
   - 1 unit PRBC's
   - 2 units platelets
   - 1 unit FFP
3. Order the following:
   - X ray plate positioned in container beneath patient
   - 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.
4. Discuss with Surgery and Anesthesia teams any specific needs for other blood products, medications or special equipment.
5. Intra-operative fluids will be administered via the ECMO circuit; however, the anesthesiologist should be provided an IV site for emergency use.
6. 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. 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.
7. Target ACT values:

Usual Ranges	New Method	Previous Method
During Surgery	120-140 sec	140-160 sec
0-24 Hours Post-OP	130-150 sec	150-170 sec
24-48 hours Post-Op	160-180 sec	180-200 sec

8. 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.

Control of Breathing

Control of breathing can be understood as a simple feedback loop. The goal is breathing that is rhythmic rather than irregular or oscillatory. Respiratory drive originates in the CNS (the initiator), and signals are transmitted via afferent pathways to the remote respiratory pump mechanism (the responder). Information regarding the response of the respiratory pump is relayed back to the CNS, which automatically adjusts the nature of subsequent breaths. This modulation function is facilitated by certain modifiers, which promote more precise adjustment of the control-of-breathing mechanism.

Periodic breathing consists of short, recurring pauses in respiration of 5-10 second duration. Pathologic apnea is usually defined as the complete cessation of airflow for 15-20 seconds or greater, typically associated with bradycardia and/or oxygen desaturation. However, hypoxia or bradycardia may occur with pauses of shorter duration. The incidence of apnea increases progressively with decreasing gestational age, particularly below 34 weeks. Apnea may be central or obstructive but in premature infants usually is mixed.

Control-of-breathing disorders and their management focus on three primary areas:

- central respiratory drive,
- maintenance of airway patency, and
- the respiratory pump.

Central Respiratory Drive

Fetal respiratory control is characterized by periodic breathing alternating with periods of apnea. Fetal respirations are accompanied by normal heart rate variability, an important sign of fetal well-being. The prematurely delivered fetus continues to exhibit alternating periodic breathing and apnea in the postnatal state. Maturation is the most important factor determining rhythmic respiratory drive in the neonate. **In premature infants, central respiratory drive is diminished and improves progressively with increasing PCA (particularly beyond 34 weeks).**

Modifiers

Sleep State

Control of breathing is most disorganized and periodic during REM sleep. Immature infants spend most of their time asleep, and approximately 65% of sleep time is REM sleep. Therefore, they are quite vulnerable to apneic episodes.

Temperature

A stable thermal environment promotes rhythmic breathing; thermal

Fluctuations promote apnea. In one classic study up to 90% of apneic episodes in premature infants occurred during fluctuations in the thermal environment. About two thirds occurred during an increase in air temperature; the rest when the temperature was falling. Therefore, use of techniques to maintain stability of the thermal environment, such as servo-control, are essential to the proper management of an infant with apnea.

Chemoreceptors

Chemoreceptor function is impaired in immature infants as indicated by:

1. Depressed ventilatory response to CO2 which is more pronounced in infants with apnea.
2. Hyperoxia reduces carotid body response, which may induce apnea.
3. Preterm infants exhibit a biphasic ventilatory response to hypoxia. Initially peripheral chemoreceptor (carotid body) activity is stimulated and induces a transient increase in minute ventilation. However, by 3-5 minutes this response becomes blunted due to superimposed central respiratory depression. This depressed ventilatory response may exacerbate frequency or severity of apneic episodes.

Lung Volume

Maintaining an ideal resting lung volume (functional residual capacity [FRC]), enhances rhythmic respiratory drive while a low lung volume exacerbates periodic breathing and apnea. Maintaining lung volume is a role of the respiratory pump.

Airway Patency and Airway Receptors

A system of conducting airways and terminal lung units exist to promote respiratory gas exchange between the environment and the alveolar-capillary interface as well as providing for proper humidification. A complex set of neuromuscular functions and reflexes protects the patency of the upper airway and may be impaired by immaturity, illness or drugs. Like the other components of control of breathing, maintaining airway patency is primarily a function of maturity, but this function may be further modified by additional factors. Disorders of upper airway function that affect control of breathing do so primarily in the form of fixed obstruction or hypopharyngeal collapse.

Nose

Newborn infants usually are considered obligate nasal breathers and, thus, depend upon nasal patency for adequate ventilation. However, about 30% of term infants demonstrate mixed oro-nasal breathing during both quiet sleep and REM sleep. During such episodes, the distribution of tidal volume is 70% nasal and 30% oral. About 40% of term infants respond to airway occlusion with sustained oral breathing, although with reduced tidal volume. In a premature infant, however, compensatory mechanisms are poor and nasal obstruction commonly exacerbates apnea. **It is essential to assure adequate nasal patency in such infants.**

Hypopharynx

Intact hypopharyngeal function is the most important factor in maintaining upper-airway patency during infancy and inadequate integration of this complex function is the primary cause of obstructive apnea. The upper airway is a collapsible tube subjected to negative pressure during inspiration. When airway resistance increases (as in neck flexion or nasal obstruction), the upper airway is subjected to greater inspiratory negative pressure.

Most infants avoid collapse of the pharynx and keep the upper airway open during inspiration by active contraction of a system of hypopharyngeal muscles. When hypopharyngeal muscle tone is absent, the upper airway collapses at pressure only slightly below atmospheric (-0.7 cm H_2O).

Pharyngeal muscle function is immature and poorly coordinated in very preterm infants and is further impaired during sleep. This reduced hypopharyngeal tone leads to pharyngeal collapse and obstructive apnea. Flexion of the neck exacerbates the degree of airway obstruction. These factors are the main contributors to obstructive apnea in premature infants.

The primary effect of CPAP in managing apnea is that of splinting the hypopharynx and opposing pharyngeal collapse and obstructive apnea. Xanthines enhance the function of the hypopharyngeal musculature. Avoid flexion of the neck at all times. Most sudden flurries of apnea in premature infants are related to the loss of upper-airway patency.

Larynx and Trachea

The larynx and trachea are more rigid than the hypopharyngeal structures and are more resistant to airway collapse. However,

laryngeal function may be impaired by immaturity, edema, or vocal cord dysfunction. Any of these entities producing airway obstruction would exacerbate control-of-breathing problems.

Respiratory Pump

The respiratory pump mechanism consists of the lungs, the bony chest cage, the diaphragm, the intercostal muscles, and the accessory muscles of respiration. The developmental and functional aspects of each are closely related to gestational age. The respiratory pump serves 2 important functions in relation to control of breathing:

1. Maintains an adequate resting lung volume (Functional Residual Capacity), which facilitates rhythmic, rather than oscillatory, central respiratory drive. An ideal FRC allows each breath to be taken from an efficient point on the pressure-volume curve and is a reservoir for continued oxygen uptake between tidal breaths.
2. Produces adequate tidal gas exchange and normal oxygen and carbon dioxide tensions in arterial blood, which provides normal chemoreceptor feedback to maintain rhythmic central respiratory drive.

The structurally and functionally immature respiratory pump of a premature infant is a main contributor to apnea of prematurity.

Bony Thorax

Ribs are rigid, bony structures that lift the chest cage and expand its volume when the intercostal muscles contract during inspiration. In an immature infant, the ribs are thin and poorly mineralized. These pliable, cartilaginous structures may be unable to resist the retractive forces of the lung and chest wall and may fail to maintain an adequate FRC. On occasion, the chest cage may be so pliable that the chest wall collapses during inspiration, resulting in inadequate tidal volume and uneven distribution of ventilation. Lack of rigidity in the bony thorax of a premature infant is an important component in apnea of prematurity.

Intercostal Muscles

The intercostal muscles contract to expand the bony thorax during inspiration. They also maintain resting tone at end-expiration to promote the continuous negative pleural pressure necessary to maintain an adequate FRC. This mechanism is disorganized during REM sleep in premature infants, resulting in loss of chest wall stability, leading to loss of lung volume and exacerbation of apnea. These effects of immaturity can be opposed with the use of CPAP and xanthines.

Diaphragm

The diaphragm works in conjunction with the bony chest cage and intercostal muscles to promote uniform expansion of the internal thoracic volume. This promotes efficient tidal breathing and maintains FRC. Functional efficiency of the diaphragm may be impaired by reduction in muscle fiber mass or contractile strength, supine posture, or changes in configuration. Postural tone loss in the diaphragm often occurs during REM sleep in premature infants. Strength of contraction and efficiency of resting tone are enhanced by xanthines.

Management of Apnea

Central respiratory drive and upper-airway patency are poorly integrated in infants less than 32-34 weeks' gestation. Thus, the incidence of apnea is high in such infants. These infants are extremely vulnerable to the effects of REM sleep, nasal or pharyngeal airway obstruction, or intercurrent illness. Infants born at 25 weeks gestation or less may continue to exhibit immature control of breathing at term and, occasionally, out to 44 weeks PMA. Basal control of breathing improves significantly in many infants after 32-34 weeks but introducing new tasks, such as feeding, may be accompanied by episodes of cyanosis, hypoxemia, or bradycardia. These are not episodes of apnea and they occur during the waking state. They are manifestations of immature pharyngeal mechanisms resulting in impaired coordination of suck/swallow and breathing.

Improved understanding of control of breathing in infants has led to the introduction of effective management tools to deal with apnea of prematurity. Usually it is possible to significantly reduce the frequency and severity of such episodes. Decisions to treat are based on frequency of episodes and whether the episodes produce bradycardia or hypoxemia that requires significant intervention.

General Measures

All infants with apnea should be nursed in a stable thermal environment. The most constant environment, suitable for the most immature infants, is that provided by 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 need low-flow, supplemental oxygen to maintain the desired target range of SpO_2, but hyperoxemia must be avoided. Monitor adequacy of nasal patency.

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. Over 75% of apnea of prematurity episodes can be significantly modified with xanthine therapy alone.

Caffeine citrate is the xanthine of choice for apnea of prematurity because of its wide therapeutic index and reduced 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. 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 a role for routine monitoring of serum caffeine levels because of poor correlation between serum levels and adequacy of control of apnea. We typically discontinue caffeine at 34 to 36 weeks PMA if no apnea spells occur for 5 to 7 days. Cardiopulmonary monitoring should continue for another 7 days until caffeine has been eliminated.

Nasal CPAP

Nasal CPAP enhances rhythmic control of breathing primarily by opposing pharyngeal collapse and minimizing obstructive apnea. By itself, the technique is effective in controlling about one third of apneic episodes in premature infants. Nasal CPAP is most effectively delivered using short, silastic, double nasal prongs, which minimize nasal trauma and have the lowest possible flow resistance. 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. Although transfusion of PRBCs reduces the frequency of apnea in such infants, neither the incidence of apnea nor the response to transfusion is related to the actual hematocrit value.

Preparation for Discharge

Most preterm infants achieve physiologic stability between 36-37 weeks PMA. However, premature infants have greater risk of "extreme" apnea events than term infants up to 44 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 out to 43-44 weeks PMA in babies born at very early gestational ages or those with a complex medical course. Otherwise healthy preterm infants off of xanthines have a low risk of significant episodes of recurrent apnea if they are apnea free for an observation period of 7-10 days **(Pediatrics 1997; 100:795-801 and Pediatrics 2011;128;e366.)**. Significant apnea does recur beyond this threshold in a small number of infants but most of these have additional risk factors such as chronic lung disease.

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. Most such infants remain hospitalized until apnea events have resolved or become insignificant. Home monitors are not indicated for prevention of SIDS in preterm infants **(Committee on Fetus and Newborn, AAP, 2008).** Pneumograms are of no value in predicting SIDS and are not helpful in identifying patients who should be discharged on home monitors. **(Fetus and Newborn Committee, AAP, 2008)**

Use of laboratory analysis of breathing patterns (pneumogram) and consideration for home monitoring may be indicated in the rare infant with severe, prolonged apnea/bradycardia or those suspected of apnea events secondary to some other process (GER, feeding disorder, prior ALTE, upper airway dysfunction or discrepancy between clinical and bedside monitor data regarding event frequency).

Bronchopulmonary Dysplasia

BPD–also termed neonatal chronic lung disease (CLD)–is the clinical evolution of an injury sequence initiated by perinatal factors that disrupt pulmonary angiogenesis and/development, stimulate inflammation or produce physical injury to the highly vulnerable immature lung (e.g. mechanical ventilation). Up to 42% of VLBW infants require supplemental oxygen at 36 weeks PMA. A physiologic definition of BPD correlates best with pulmonary outcome and reduces unnecessary use of oxygen. Diagnostic criteria include treatment with supplemental oxygen for at least 28 days plus:

Mild BPD - breathing room air at 36 weeks' PMA or at discharge home, whichever occurs first.

Moderate BPD - treatment with < 30% oxygen at 36 weeks' PMA or discharge to keep SpO_2 85% to 95%.

Severe BPD - treatment with $\geq$ 30% oxygen or positive pressure support at 36 weeks' PMA or discharge to keep SpO_2 85% to 95%.

Etiology and Pathogenesis

Primary antecedents for development of BPD include extremely low gestation, mechanical ventilation, oxygen use and antenatal or postnatal infection. Mechanisms of injury remain unclear, but include physical volutrauma or barotrauma, inflammation, impaired vasculogenesis and delayed alveolar development. Structural immaturity of the lung, surfactant deficiency and oxygen exposure occurring postnatally potentiate the lung injury response.

Recent research implicates volutrauma rather than barotrauma in the genesis of ventilator associated lung injury. Relative risk of BPD increases with decreasing PCO_2 during mechanical ventilation, an effect particularly striking with PCO_2 values below 29 mm Hg. In animals, if the chest is bound to prevent lung expansion, transpulmonary pressures above 50 cm H_2O may be applied without air leak or lung injury. Chest binding also prevents pulmonary edema induced by high tidal volume lung expansion. **These data suggest that acute lung injury is determined by the relationship between delivered tidal volume and maximum lung volume (V_{max}) rather than any absolute value of applied volume or pressure.** As tidal volume approaches the V_{max} of these small lungs, airways become damaged by over distension and an inflammatory process is initiated. Volume-induced injury may occur in immature lungs that have a low V_{max} even at low ventilator pressures because the delivered tidal volume plus any PEEP applied may be at or above the V_{max} for those lungs. In such circumstances, shearing and disruption is associated with necrosis of bronchial mucosa in small airways and potential for tracheobronchomalacia in large airways.

Although the exact nature of the triggering event for lung injury remains unknown, 4 pathways contribute to the clinical evolution of BPD:

1. Anatomic injury to airways and alveoli,
2. Accelerated production of elastic tissue,
3. Impaired angiogenesis, alveolarization and lung growth.
4. Activation of an intense inflammatory response.

These events promote ongoing airway and mucosal dysfunction, impaired gas exchange and interstitial edema in the lungs.

Clinical Course

Most patients with BPD today are antenatal steroid and/or surfactant-treated premature infants who weigh 1250 grams or less at birth and who require mechanical ventilation after the first 48 hours of life because of apnea, sepsis or structural immaturity of the lungs. These are said to have the "new" BPD. A subset of extremely immature infants may develop the classic course of BPD and require prolonged mechanical ventilation with high levels of support.

The "New" BPD

The hospital course of CLD in many VLBW infants today is milder and shorter in duration than that of classic BPD. Primary pathology is that of impaired alveolarization and vascular growth. Such infants may remain ventilator-dependent for several weeks, and then improve progressively. During this period of ventilator dependency, lung compliance is poor, dead space is increased and interstitial edema is present but there is less airway injury and obstruction than that of classic BPD. Lungs are opaque on X ray rather than exhibiting uneven hyperinflation. End-expiratory pressure and synchronized ventilation, combined with fluid restriction (130-150 ml/kg) and diuretics if necessary, are primary tools of management. Inhaled bronchodilators or steroids have little effect and are not indicated for routine use. Attempts can be made to wean from ventilator support by periodic attempts to reduce PIP and FiO_2. However, such attempts should be monitored closely for resulting deterioration in oxygenation targets, rising PCO_2 or increased work of breathing.

Classic BPD

A subgroup of premature infants evolve into the more severe and prolonged course of "classic" BPD. Uneven airway obstruction, bronchomalacia and hyperinflation dominate the course of these patients. The course of classic BPD can be divided into 3 clinical phases.

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 X ray. Wide swings in PaO_2 and O_2 saturation values are characteristic. Despite treatment of PDA, aggressive management of apnea, and no evidence of infection, the infant remains ventilator-dependent. Microvascular permeability increases, leading to symptomatic pulmonary edema. Necrosis of bronchial mucosa is widespread, producing increasing uneven airway obstruction. Airway obstruction by necrotic debris promotes atelectasis alternating with areas of gas trapping within the lung. A process of exclusion establishes CLD as the cause of persistent ventilator dependency.

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.

Oxygen requirement gradually falls to 40% or less, and most patients can be slowly weaned from ventilator support at this point and subsequently extubated. However, the infant remains vulnerable to pulmonary edema and reactivation of the inflammatory process within the lungs with deterioration in function. Most patients continue to exhibit significant pulmonary hypertension and attempts to wean oxygen or positive pressure support too rapidly may precipitate acute cor pulmonale.

Discharge Planning and Transition to Home Care

After 5-6 months of life, active inflammation diminishes and the process of repair and remodeling of the lung becomes more orderly. Lung growth and remodeling slowly progresses, allowing improving pulmonary function and decreasing need for positive pressure support. However, lung mechanics remain quite abnormal; hyperinflation, fibrosis, and cysts may remain visible on radiographs. Most such infants can be discharged to continue care at home. Many of these infants exhibit persistent evidence of fixed airway obstruction and some have episodes of typical asthma. Close monitoring of adequacy of oxygenation remains essential to avoid a subtle rise in PVR and insidious development of corpulmonale.

Cardiopulmonary Physiology

Severe BPD exhibits increased lung water, increased uneven airway resistance, and decreased dynamic lung compliance, which becomes frequency dependent. Physiologic dead space is high and respiratory rate is increased. Uneven airway obstruction leads to gas trapping and hyperinflation with severe pulmonary clearance delay. Bronchomalacia is common and may produce acute episodes of expiratory airway collapse associated with absent air entry and severe hypoxemia. Such events are often mistaken for asthma and treated with bronchodilators, which may exacerbate airway collapse. Pulmonary function testing during the first 6 months of life reveals little improvement in lung mechanics. However, significant improvement occurs after the first year. By 3 years of age, compliance is near normal and airway resistance has improved. However, in most patients abnormal airway resistance persists indefinitely, and worsens in some. Although classic asthma develops in some, more than half of these children have little response to bronchodilators.

The BPD injury sequence also is associated with impairment of structure, growth, and function of the pulmonary circulation. There is obliteration of small pulmonary arterioles, smooth muscle proliferation, diminished angiogenesis and abnormal vasoreactivity.

Cardiac catheterization studies of BPD patients have demonstrated resting elevations in pulmonary vascular resistance and a marked increase in pulmonary artery pressure in response to even mild hypoxia. Many of these infants exhibit echocardiographic evidence of moderate pulmonary hypertension (abnormal tricuspid flow velocity, RVH ordysfunction of the interventricular septum) and the elevated RV pressures can quickly rise to systemic levels with even small changes in pulmonary function. Chronic pulmonary hypertension, RVH and high right-ventricular filling pressures can impair lymphatic drainage of the lung and exacerbate

pulmonary edema. This may result in further deterioration of pulmonary function and a downward spiral to frank corpulmonale. Persistent echocardiographic evidence of severe pulmonary hypertension has been associated with high mortality risk in BPD. 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.

Understanding this fragile heart-lung interaction is critical in patient management. Only time and lung growth actually improve underlying lung function in the BPD patient. The primary goal of day-to-day management is maintenance of an environment that minimizes pulmonary vascular resistance by optimizing ventilation and alveolar PO_2. This prevents the vicious cycle of pulmonary edema causing deterioration in pulmonary function, increasing hypoxemia time and progressive worsening of pulmonary hypertension. If unchecked, such a course can result in cor pulmonale, right ventricular failure, and death.

Tracheobronchomalacia

Airway obstruction in BPD may be produced by (1) intraluminal accumulation of mucous and epithelial debris, (2) extraluminal compression of small airways by interstitial edema fluid and/or (3) increased airway smooth muscle tone. In addition, 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 the course of bronchomalacia. At present, bronchomalacia is much more common than reactive airway disease in BPD patients less than 6 months old. Infants with this type of episodic events should undergo bronchoscopy while breathing spontaneously. Many will have 50%-100% airway collapse on evaluation and effect of PEEP can be evaluated during the procedure. PEEP is the mainstay treatment for opposing airway collapse while awaiting growth and improved stability of the airway tree. PEEP values of 8-18 cm H_2O have been reported in the management of these patients but use of levels above 10-12 cm H_2O may produce significant patient discomfort or impairment of ventilation and circulatory function. Infants receiving unusually high levels of PEEP must be monitored closely.

Management

Primary goals of management are to:

1. provide complete nutrition to optimize lung growth and remodeling of the pulmonary vascular bed, and
2. prevent cor pulmonale.

Adequate lung growth for recovery of an infant with severe BPD requires months. During this period, pulmonary care is largely supportive and aims to optimize lung mechanics and minimize pulmonary vascular resistance.

Supportive Care and Nutrition

Complete nutrient intake must be provided despite significant fluid restriction. Although adequate calories may be provided using fat or carbohydrate additives, the intake of protein, minerals, and micronutrients will be insufficient unless they, too, are supplemented. Long-term dietary intake should meet all guidelines of the AAP for term and preterm infants. Periodic evaluation by a pediatric nutritionist is essential.

Fluid Restriction

Infants with BPD have increased lung water and may benefit symptomatically from fluid restriction to control pulmonary edema. The balance between fluid restriction, adequate growth, and stability of lung function requires frequent reassessment. 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, 24-calories-per-ounce, mineral-enhanced premature formulas. These provide good quality protein intake, trace nutrients, and increased calcium and phosphorus supplements to optimize bone mineral uptake. When the infant reaches term, a standard or mineral- and protein-enriched transitional formula may be substituted. Severe impairment of lung mechanics may necessitate restricting fluids to 110-130 mL/kg/ day. (**See Chapter 13 - Nutrition Support.).** The Nutrition Support Team should monitor all such patients.

Diuretics

Infants with BPD have increased lung water and are susceptible to gravity-induced atelectasis and alveolar flooding. Systematic reviews have demonstrated improvement in short-term lung mechanics and reduced need for supplemental oxygen among premature infants with BPD treated with diuretics. However, no long-term benefits have been established on mortality, duration of oxygen supplementation, length of stay, or need for subsequent re-hospitalization. Potential side effects include severe electrolyte imbalance, increased calcium loss and osteopenia, ototoxicity and nephrocalcinosis. Two specific diuretics have been used: thiazides and furosemide. If diuretics are necessary in addition to fluid restriction, use of thiazides is preferred whenever possible. However, some chronically ventilator dependent infants will require periodic furosemide for control of symptoms.

Thiazides

Thiazide diuretics act upon the early distal renal tubule. **Hydrochlorthiazide** (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. However, they may be adequate in many infants, especially those already fluid restricted to 130 mL/kg/day or less. In the single RCT available, addition of spironolactone to a thiazide regimen did not alter lung mechanics, oxygen requirement or electrolyte balance **(Hoffman, 2000).** Although thiazides sometimes are used in attempts to prevent or ameliorate nephrocalcinosis, evidence of efficacy of this strategy is lacking.

Furosemide

Furosemide, a potent loop diuretic, improves short term lung function by both its diuretic effect and a direct effect on transvascular fluid filtration. Furosemide, in periodic doses, should only be used in patients inadequately controlled by thiazides alone.

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.**

Oxygen

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-severe BPD supplemental oxygen is the primary tool 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 CLD who have not reached full retinal maturation, adjust FIO_2 to maintain SpO_2 in the 90-95% range. In term and older infants who have achieved retinal maturation (no active ROP) the American Heart Association/American Thoracic Society **(2015)** recommend supplemental oxygen to keep SpO_2 92-95% for most infants. Older infants with severe BPD or echocardiographic evidence of pulmonary hypertension require close attention to oxygen use and monitoring with daily review of stability of oxygenation. Such infants require collaboration with the Pulmonary and Cardiology Services in determining an appropriate SpO2 target.

Insidious hypoxemia is particularly common during feedings and sleep and additional oxygen supplements may be necessary during these periods. Periodic use of timed oxygen saturation recordings during both waking and sleep periods may be necessary to identify and quantitate daily hypoxia time. The need for supplemental O_2 often extends well beyond the period of positive pressure ventilator support. The impact of oxygen on 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. Overzelous attempts to wean supplemental O_2 may precipitate acute RV failure and even death.

Chronic Mechanical Ventilation

See section on Chronic Mechanical Ventilation in Chapter 2 – Cardiopulmonary Care.

Inhaled Medications

Use of inhaled bronchodilator and anti-inflammatory agents is a complex issue in management of BPD. Numerous studies have demonstrated increased resting airway resistance in older infants with classic BPD and have reported variable responses following administration of beta-2 agonists or inhaled steroids to ventilator-dependent infants. However, these studies report only short-term results. Evidence for long-term benefit is lacking and no evidence based guidelines currently exist for use of these agents in management of BPD. The only model for use of these agents currently available is that provided by the recommendations of the NIH Asthma Consensus Panel **(Expert Panel Report 3: Guidelines for Diagnosis and Management of Asthma. 2007-www.nhlbi.nih.gov.)** It is recognized that BPD is not asthma but episodic wheezing and signs of reactive airway disease increase in frequency in BPD patients after 1-3 months post-term. Metered dose inhaler (MDI) systems with valved spacers are the currently recommended method for delivery if inhaled medications are used.

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 CLD. **Bronchomalacia and airway collapse are being recognized with increasing frequency in infants with signs of airway obstruction or sudden onset of reduced air flow.** 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.**

Short Acting Beta-Adrenergic Agents

Denjean described a dose-response relationship for ventilator-dependent premature infants using an MDI to administer 1 or 2 puffs (0.09 or 0.1 mg) of albuterol via a commercial spacer device. Resting airway resistance was significantly reduced and lung compliance improved. However, this was a short term observational trial only performed upon babies 2 to 3 weeks of age with evolving BPD. A subsequent 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.** In chronic lung disease, SABA's such as albuterol or L-albuterol should be restricted to rescue therapy in select patients with objective evidence of reactive airway disease and a response to inhaled therapy and 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.

Inhaled Corticosteroids

Current evidence does not support the use of inhaled steroids to prevent BPD or as treatment of ventilated premature infants during the first 2 weeks of life. No benefits on survival, duration of oxygen use, or long-term outcome have been established **(Cochrane Reviews 2012).** However, use during acute episodes of airway obstruction in older ventilator dependent infants may be appropriate.

Use of Systemic Steroids in Management of Severe Chronic Lung Disease

Postnatal corticosteroids have been used in neonatal cardiopulmonary care for:

- Symptomatic management of refractory hypotension **(See Circulatory Disorders Section)**
- Early treatment to prevent BPD

- Treatment after 7 days of age to ameliorate the evolving lung injury sequence and facilitate extubation.
- Treatment of severe respiratory failure requiring very high ventilator and oxygen support.

Despite numerous RCT's and systematic reviews, serious concern and controversy remain regarding use of corticosteroids to prevent or treat BPD. Postnatal dexamethasone use is associated with **short term** improvement in pulmonary function and reduced risk of BPD or death at 36 weeks PMA - but increased risk of neurodevelopmental impairment. Hydrocortisone appears to have lower risk of adverse neurologic outcome but pulmonary benefits of treatment after the first week of life have not been demonstrated in studies to date. Prophylactic hydrocortisone, initiated at birth, was associated with improved survival without BPD in one recent RCT **(Baud 2016).** However, meta-analysis of eight previous trials failed to demonstrate an overall benefit on pulmonary outcome **(Doyle 2010)**.

The most recent AAP Policy Statement regarding postnatal use of systemic steroids (**Pediatrics 2010; 126:800-808 (Reaffirmed 2014)**. concluded:

- Significant risk is associated with the use of high dose dexamethasone (0.5 mg/kg/day) and use of this therapy is not recommended for prevention or treatment of BPD.
- Low dose dexamethasone (<0.2 mg/kg/day) may facilitate extubation and may decrease short and long term adverse effects associated with high dose dexamethasone. Current data are insufficient to allow specific recommendations.
- Low dose hydrocortisone (1 mg/kg/day), given from birth, may increase survival without BPD without adversely affecting neurodevelopmental outcome, particularly for infants delivered in association with chorioamnionitis. However, there is increased risk of intestinal perforation in association with indomethacin use. Data are insufficient at present to recommend routine use for all infants at risk for BPD.
- Higher dose hydrocortisone (3-6 mg/kg/day) given after the first week of life has not been shown to improve rates of survival without BPD in any RCT. Existing data are insufficient to make a recommendation regarding treatment with high dose hydrocortisone,

A Canadian Pediatric Society Position Statement **(Reaffirmed January 2015)** concluded:

- Use of postnatal corticosteroids within the first seven days of life to prevent BPD is not recommended.
- High dose dexamethasone (0.5-0.2 mg/kg/day) to prevent or treat BPD is not recommended.
- Routine use of low dose dexamethasone for all infants requiring assisted ventilation after 7 days of life is not recommended.
- Hydrocortisone is not recommended for treatment of CLD.

However, both organizations acknowledge that select groups of infants may exist in which the benefits of a short course of corticosteroid therapy to mitigate BPD may outweigh risks. A complex meta-regression analysis of 20 RCT's **(Pediatrics 2005; 115:655, J Pediatr 2014; 165:1258)** reported that postnatal corticosteroid treatment of infants with BPD risk > 65% resulted in reduction in occurrence of death or CP compared to controls. Most studies involved use of dexamethasone.

Infants 23-24 weeks gestation that remain on mechanical ventilation > 14 days with an oxygen requirement > 30% are at very high risk for BPD. The clinician might choose, with parental agreement, to administer a short course of corticosteroid therapy under these circumstances.

If a decision is made to initiate corticosteroid therapy, we recommend low dose dexamethasone given twice daily according to the following tapering schedule:

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/day
(Canadian Pediatric Society 2015 and DART Study 2006).

We do not recommend routine use of corticosteroid therapy for infants > 25 weeks gestation.

Corticosteroid Treatment Beyond the Newborn Period. 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.

Exacerbation of Acute Lung Inflammation

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. In this circumstance, recommendations of the NIH Expert Panel III for treatment of acute exacerbations of asthma in young infants should be followed.

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 tracheo-bronchomalacia. 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.

Monitoring the BPD Patient

Comprehensive cardiopulmonary monitoring is necessary to achieve ad equate growth and avoid progressive cor pulmonale. Periodic assessment of neurodevelopmental status is included in this process.

Nutritional Monitoring

Patients should be weighed every 3-7 days; measure length and head circumference weekly. Serum urea nitrogen, calcium, phosphorus, and alkaline phosphatase values should be determined periodically. Nutritional and growth parameters should be reviewed frequently with a pediatric nutritionist.

Oxygen Monitoring

Long-term maintenance of adequate oxygenation is essential to reduce risk of cor pulmonale. Use continuous pulse oximetry and attempt to maintain SpO_2 92- 95% in term and older infants with retinal maturity **(American Thoracic Society 2015).** However, each infant requires individual evaluation of multiple factors in determining optimal oxygen saturation targets. Maintain SpO_2 90-95% in preterm infants who have not achieved retinal maturity or those with active ROP. Periodically obtain arterial blood gas samples or timed recoding of SpO_2 trends. Give particular attention to adequacy of oxygenation during sleep and feeding.

Echocardiograms

The presence of moderate to severe pulmonary hypertension in BPD patients has been associated with significant mortality risk. Several studies have described the role of echocardiography in screening for pulmonary hypertension and assessing response of the pulmonary vascular bed to oxygen. Preterm infants with BPD who meet the following criteria at 36weeks PMA should have a screening echocardiogram:

1. Still requiring mechanical ventilation or CPAP.
2. Still requiring supplemental oxygen > 30% or > 1/4 LPM to keep SpO_2 > 92%.
3. PCO_2 value of 60 mm Hg or greater with or without oxygen requirement.

Specific echocardiographic measurements should include Doppler flow velocity of tricuspid valve regurgitation with Bernoulli calculation of RV systolic pressure and simultaneous measurement of systemic BP (systolic/diastolic). Position and motion of the intraventricular septum should also be reported. If RV/SYST pressure ratio is > 0.5 the case should be discussed with the medical Director or a BPD physician. Pulmonary and/or Cardiology consultation may be appropriate. Findings suggesting a persistent RV/SYST ratio > 0.5 are associated with increased mortality risk. Such patients should be monitored with a repeat echo study monthly as a minimum.

Any approach to treatment of chronic pulmonary hypertension begins with optimizing oxygenation. Treatment plans should be formulated in conjunction with a Neonatology Section BPD physician and the Pulmonary Hypertension Team. Evidence of efficacy of pulmonary vasodilators such as iNO or sildenafil in BPD is limited but use is increasing. Use of such agents is considered in face of persisting evidence of significant pulmonary hypertension (by echocardiogram or cardiac catheterization) in conjunction with a Neonatology Section BPD physician and Pulmonology Service recommendation. Pulmonary Service and/or Pulmonary Hypertension Team consultation should be obtained. A role for brain naturetic peptide BNP determinations in BPD has not been established, but monitoring trends in these values may be of value in some patients.

Developmental Screening

Perform hearing screening before 6 months (or by 34-3 6 weeks PMA if no longer on mechanical ventilation) of age to allow early intervention by an audiologist, if needed. 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.

Goal-directed Multidisciplinary Care

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.

Use of multidisciplinary team care has been associated with improvement in neurodevelopmental outcome and reduction in need for hospital re-admission post NICU discharge **(Shepherd 2011).**

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. Parents and care providers must work together to plan a friendly, play-oriented environment that includes the infant's own toys and possessions. 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.

Discharge Planning

This encompasses the transition from mechanical ventilation to the home environment. In some cases, it involves preparation for home care requiring mechanical ventilation. Although the lungs have improved, both structure and function remain quite abnormal. Even in infants no longer requiring ventilator support, additional months of lung growth will be required to overcome the remaining derangements of mechanics. The pediatric pulmonologist plays a central role in coordinating post discharge care and must be closely involved in discharge planning. Close monitoring of adequacy of oxygenation is essential to prevent subtle increases in PVR leading to insidious

development of cor pulmonale. Influenza vaccine is particularly important for these patients. After discharge, palivizumab prophylaxis against RSV infection also is recommended for infants with BPD who are younger than 2 years of age and have required medical therapy for CLD within 6 months of the anticipated season for RSV. Nutrition follow-up is essential.

Prevention of Chronic Lung Disease

Several strategies have been shown to reduce the incidence or severity of BPD.

Early nasal CPAP – Two meta-analyses have demonstrated a reduction in death or BPD associated with early application of NCPAP in combination with **selective** administration of surfactant. However, this strategy has a high failure rate in babies 23-25 weeks gestation. A failed trial of early CPAP should not preclude ongoing attempts to wean an infant from the ventilator. It is recommended that excess fluid administration be avoided and attempts be made to maintain infants who are receiving mechanical ventilation with even or slightly negative water balance during their early course.

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.

Vitamin A - Meta-analysis of 9 RCT's demonstrated a modest reduction in incidence of BPD associated with intramuscular administration of vitamin A 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.

Volume Targeted Ventilation - A Recent Cochrane meta-analysis of 12 RCT's reported significant reductions in death or BPD associated with strategies of volume targeted ventilation (VTV). We recommended VTV in the form of Volume Guarantee (VG) for initial ventilation of acute neonatal lung diseases.

Tracheostomy for Prolonged Mechanical Ventilation

The role of tracheostomy and impact of this procedure on outcome of young infants with prolonged ventilator dependency remain unclear. Limited data available comes from case series and retrospective reviews. The following guidelines primarily relate to infants requiring prolonged mechanical ventilation. Infants with upper airway anomalies, airway obstruction and disorders producing central hypoventilation must be individualized and may require consideration for tracheostomy early in the clinical course.

Prolonged Ventilator Dependency

Preterm infants still requiring mechanical ventilation by 2-3 months of age have significantly increased mortality risk **(Wheater, Abman).** ELBW infants still requiring ≥ 25% oxygen or greater support at 14 days of age have a 52-69% risk of CLD **(ELGAN study, 2011).** A recent retrospective analysis reported that among infants with Respiratory Severity Score (MAP X FiO2) ≥ 6 at one month of age, 81% still required mechanical ventilation or CPAP at 36 weeks PMA **(Malkar, in press 2014).** Thus the need for prolonged ventilation can be anticipated most infants and a comprehensive care plan initiated.

Infants still requiring mechanical ventilation at one month postnatal age should be evaluated with a Respiratory Severity Score. RRS ≥6 is associated with increased mortality risk and duration of MV. Infants still ventilator dependent at 6-8 weeks postnatal age are considered to have "prolonged ventilator dependency". They should be directed into a defined and consistent program of respiratory, nutritional and developmentally supportive care to include specific periodic monitoring parameters. An algorithm for this process and its benefits on outcome has been reported **(Shepherd 2011).** Once the patient is assimilated into this comprehensive care environment, family members should receive a detailed discussion regarding the care of chronically ventilator dependent infants. By 3 months of age, the care team should consider tracheostomy and discuss the potential role of this procedure with parents. Some infants may clearly be candidates, while others may be showing evidence of improvement and warrant further observation. In patients remaining intubated beyond 3 months, the clinical course should be reviewed every 2-3weeks regarding progress toward extubation versus likely benefits of tracheostomy.

Nutritional Care

Each infant should be evaluated and monitored by the Neonatal Nutrition Team and have a specific, individualized plan for feeding and monitoring of growth status

Developmental Care and a Supportive Physical Environment

Infants with prolonged ventilator dependency (with or without tracheostomy) should be managed by a comprehensive team in a supportive care environment. The core care team includes neonatologists, pulmonologists, nurses, NNP's and respiratory therapists, Specialty resources include OT/PT, Child Life, Speech Therapy, a Social Worker, a Pharmacy specialist and a case manager. Consultation with Cardiology and ENT should be obtained as needed, Infants with pulmonary hypertension should be followed by the Pulmonary Hypertension team. All infants requiring prolonged ventilation should be evaluated periodically by a Speech Therapist and Developmental Pediatrics specialist.

Using these multi-disciplinary resources, a specific developmental care plan should be implemented for each infant. Each infant should have an initial evaluation in a sound developmentally appropriate care program that include the following major components:

Major components of a sound developmental care program include:

- Physical area able to control light and noise
- Promotion of normal sleep-wake cycles
- Encouragement to play and explore
- Minimal use of sedation and physical restraints
- Individualized OT/play therapy program for each patient
- Individualized, consistent physical therapy program for each patient

- Individualized developmental intervention should be performed 3-5 times per week to include tactile, positional, visual and auditory stimuli.

Developmental Care for NICU Patients Requiring Tracheostomy

"Infants with chronic illness or dependency on technology often remain hospitalized for prolonged periods of time. Due to their illness or fragility, these infants may not have the opportunity for typical experiences that enhance developmental progress and functional organization of the CNS. Intervention should begin as soon as possible to foster optimal outcomes for NICU graduates. Ongoing assessment, support, and guided intervention is based upon each infant's observed thresholds, sensitivities, competencies and tolerance." **(National Association of Neonatal Nurses, 2012)**

1. **Environmental considerations: Light, Sound, Space.**
   a. Encourage sleep/wake patterns appropriate for corrected gestational age.
   b. Adequate space should be provided for infants, families, and ancillary staff for age-appropriate activity, including purposeful play and feeding of solid foods when appropriate.
   c. "Creative" staffing solutions may be required to provide adequate nursing care.
2. **Bonding/attachment considerations: Promote care-by-parent as the rule rather than the exception.**
   a. Recognize that the development of the maternal-infant dyad has long-lasting implications for relationship between mother and child, and thus post-discharge care and quality of home life.
   b. Seek parental input on infant status and collaborate to design plan of care on a daily basis.
   c. Provide positive reinforcement of maternal behaviors that demonstrate bonding/attachment.
   d. Educate parents about infant cues and developmentally appropriate activities for corrected gestational age, and encourage meaningful ways to contribute to care.
3. **Developmental Considerations: Assessment-Driven and Interdisciplinary Care and Follow-up.**
   a. Timely and ongoing developmental assessment should drive care interventions.

Role of Feeding Gastrostomy

The potential role of a feeding gastrostomy should be evaluated and discussed in parallel with consideration for tracheostomy. Many factors are involved in this decision and it should be individualized for each patient. Consultation with ENT and Pediatric Surgery colleagues is advised in determining suitable candidates for feeding gastrostomy.

Short Term Post Tracheostomy Care

The first tracheostomy change will typically occur on postop day 5. Until that time, infants should receive adequate analgesic/sedative to prevent agitation related to pain/discomfort. Routine post-op neuromuscular blockade is not required but may be necessary in occasional special circumstances.

General References

1. Clinical Consensus Statement: Tracheostomy Care. *Otolaryngology – Head and Neck Surgery* 2013; 138(1); 6-20.
2. Care of the child with a chronic tracheostomy. The official statement of the American Thoracic Society. *Am. J. Respir Crit Care Med* 2000; 161(1); 297-308.

Selection and Preparation of Patients for Home Ventilation

A decision to undertake home ventilation requires careful patient selection, frank discussions with family members and a firm commitment by them to this complex home care. Only a small proportion of infants requiring chronic ventilation are suitable candidates. If home ventilation appears appropriate and is the desire of the family, consult the Discharge Planning Coordinator to begin investigation of available home care services. As planning develops the care team will be asked to order specific equipment and supplies for home care needs.

- Consult a Pediatric Pulmonologist to determine **(a)** can they accept the role of home ventilator care in the patient **(b)** what specific ventilator support modes and monitoring do they anticipate will be used at home and **(c)** what additional testing do they require in preparing for home care.
- The Nurse Manager responsible for the patient's NICU care team. The Nurse Manager, in conjunction with a tracheostomy care educator, will be responsible for assuring completion of parent teaching and documentation in the medical record.

Criteria for DC to Home Ventilation

- Parent commitment and completion of all aspects of training for the prescribed care at home by family caretakers. The AAP recommends training at least two family caregivers and assessment of their ability prior to discharge. Acquisition of parent skills should be documented in the nursing discharge teaching records.
- Stable recent respiratory course with $FiO_2 < 40\%$. Discharge of a patient with persistent PCO_2 values of 70 mm Hg or greater would be feasible only in face of normal pH, otherwise stable course and close collaboration with Pulmonary Service.
- Tracheostomy in place and mature. At present non-invasive modes of support (BIPAP, NCPAP, and Mask CPAP) are not used in our program for BPD home care. When tracheostomy is considered for long term ventilator care, the potential role of a feeding gastrostomy should be discussed.
- Minimal weight for home ventilation is usually > 2500 g. Specifications for the LTV 1150 home ventilator recommend weight 5 kg or 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.
- Stable respiratory course maintained for several days following switch to pediatric circuit and home ventilator.
- Evaluation of family circumstances by Social Services Department.

- Evaluation of physical adequacy of home setting by the home care company (lighting, power supply, access to emergency hospital facilities, etc.) The physician should work with Social Services and the Discharge Coordinator to make formal request to the electric power provider company to place patient on a priority list for assistance in case of prolonged outage.
- One family member should be completely trained in all aspects of home ventilator care. A second family member should be trained in infant CPR, recognition of airway emergencies and replacement of tracheostomy tube.

Migration to Home Ventilator

Most patients initially will receive SIMV/PSV at home but this will vary depending upon status. Some patients may be moved to volume control ventilation on their conventional ventilator and average expired tidal volume recorded for several days. In older infants, an expired CO_2 monitor may be useful also during switch to home ventilator. If patient is stable 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 **(see section below).**

Current home ventilators are approved for weight 5 kg or above and minimal TV of 50 ml. Some infants otherwise ready for home ventilator care may be too small for the minimal TV limit of 50 ml and must remain on pressure controlled SIMV/PSV or SIMV only.

Monitoring and Equipment for Home Ventilation

- Pulse oximeter
- Suction machine and supplies (including replacement tracheostomy tubes)
- Portable O_2 tank
- Tracheostomy care supplies
- O_2 concentrator
- Mask/bag

Special Issues

- 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, however, a period of 1-2 hours without humidification is acceptable.
- Use of speaking valves in home ventilation/tracheostomy patients may be introduced for short periods prior to discharge. However, some patients may not yet tolerate these (especially those with significant bronchomalacia on PEEP > 8cm H_2O.

An Approach to the Management of Ambiguous Genitalia

Definition

Infants whose genitalia cannot be clearly demarcated into the male or female phenotype are considered to have disorders of sexual differentiation (DSD). In these disorders, anatomical sex and hormonal sex may be discordant with the sex chromosomes. DSDs occur in approximately 1 in 4,500 live births.

Minor degrees of male undervirilization and female virilization are more common, occurring in approximately 2% of live births. The genitalia are considered ambiguous if any of the following abnormalities are present:

- micropenis with bilateral non-palpable testes,
- hypospadias with unilateral non-palpable testis,
- penoscrotal or perineoscrotal hypospadias with undescended testes,
- apparent female genitalia with an inguinal or labial mass, discrepancy between antenatal karyotype and postnatal phenotype.

Multidisciplinary Team Management of Disorders of Sexual Differentiation

When an infant is recognized at birth to have a DSD, it is of critical importance **NOT** to assign sex. The experience of parents argues that being told one sex, only to have the sex assignment changed a few days later to the other sex, is more difficult than having to wait. The clinician should say, 'Baby Smith,' while the infant undergoes a comprehensive multidisciplinary evaluation.

The Gender Medicine Team at Texas Children's Hospital is composed of pediatric endocrinologists, geneticists, pediatric urologists, pediatric gynecologists, neonatologists, child psychiatrists, and ethicists. This multidisciplinary team defines the appropriate studies, gathers the data, and makes a recommendation to the parents concerning gender (sex) assignment. Gender identity is complex, and the multidisciplinary team may recommend that the parents delay sex assignment until the results of the investigations are available. Under these circumstances, irreversible surgical intervention should also be delayed. When the results are available (usually 14–21 days), the team explains to the family the discordance between the different components of sex assignment: chromosomes, anatomical sex, and hormonal sex. Assignment of sex is decided with the parents' participation.

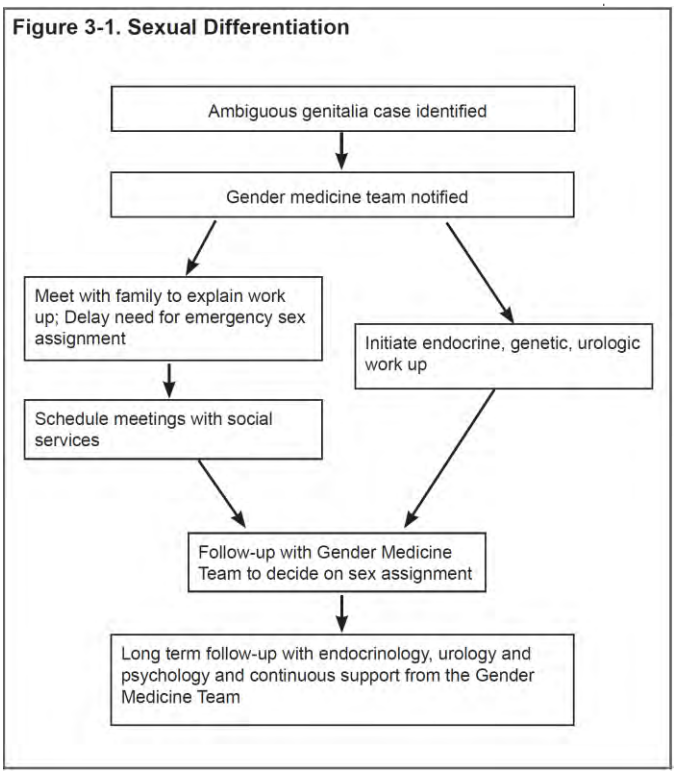
Evaluation of a Baby with Ambiguous Genitalia

History

Maternal

- Drug history (virilizing drugs, e.g., progestins, finasteride, or phenytoin), or
- Maternal virilization (androgen-secreting tumors in the adrenals or the ovary).

Figure 3-1. Sexual Differentiation



Familial

- Consanguinity of the parents
- Genital ambiguity in siblings or in the family
- Neonatal deaths
- History of infertility or amenorrhea

Physical Examination

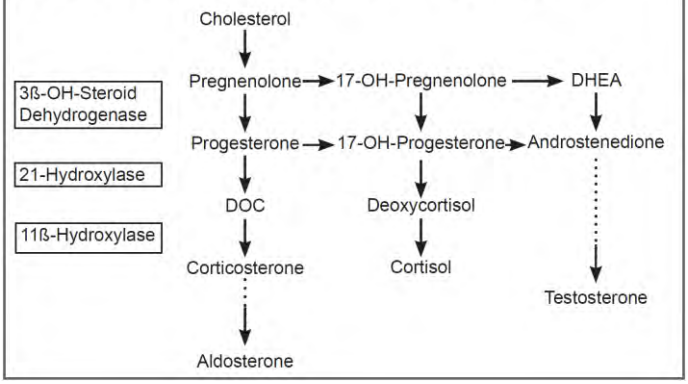
General Examination

1. Dysmorphic features suggest genetic syndromes (e.g., Smith-Lemli Opitz syndrome, Denys-Drash syndrome)
2. Midline defects suggest hypothalamic-pituitary causes for hypogonadism.
3. 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.
4. Hyperbilirubinemia may be secondary to concomitant thyroid or cortisol deficiency.

External Genitalia

- Assess the development of the genital tubercle (which forms the penis in the male and the clitoris in the female) and the genital folds (which form the scrotum in the male and the labia in the female).
- Carefully examine for hypospadias and cryptorchidism (unilateral or bilateral), true clitoral hypertrophy, or a mass in the inguinal canal in a newborn with a female phenotype.

Figure 3–2. Pathways of adrenal hormone synthesis



- Assess penile length. The normal male newborn's stretched phallic length from the pubic tubercle to the tip of the penis is 3 cm. Penile length <2.5 cm is considered a micropenis. A mean penile length with associated 95% confidence intervals is described for infants between 24 and 36 weeks inclusive. The relationship between penile length (PL in cm) and gestational age (GA, weeks) was: PL=2.27+0.16 GA. (See suggested reading.)
- Determine presence of chordee, hypospadias, and the position of the urethral meatus.
- Assess clitoral size. Clitoromegaly is present if clitoris >1 cm.
- Note the degree of labioscrotal fusion and its rugosity and the presence or absence of a separate vaginal opening.
- Examine for hyperpigmentation of the genital skin and the nipples; this may indicate excessive ACTH and pro-opiomelanocortin in some cases of CAH. Do not confuse normal genitalia in the pre- term infant (usually <34 weeks' gestation), which may consist of prominent clitoris and labia minora in girls and undescended testes in boys.
- Note palpable gonads in the inguinal region. This may be an important diagnostic criterion to differentiate undervirilized males from overvirilized females.

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.

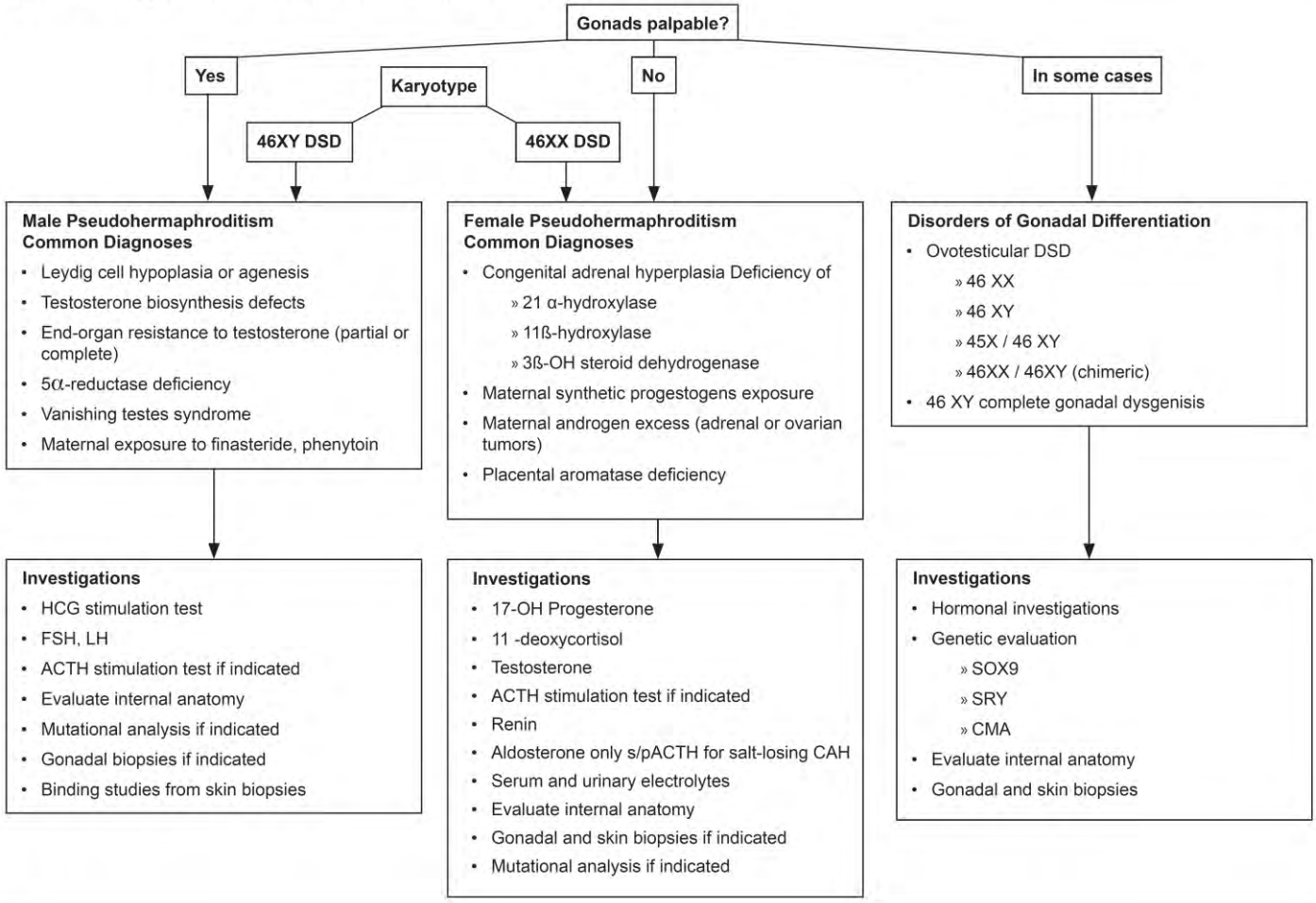
Stage II - a narrow vestibule at the end of which the vagina and the urethra open.

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.

Figure 3–3. Approach to disorders of sexual differentiation



Investigations

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.

Internal Genitalia

Pelvic ultrasound exam should be ordered to assess anatomy of the vagina, urogenital sinus, uterus, and to exclude renal anomalies, and visualize adrenal glands or inguinal gonads.

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

- Human chorionic gonadotropin (HCG) stimulation test is used to determine the function of Leydig cells to evaluate testosterone biosynthesis defects and the presence of testicular tissue.
- Anti-mullerian hormone (AMH) and inhibin levels are used to evaluate Sertoli cell function.
- Raised basal levels of gonadotrophins (FSH and LH) are consistent with primary gonadal failure.
- CAH tests: serum 17-OH progesterone is useful to diagnose 21-OH hydroxylase deficiency (responsible for 90% of CAH). If the levels are non-diagnostic, perform an ACTH stimulation test. This will accentuate the block in the metabolic pathway and is necessary to diagnose non-classical CAH.
- DNA analysis and evaluation of 5α-reductase activity could reveal the mutation. Androgen Receptor (AR) gene mutations are seen in cases of androgen insensitivity. Mutations in SRY, NR5A1, DHH, and NROB1 can be seen in gonadal dysgenesis. Gonadal tissue biopsy may be necessary for the diagnosis of gonadal dysgenesis.

Investigations Should Be in Order of Priority

Electrolytes, Glucose, 17 OHP, D4 Androstenedione, DHEA, Testosterone, 11 deoxycortisol, Testosterone, Dihydrotestestosterone, karyotype, LH/ FSH, Pelvic ultrasound. However, phenotype and clinical presentation should guide the lab priorities.

*250 mcg ACTH stimulation test: necessary for evaluation of CAH, 125 mcg if the body weight of the neonate <3 kg.

The Role of the Parent

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.

Table 3–1. Thyroxine values according to gestational age

Gestational Age (wks)	No. Infants	Thyroxine mcgdL	Hypothyroxinemia Mild No. (%)	Mild Thyroxine mcg/dL	Severe No. (%)	Severe Thyroxine mcg/dL
<24	11	6.5 ± 3.8	5 (45)	6.7 ± 1.7	3 (27)	2.0 ± 1.5
25	18	7.1 ± 3.8	8 (44)	7.3 ± 1.4	8 (44)	4.8 ± 1.8
26	27	7 ± 3.5	15 (56)	5.6 ± 1.2	5 (19)	4.3 ± 1.9
27	32	7.1 ± 3	12 (38)	7.5 ± 1.5	13 (41)	4.4 ± 1.4
28	45	7.2 ± 2.4	26 (58)	7.7 ± 1.8	12 (27)	4.5 ± 1.2
29	57	7.1 ± 3.2	33 (58)	6.8 ± 2.4	13 (23)	4.4 ± 1.9
30	76	8.1 ± 3.9	38 (50)	6.6 ± 1.9	12 (16)	4.2 ± 1.4
31	99	8.7 ± 3.4	60 (61)	7.3 ± 1.9	6 (6)	4.5 ± 0.7
32	94	9.5 ± 3.8	45 (48)	7.4 ± 1.8	7 (7)	5.0 ± 2.0
33	77	10.1 ± 3.6	32 (42)	7.4 ± 1.7	3 (4)	5.2 ± 3.3
Total	536	8.4 ± 3.5	274 (51)	7.1 ± 1.9	82 (15)	4.4 ± 1.7

Plus-minus (±) values are means +SD. Mild hypothyroxinemia was defined as a standard thyroxine concentration 1.3–2.6 SD below the mean, and severe hypothyroxinemia as a standardized thyroxine concentration >2.6 SD below the mean. To convert thyroxine values to nanomoles per liter, multiply by 12.9.

Adapted with permission from: Reuss ML, Paneth N. Pinto-Martin JA, et al. The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. *N Engl J Med* 1 996;334(1 3):821–827. Copyright © 1996 Massachusetts Medical Society. All rights reserved.

Table 3–2. Thyroxine and thyrotropin levels according to gestational age

Age Groups	Age weeks	Free T4 pmol/L	Free T4 (ng/dL)	Thyrotropin mU/L
Premature	25–27	7.7–28.3	(0.6–2.2)	0.2–30.3
	28–30	7.7–43.8	(0.6–3.4)	0.2–20.6
	31–33	12.9–48.9	(1.0–3.8)	0.7–27.9
	34–36	15.4–56.6	(11.2–4.4)	1.2–21.6
Combined premature	25–30	6.4–42.5	(0.5–3.3)	
	31–36	16.7–60.5	(1.3–4.7)	
	25–36			0.5–29
Term	37–42	25.7–68.2	(2–5.3)	1–39

Adapted from J Pediatr 126(1), Adams LM, Emery JR, Clark SJ, et al. Reference ranges for newer thyroid function tests in premature infants, p.122–127. Copyright © 1995, with permission from Elsevier.

Suggested Reading

1. Murphy C, Allen L, Jamieson M. Ambiguous genitalia in the new- born: An overview and teaching tool. *J Pediatr Adolesc Gynecol.* 2011 Oct;24(5):236-50
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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 (NB S) 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, then obtain an endocrinology consultation after ordering 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).

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 analysis does not support the treatment of transient hypothyroxinemia of prematurity to reduce neonatal mortality, improve neurodevelopmental outcome, or to reduce the severity of respiratory distress syndrome. The power of the meta-analysis used in the Cochrane review to detect clinically important differences in neonatal outcomes is limited by the small number of infants included in trials. Future trials are warranted and should be of sufficient size to detect clinically important differences in neurodevelopmental outcomes.

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.

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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 have the needed effect of inducing 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 actions, 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 which lasted >2 weeks. If the evaluation demonstrates 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 and check cortisol level 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 (see above) the following treatment should be provided during a surgical procedure or when experiencing significant clinical Illness e.g., NEC, sepsis. Treat with "stress dose" of hydrocortisone 30–50 mg/m2 per day for mild to moderate illness in infants suspected or proven to have adrenal insufficiency or suppression. May use 50–100 mg/m2 per day for severe stress. Once infant has stabilized, start to wean hydrocortisone dose immediately towards physiologic replacement doses (8–10 mg/m2 per day) with the goal of tapering off steroids over the course of 5–10 days or faster if there are no blood pressure issues.

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Hypoglycemia

Neonatal hypoglycemia is common and appropriate management remains a subject of controversy. However, recent evidence has clarified important physiologic and prognostic differences between transient neonatal hypoglycemia occurring during the first 24-48 hours of life and hypoglycemia persisting beyond that time period or presenting later.

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

Although point of care testing (POCT) devices are convenient for glucose screening, their accuracy is limited in the hypoglycemia range. It is essential to confirm low plasma glucose (PG) values with a clinical laboratory determination. However, if a POCT value is low, appropriate intervention should not be delayed while awaiting confirmatory lab tests. Whole blood glucose values are~15% lower than PG values.

Transitional Neonatal Hypoglycemia (≤48 hours of life)

Fetal plasma glucose (PG) values are similar to those of the mother (about 10 mg/dL less at term). Fetal insulin is responsive to fetal glucose concentrations but fetal glucose values primarily are 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 2 days. Following birth, mean PG 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 impairment of the metabolic transition from intrauterine to extrauterine life. Transitional neonatal hypoglycemia typically resolves by 48 hours.

Infants at high risk for this include:

- Infants of diabetic mothers
- LGA infants
- Infants with fetal growth restriction (SGA infants)

- Preterm infants <34 weeks GA, especially those requiring NICU care.
- Other neonates with unstable cardiopulmonary function, infection or neurologic injury

Approximately 50% of infants in these risk groups exhibit at least 1 PG 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 **(Harris 2012, McKinlay 2015)**. Most symptomatic neonates have PG values <25 mg/dL, as do those with hyperinsulinism or genetic hypoglycemic disorders **(AAP, Pediatrics 2011; 127: 575). Importantly, symptoms of hypoglycemia are non-specific and can occur with other neonatal conditions.**

Recent evidence **(Stanley, J Pediatr 2015; 166: 1520) (Pediatric Endocrine Society, J Pediatr 2015; 167: 238)** suggests that Transitional Neonatal Hypoglycemia 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. Although the majority of infants with transient neonatal hypoglycemia remain asymptomatic, plasma glucose values fall to quite low levels in some.

Management of TNH

Evidence linking hypoglycemia and adverse neurologic outcome has been conflicting **(Lucas 1988, Tin 2012, Kaiser 2015, Harris 2015**). Although some studies have suggested that even asymptomatic hypoglycemia may contribute to developmental delay and poor academic achievement, current evidence does not identify a specific plasma glucose value or threshold below which cerebral injury will occur. Treatment studies have also reported conflicting outcomes **(Harris 2015, McKinley 2015).**

Glucose screening. Babies in the high risk categories noted above should receive glucose screening between 30 minutes to 2 hours of life. Some may require continued monitoring during the first 24 to 48 hours. Several clinical scenarios occur among these high risk patients. Management strategy must be individualized and depends upon PG value, risk and clinical findings. Need for Intervention will usually involve one of the following clinical scenarios:

Symptomatic neonates. Symptomatic infants (seizures, lethargy, apnea, inability to orally feed or marked jitteriness) with a PG 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/minute **(AAP 2011).** 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.

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 PG tested 30 minutes after the feed. Frequent feeding should continue every 2-3 hours with PG monitoring prior to each feed **(AAP, 2011).** The initial treatment target is progressive rise in PG value to >45 mg/dL. Monitoring of PG values should continue for 12-24 hours. If PG values >45 mg/dL cannot be achieved with frequent feedings, supplementation with IV glucose will be necessary. When PG values are stable >60 mg/dL transition to normal feedings alone can be attempted.

At risk neonates who are NPO and asymptomatic. Perinatal conditions requiring NICU care place infants at risk for hypoglycemia and delay 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 infusion providing 5.5-7 mg glucose/kg/min and have PG checked at 30-60 minutes of life. Babies <25 weeks gestation should be started at a GIR of 4.5-6 mg/kg/min. This GIR is effective in preventing hypoglycemia in most high-risk patients. However if PG > 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%.

Subsequent Management

Transitional Neonatal Hypoglycemia should resolve by 48 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 PG values during several feed-fast cycles on a routine diet. **(AAP, 2010).** This is particularly important if the infant required intervention with IV glucose or exhibited symptoms. Those with symptoms, very low values or need for high levels of IV glucose supplementation are suspect for a persistent disorder of glucose metabolism. They 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.

Glucose Calculations

Glucose Infusion Rate (GIR) = mg Glucose/kg/minute

Multiply concentration of glucose by volume (e.g., $D_{12.5}W$ at 130 ml/kg/day is 12.5 × 130/100 = 16 g/kg/day).

To compute mg/kg/min, divide g/kg/day by 1.44 (1.44 = 1440 minutes/day divided by 1000 mg glucose).

[1 mg glucose /kg/min = 1.44 grams glucose/kg/day (1 mg glucose/kg x 1440 minutes/day ÷ 1000 mg = g/kg/day)]

Calculation of Dextrose Order (g/100 mL) based on GIR and fluid goals (mL/kg per day)

GIR Goal (mg/kg per min) x 1.44 g = glucose g/kg/ per day ÷ fluid goals /kg = dextrose per mL x 100 = g/ 100 mL (Dextrose % order) (e.g. GIR goal of 8 mg /kg/ min in 90 mL/kg per day 8 mg/kg per min x 1.44 = 11.5 g/kg/day ÷ 90 x 100 = 12.8 g/100 mL (12.8 %)

Persistent Hypoglycemia

Persistent hypoglycemiis defined as the need for glucose supplementation beyond 48-72 hours of life to maintain blood glucose values > 60 mg/dL. A thorough diagnostic work up is essential because many entities producing persistent hypoglycemia impair mobilization of glucose or availability of alternate energy pathways, especially those providing fuel sources for cerebral metabolism. As a result, the entities discussed here are associated with high risk of severe symptomatic hypoglycemia with resulting brain injury. Disorders producing hyperinsulinism or impairment of fatty acid oxidation are particularly important. The diagnosis of hyperinsulinimic 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 about of hypoglycemia.

Lab tests should be obtained when the infant becomes hypoglycemic (plasma glucose < 45 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 to assist in prioritizing laboratory tests and managing titrations of glucose infusions.

Causes of persistent hypoglycemia are listed below along with the recommended laboratory tests to determine the etiology.

Causes of Persistent Hypoglycemia

Disorders of Insulin Secretion and Production

Persistent hyperinsulinemic hypoglycemia of infancy (congenital hyperinsulinism)

- Infants of diabetic mothers
- Erythroblastosis fetalis
- Beckwith-Wiedeman Syndrome

Endocrine Abnormalities

- Hypothalamic/ Pituitary dysfunction
- Central adrenal insufficiency
- GH deficiency
- A combination GH and adrenal insufficiency as part of panhypopituitarism
- 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
- Proprionic academia
- Methylmalonic academia

Inborn Errors of Glucose Production: Gluconeogenic Disorders

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

Evaluation of Persistent 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 acylcarnitine concentrations.

Suggested Laboratory Evaluation for Persistent Hypoglycemia

(Baylor Pediatric Endocrine Service)

Check blood sugar every 3 hours

When blood sugar < 60 mg/dL, check every 1 hour *

When blood sugar < 45 mg/dL, draw critical blood samples before treating hypoglycemia

- Plasma glucose level
- Plasma insulin level
- Free fatty acids
- Plasma cortisol and growth hormone
- Serum beta-hydroxybutyrate

After drawing critical blood samples, treat with glucagon 30 mcg/kg IV or IM and recheck blood glucose at 30 minutes and serum cortisol and growth hormone at 60 minutes. Start IV dextrose as appropriate to maintain blood sugar above 60 mg/dl. If patient unstable while hypoglycemic may bolus with 2 cc/kg of $D_{10}W$.

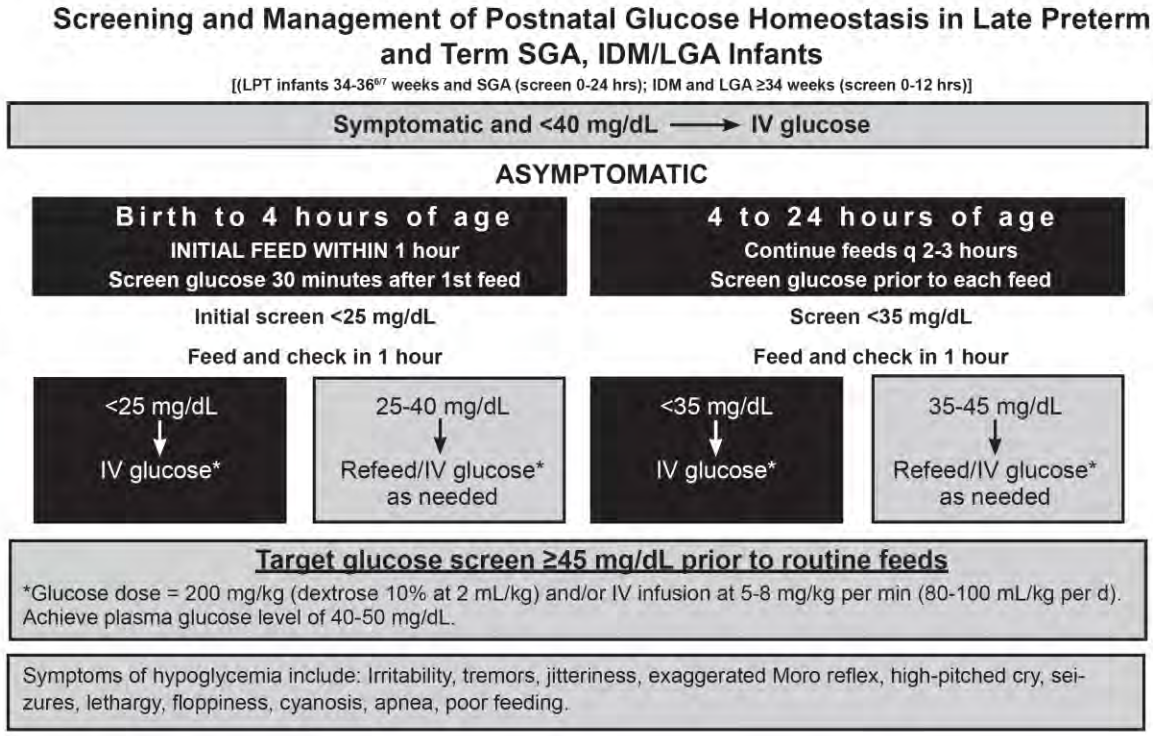
Other laboratory studies that may be necessary in identifying specific disorders include:

- C-peptide
- Acycarnitine profile Plasma amino acids
- Pyruvic acid **
- Serum ammonia and lactate
- Urine organic acids and ketones

* Run glucose levels in the lab STAT rather than by POC alone.

** Immediately after blood is drawn, add exactly 1 ml of whole blood to a chilled pyruvate collection tube (available from send out section of lab). Mix well and place on ice. Deliver to lab ASAP.

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 born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. LPT and SGA (screen 0-24 hours), IDM and LGA ≥ 34 Weeks (screen 0-12 hours). IV indicates intravenous.



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NICU Environment

The environment of NICU infants includes inanimate and animate sources of stimulation. The inanimate environment includes sound, lighting, bedding, temperature, odors, and airflow. The animate environment includes 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.

Effects of Environment

Manipulating the perinatal sensory experience of embryos and neonates 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 yet have an accumulated evidence base to support use in the NICU. Prevention of harm takes precedence over the developmental and environmental stimulation of a baby where the baby may be fragile or immature. Avoiding the under stimulation of a stable and more maturely functioning infant is encouraged. Seeking further guidance regarding an individual baby's developmental-behavioral needs and interventions, is advised.

The onset of function of sensory systems proceeds sequentially:

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

The first four systems become functional in the protected intrauterine environment, while the visual system is relatively unstimulated prenatally. The intrauterine environment buffers the fetus by reducing concurrent or multimodal stimulation; likewise, the NICU environment offers low stimulation to earlier developing systems such as the tactile, vestibular, gustatory, and olfactory systems. However, the type, timing, and amount of substantially increased unfiltered auditory and visual stimulation are dramatically different from what nature intended for a developing fetus.

Observation of each infant's physiologic and behavioral responses to the environment assists caregivers and parents in determining appropriate modifications and adaptations that support an infant's continued stability and smooth 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 the age of viability. Tactile sensation forms the basis for early communication and is a powerful emotional exchange between infants and parents.

Handling and positioning techniques are used to 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 by monitoring physiologic and behavioral signs, initiates the bond between infant and family and can be started early. Since all infants in the NICU are examined and undergo tests and procedures, balancing routine or aversive tactile stimulation with pleasurable or benign touch is essential. The type, timing, and amount of stimulation must be considered individually in relation to an infant's stability and medical condition.

Handling

The extent of handling can effect various 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. The impact of repositioning might be reduced by slowly turning an infant while its extremities are contained in a gently tucked, midline position.
- Blanket swaddling and hand containment. These decrease physiologic and behavioral distress during routine care procedures such as bathing, weighing, and heel lance. Immediately return 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. During KC, physiologic and behavioral parameters improve including:

- state organization,
- increased weight gain,
- decreased nosocomial infection rates,
- increased maternal milk volume,
- maintenance of skin temperature,
- less variability in heart rate and transcutaneous oxygen,
- decreased apnea, bradycardia, or both
- increased frequency and duration of sleep states,
- less crying, and
- lower activity levels.

Mothers who provide 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. At 6 months, KC infants are more socially engaging and score significantly higher on the Bayley Motor and Psychomotor developmental indices.

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, and
- 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 frequently are positioned toward the right. In time, muscle contractures and repetitive postures can lead to abnormal posture and movement. Therapeutic positioning is designed to promote neurobehavioral organization, musculoskeletal formation, and neuromotor functioning.

Containment

Infants who are unable to maintain a gently flexed position may benefit from containment using blanket or commercial boundaries strategically placed to achieve a tucked, flexed position. These gentle, flexible boundaries contain while allowing controlled movements that promote flexor–extensor balance without the disorganization or stress of uncontrolled movement due to neuromotor immaturity. 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.

Just as in the womb, a newborn's postnatal resting posture is biased toward 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, and
- secure 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 avert certain deformities.

Deformational plagiocephaly - is the abnormal molding of an infant's head shape due to external forces applied either pre- or postnatally.

Dolichocephaly - refers to the lateral flattening or narrow, elongated head shape of preterm infants that occurs over time due to their soft, thin skulls.

Brachycephaly - includes 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, and
- 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. Brachycephaly prevention is recommended by the American Academy of Pediatrics through the "tummy to play" program. Physical therapy, helmets, or both are common interventions for progressive head reshaping. Surgery usually is not 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.
- Occupational and physical therapists, especially in difficult cases, 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 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, and
- 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, fluctuating vital signs, agitation, crying, irregular respirations, decreased oxygen saturations, mottled skin, increased motor activity, and apnea, bradycardia or both. Such disruptions can interfere with an infant's clinical progress and stable behavioral functioning. It remains to be seen 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 known loud procedures.
- 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, and
  - » close incubator portholes quietly.
- Rouse infants gently with soft speech before 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's breast 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.

Conclusion

Application of an environmental intervention or modification requires an understanding of developmental principles and careful consideration of medical status, corrected age, current thresholds and sensitivities, emerging capabilities, risk of harm, and potential benefits. What works for one infant may not be appropriate for another. Assessment of infant response during and after any environmental modification is essential.

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Thermal Regulation

Large surface area and increased thermal conductance (poor insulation) accelerate heat loss in infants. 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 **(see 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%

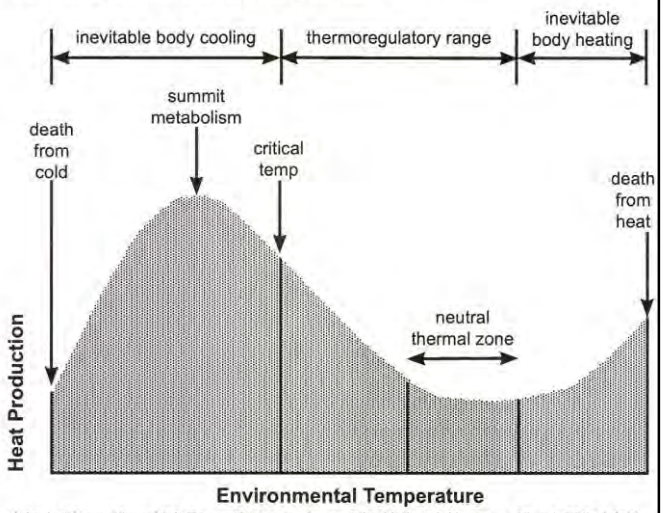
Responses to Cold Environment

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 **(see Figure 4-1)**. Hypoxia inhibits the metabolic response to cold.

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



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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.

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)**.

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 O2 consumption minimal)

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

Management

Delivery Room

Recommended DR air temperature:

- WHO – 25°C (77°F)
- NRP – 26°C (78°F)
- AAP/ACOG – 26º C (78º F)

Dry off amniotic fluid thoroughly. Perform resuscitation and stabilization under a radiant warmer. Minimize evaporative and radiant losses by covering infant or swaddling in a plastic bag or with plastic wrap blanket.

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 99.3 °F.

Selection of Appropriate Thermal Environment

- Place infant < 32 weeks and/or < 1250 grams in a pre-warmed convertible incubator (e.g. Giraffe Omnibed®). 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 (>85%) environment during the first 7 days of life.
- Place infants between 32 and 35 weeks and > 1250 grams in a pre-warmed standard incubator.
- Place infant's > 35 weeks and/or 1700 grams on a pre-warmed Radiant Warmer or Open Crib.

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.

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
	1200–1 500 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	32.6	31.6–33.6
	>2500 g[1]	32.1	30.7–33.5
36–48 h	<1200 g	34.0	34–35
	1200–1 500 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
	1200–1 500 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
	1200–1 500 g	33.5	33–34
	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

Adapted from: Klaus M, Fanaroff A, Martin RJ. The physical environment. In: Klaus MH, Fanaroff AA, eds. Care of the High-Risk Neonate. 2nd ed. Philadelphia, PA: WB Saunders Company; 1979:102–103. Used with permission.

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 (see below) 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 from 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 28.5^0 C by the skin temperature servo control mechanism.

Weaning from incubator Air Control to Open Crib

Weaning should begin when the following criteria have been met:

- Infant is $\geq$ 1500grams or $\geq$ 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 less than 28.5º C for at least 8 hours

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 (see above). Humidification of the environment obviates the need for a plastic wrap blanket.

Humidity - decreased transepidermal water loss and minimizes evaporative heat loss. Increased Humidity (> 85%) is recommended for all infant's < 29 weeks and/ or < 1250 grams for the first 7 days of life.

Weaning to Open Crib

Delay in weaning prematures 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 **(see above)** with incubator air temperature of approximately 28-28.5º C, infant may be placed in an open crib with frequent temperature monitoring initially.

The Hypothermic Infant

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. Controversy has long existed regarding rapid versus slow re-warming for hypothermic infants. Evidence does not suggest superiority of one over the other. The simplest approach is to place infant under a radiant warmer with servo control of anterior abdominal wall skin temperature and set point at 36.5º 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 VLBW infants.**

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 older preterm or full term infants. Mortality can be as high as 30% with a high rate of 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 has reduced 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 discoloration. Systemic manifestations are similar to those that indicate sepsis. Symptoms may progress to frank apnea and bradycardia followed by cardiovascular collapse.

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.

Diagnosis

The differential diagnosis includes ileus secondary to sepsis, isolated perforation, meconium peritonitis, Hirschsprung-associated enterocolitis, cow's milk protein intolerance, and malrotation with volvulus.

Treatment

For suspected or proven cases of NEC, enteral feeding is discontinued and total parenteral nutrition (TPN) is initiated. A Replogle tube, with low intermittent suction, is placed in the stomach.

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.

Antibiotics are begun empirically with either ampicillin or vancomycin, and gentamicin. Clindamycin is added if perforation or bowel necrosis is suspected.

Pediatric surgery is usually 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 staged resection and enterostomy, or
- Placing a percutaneous peritoneal drain.

Despite the potential interventions and optimal medical management, the mortality rate remains between 10% and 30%. At this time, there is insufficient evidence to recommend the use of prebiotics and/or probiotics in neonates for the prevention or treatment of NEC.

Complications that can occur after NEC include malabsorption, intestinal stricture formation, intestinal failure, and long term neuromorbidity.

References

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Intestinal Failure and Rehabilitation

Intestinal failure (previously described as short bowel syndrome) is a condition of malabsorption and malnutrition, following small bowel resection or congenital anatomical defect that requires prolonged total parenteral nutrition (TPN).

While no absolute number can be placed on the length of remaining bowel necessary for successful enteral nutrition, previous studies have shown that infants with less than 10% of their expected normal small bowel length for age have a nearly 80% chance of mortality. Currently however, 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.

Importance

The management of infants with intestinal failure is clinically challenging. Close monitoring is needed to ensure proper growth and nutrition, as well as, recognize and treat associated

complications. Although the survival of these patients has improved with the advent of TPN, there is still significant morbidity associated with this form of nutrition including prolonged hospitalization, line associated sepsis, and parenteral nutrition associated liver disease (PNALD). Thus, an important goal is to promote optimal 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, GI and surgical teams, is key to successful intestinal rehabilitation.

Goals

The primary goal is to identify patients at high risk for the development of intestinal failure and its complications in order to formulate a management plan early in the clinical course to maximize intestinal rehabilitation and provide liver protection from PNALD. These patients would include any neonate/infant who:

1. Has undergone small bowel resection of either more than 30% of the total small intestine or more than 50 cm of small intestine.
2. Has undergone a small bowel resection of any length and develops a conjugated hyperbilirubinemia ≥ 1.5 mg/dL.
3. Has not achieved full enteral feedings within 1 month of initiation of enteral nutrition regardless of the amount of bowel loss.
4. Has a history of abdominal wall defect or congenital intestinal atresia.

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 choice for these feedings because of the immunoglobulins and trophic factors it contains. If malabsorption and feeding intolerance persist, however, it is likely that an amino acid based formula (Neocate, Elecare, or Alfamino) may be necessary for some portion of the feedings, although many infants are best managed with primarily human milk feedings and TPN. Bottle or breast feedings, even in small volumes, should be considered if the infant is deemed ready to tolerate enteral feeds. This proactive approach to initiate oral feeding can dramatically reduce oral aversion and aid in the rehabilitation process.

Long-term Goals

Intestinal growth and adaptation is a slow and progressive process, and advances in enteral nutrition need to be undertaken with this in mind. In severe cases of intestinal failure, the goal of full enteral feeds might not be achieved during the course of hospital stay. Such infants will require home TPN until that goal is achieved. Frequent re-evaluation of progress in enteral nutrient intake, and careful watch for PNALD must be undertaken. Discharge planning should be initiated well in advance of planned discharge if home TPN is to be used. This includes cycling of TPN and initiation of post-discharge training.

Bacterial Overgrowth

Bacterial overgrowth is a common complication of intestinal failure. 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. One of the medical treatments of bacterial overgrowth is administration of enteral/oral Metronidazole (Flagyl) at 7.5 mg/kg/dose given twice daily for one week each month. Bacterial overgrowth prophylaxis or treatment is typically not administered in patients that are NPO. Initiation of bacterial overgrowth prophylaxis or treatment should be discussed with the Intestinal Rehabilitation Team.

Iron therapy

Since TPN is lacking in iron, infants who have been on TPN for more than 6 weeks are at increased risk for iron deficiency. Infants with limited absorptive capacity may require intravenous iron. If such an infant is on minimal feeds and is anticipated to require TPN for an additional 4 weeks, serum ferritin levels should be obtained. Since blood transfusions elevate serum ferritin levels, withhold obtaining ferritin levels for at least two weeks after a transfusion. Newer forms of parenteral iron are available that are safe for use. The nutrition team should be consulted to consider maintenance iron therapy in such infants.

Replacement Fluids for Losses- Combined Replogle and Ostomy Output

0.9% normal saline without any additives is the preferred replacement fluid for Replogle and ostomy losses. 0.45% NS, or 0.9% NS with dextrose or electrolyte additives are not recommended except in special circumstances [1]. If additional electrolyte supplementation is required, adjustments should be made to TPN 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 amount of output, the frequency and amount of replacing losses should be increased as below:

Table 5-1. Replacement Fluids for Losses

Combined Output	Replacement Fluids[2]	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[1]
>40 mL/kg/day	0.5 mL NS for 1 mL output over 4 hours	Every 4 hours	Daily electrolytes[1]

[1] If Sodium greater than 140 mmol/L, may consider the use of ½ 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.
[2] Replace the full volume of output at 0.5 mL NS to each 1 mL output.

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Cholestasis

Neonatal cholestasis is defined as an impairment in the formation or flow of bile and is important to diagnose in a timely manner. It can be caused by diseases that need prompt surgical intervention, such as biliary atresia, or diseases that need immediate medical intervention, such as metabolic diseases. 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" and "conjugated" tests. "Direct" tests are used at many hospitals (including Ben Taub General Hospital and most of the referring hospitals), whereas only "conjugated" tests are performed at TCH. "Direct" tests often are higher because they also measure the "delta" bilirubin fraction. As a result, "conjugated" tests results are preferred for management decisions. Conjugated hyperbilirubinemia in a neonate is defined as a serum conjugated bilirubin (CB) ≥1.0 mg/dL if the total serum bilirubin (TSB) is <5.0 mg/dL or greater than 20 percent of the TSB if the TSB >5.0 mg/dL. In infants with PNALD, usually a serum CB ≥2.0 mg/dL is used for defining cholestasis. However, therapeutic measures are instituted in infants with PNALD when CB reaches 1.5 mg/dL.

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 by 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 week 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, the pediatric liver service should be consulted immediately.

Importance

Unlike unconjugated bilirubin, conjugated bilirubin is not directly toxic to tissues but can be a sign of significant, potentially fatal, underlying liver disease.

Etiology

The most common causes of conjugated hyperbilirubinemia include: biliary atresia, neonatal hepatitis, Alagille syndrome, choledochal cysts, sepsis, parenteral nutrition associated liver disease (PNALD), and genetic or metabolic liver diseases (e.g., galactosemia, tyrosinemia, hypothyroidism, alpha-1 antitrypsin deficiency, and neonatal hemochromatosis).

Assessment

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

An abdominal ultrasound should be performed to exclude anatomical abnormalities (e.g. biliary atresia, choledochal cyst).

Table 5-2. Laboratory investigations

Liver function panel	ALT, AST, alkaline phosphatase, GGT, unconjugated bilirubin, conjugated bilirubin, albumin
Liver synthetic capacity	Glucose, albumin, INR
Viral hepatitis	Hepatitis B, CMV and EBV, as well as, cultures for adenovirus, enterovirus, parvovirus
Metabolic causes of hepatitis	Alpha-1 antitrypsin phenotype, serum amino acids, ammonia, urinary organic acids, urine succinylacetone, urine ketones, serum lactate and pyruvate, ferritin, urine reducing substances, urine bile acids by GCMS
Thyroid function tests	Free T4 and TSH
Cystic fibrosis	Genetic, immune reactive trypsin, or sweat test
Neonatal hemochromatosis	Ferritin, transferrin saturation
Histocytosis	Ferritin, triglycerides, NK studies
Mixed causes of unconjugated and conjugated hyperbilirubinemia	Peripheral smear for red cell morphology, blood typing (maternal and infant), and Coombs test

Consultations

A Liver Team consult should be requested when a diagnosis other than sepsis or PNALD is suspected. The Liver Team will help guide the evaluation, including determining whether 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; hence, an earlier Liver Team consult is preferred.

A Genetics consult should be considered if there is a family history of conjugated hyperbilirubinemia, or liver disease, or if dysmorphic features, or a cardiac murmur are present.

Treatment

The treatment of cholestasis should primarily be directed toward the underlying condition. Other supportive treatments include:

- **Feeding** - Treatment of PNALD includes the reestablishment of enteral nutrition, as tolerated. Feeding human milk, premature infant formula, or both is 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 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, ursodiol 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. If the patient is being evaluated for a bile acid synthesis defect, then UDCA treatment should be withheld until the evaluation has been completed.
- **Fat-soluble vitamins** - TPN should provide sufficient vitamins A, D, and E (largely irrespective of volume). If bleeding occurs, 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 copper and manganese are excreted in the bile, in cholestasis they may accumulate in the liver and cause worsening hepatic dysfunction. Therefore, in the presence of cholestasis (conjugated bilirubin > 1.5 mg/dL) it is recommended to reduce trace minerals in the TPN. However, infants 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 with cholestasis while on TPN. 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 checked when medically feasible. To monitor copper and zinc levels, send a minimum of 5 mL of blood in tall dark blue tube without additives. In the presence of cholestasis (conjugated bilirubin > 1.5 mg/dL) without either jejunostomy or ileostomy, trace minerals should be provided 3 times per week (Monday, Wednesday and Friday), and parenteral zinc should be provided at maintenance levels daily. However, in infants where cholestasis is present with either jejunostomy or ileostomy, extra zinc may be provided to compensate for gastrointestinal losses.
- **Lipid limiting strategy (LLS) for PNALD -** There is evidence that limiting the Intralipid® infusion rates to 1 g/kg/day may be beneficial in infants with PNALD with a conjugated bilirubin ≥ 1.5 mg/dL. However, some VLBW infants may require 2 g/kg/day of Intralipid® for growth. Consultation with the nutrition team should be obtained in such instances. It is not necessary to prophylactically decrease the Intralipid® infusion rate in the absence of any evidence of cholestasis. When lipid limiting strategy is initiated, caregivers at TCH and other BCM affiliated nurseries should discuss the potential need of Omegaven® in the future with either Dr. Murali Premkumar or Dr. Amy Hair.
- **Omegaven®** - (**See next section**)

Fish Oil-Based Lipid Emulsions in Parenteral Nutrition Associated Liver Disease (PNALD)

Omega-3 Fatty Acids (Omegaven®)

Omegaven® (Fresenius Kabi, Germany) is an intravenous fish oil-based lipid emulsion rich in omega-3 fatty acids. Omegaven®, an intervention in the treatment of PNALD, has been shown to facilitate faster resolution of cholestasis, reduction in the rate of liver transplants, and reduction in mortality in these patients. Omegaven® is currently not approved by the FDA for general use. However, it is approved by the FDA to be used ONLY on a compassionate basis under a BCM/TCH Investigational New Drug (IND) protocol for the treatment of PNALD. The etiopathogenesis of PNALD is unclear, but is thought to be secondary to omega-6 fatty acids in the conventional soy-based lipid emulsion (Intralipid®). The beneficial effects of omega-3 fatty acid (FA) solutions have been attributed to its anti-inflammatory effect and decreased de novo lipogenesis thereby preventing or attenuating TPN-induced hepatosteatosis. The level of conjugated bilirubin is usually noted to increase over the first week following initiation of Omegaven®, before gradually decreasing with complete resolution over a median of 7 ± 2 weeks. The use of Omegaven® has so far proven to be safe with no short term side effects. Essential fatty acid deficiency, though a theoretical concern, has not been described with the use of Omegaven®.

Inclusion Criteria

- Greater than 14 days of age and less than 5 years of age
- Conjugated bilirubin >2 mg/dL
- Expected to require PN for at least an additional 28 days.

Exclusion Criteria

- Evidence of a viral hepatitis or primary liver disease as the primary etiology of their cholestasis
- Clinically severe bleeding not able to be managed with routine measures
- Congenital lethal conditions or other health conditions that suggest high likelihood of death even if the infant's cholestasis improves.

Use of Omegaven®

Once an infant meets eligibility for Omegaven®, Dr. Murali Premkumar or Dr. Amy Hair are to be consulted to confirm the eligibility and to obtain informed consent of the parent or guardian of the infant. Intralipid® is then 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 TPN is cycled in preparation for discharge. Providing more than 1 g/kg/day is not allowed by the FDA. If high triglyceride levels (>350 mg/dL) are a concern, the dose can be decreased to 0.5 g/ kg/day for a few days, recognizing this will not provide enough calories to promote growth. Omegaven® can be provided via central or peripheral line. If only Omegaven® is provided through the central line, heparin 1unit/mL in normal saline should be ordered to run as a carrier fluid. To provide sufficient calories for growth, the glucose infusion rate in the TPN may need to be increased as tolerated to 14-17 mg dextrose/kg per minute.

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. Under some circumstances, Omegaven® may be continued for conjugated hyperbilirubinemia even after full enteral nutrition is attained if the infant otherwise has ongoing need for intravenous access. This should be discussed with the nutrition team.

If a patient who has received Omegaven® in the past needs to resume TPN for any reason (e.g., post operative course), the patient may be considered for further use of Omegaven®, even if the conjugated bilirubin is < 1 mg/dL. Cases should be individually discussed with the intestinal rehabilitation team, as in some cases resumption of Intralipid® 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 due to the fact that the liver function tests may remain abnormal for several months despite normalization of conjugated bilirubin levels and the likely anti-inflammatory benefits to the provision of omega-3 FA.

Home Use of Omegaven®

Home use of Omegaven® is available with follow up by the TCH Pediatric Intestinal Rehabilitation Clinic Team. At this time, the only home health care company who has agreed to participate with Omegaven® is Coram Specialty Infusion Services; therefore, all patients to receive Omegaven® at home must use this company for their home health care needs.

If a patient comes to TCH for Omegaven® but has not previously received it at another institution, the FDA requires the patient to be admitted for a 48-hour inpatient stay for the initiation of Omegaven®. Patients transferred to TCH for home use treatment who have received Omegaven® at another institution are not required to be admitted and can be seen in the clinic directly.

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.

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, TPN-associated cholestasis warrants concern. Liver failure can develop as early as 4 months. Findings of worsening conjugated hyperbilirubinemia, elevated PT, glucose instability, worsening hepatosplenomegaly, caput medusa, ascites, and GI bleeding from portal hypertension suggest the development of 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.

SMOFlipid® (Soy Oil, Medium Chain Triglycerides, Olive Oil, and Fish Oil)

Omegaven® at 1 g/kg/day, or in some instances Intralipid® at 1 g/kg/day (lipid limiting-strategy, LLS) can be effective at limiting and reversing PNALD. However, due to the prescribed lower dosage of lipids at 1 g/kg/day, growth may be restricted in the above strategies due to inadequate caloric intake. SMOFlipid® (Fresenius Kabi AG, Germany), a new generation lipid emulsion is a mixture of soybean oil, medium chain triglycerides, olive oil, and fish oil. Compared to the above strategies, SMOFlipid® may be prescribed at an expected safe dose of 3 g/kg/day, providing 3 times more calories from lipids. SMOFlipid® provides both omega-3 and omega-6 FA in comparison to Omegaven® which provides only omega-3 FA and Intralipid® which provides only omega-6 FA.

Compassionate use of SMOFlipid® may be considered for infants with mild cholestasis (conjugated bilirubin < 2 mg/dL) that are currently receiving Omegaven® or Intralipid® (as lipid limiting strategy dose at 1 g/kg/day) with concerns for poor somatic growth. The perceived need for SMOFlipid® should be discussed with Dr. Amy Hair or Dr. Murali Premkumar.

Inclusion Criteria

- Greater than 14 days of age and less than 1 year of age,

- Body weight greater than 1.5 kg,
- Mild cholestasis (CB < 2 mg/dL),
- Currently receiving Omegaven® or Intralipid® at 1 g/kg/day (LLS)
- Evidence of inadequate growth of weight, head circumference, and/or length, and
- Be expected to require PN for at least an additional 21 days.

Exclusion Criteria

- Evidence of a viral hepatitis or primary liver disease as the primary etiology of their cholestasis
- Clinically severe bleeding not able to be managed with routine measures
- Congenital lethal conditions or other health conditions that suggest high likelihood of death even if the infant's cholestasis improves.

References

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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. In addition, 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 be provided any commercial thickening agent (Simply Thick and similar products) designed to be added to infant formula or human milk in any of our Level 2, 3 or 4 NICU settings. 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 absolutely 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, esophageal atresia repairs, 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 either H_2 receptor antagonists or proton pump inhibitors (PPIs) produce relief of symptoms and promote esophageal healing, although PPIs have superior efficacy. 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.

Ranitidine (Zantac) - a H_2 receptor antagonist, is associated with an increased risk of side effects, including NEC in preterm infants. Hence, extreme caution should be used, when this agent is utilized.

- **oral:** Post-menstrual age (PMA) <44 weeks: 2 mg/kg per dose, every 8 hours: maximum 6 mg/kg per day; PMA ≥ 44 weeks: 2-5 mg/kg per dose, every 12 hours.
- **intravenous:** 0.75 to 1.25 mg/kg per dose every 6 hours; maximum 6 mg/kg per day.

Lansoprazole (Prevacid)

- **oral:** For infants less than 10 weeks of age: 0.2 mg/kg once daily; For infants ≥ 10 weeks of age and < 1 year: 1-2 mg/kg once daily; available as suspension or solutab for older infants; maximum 15 mg/day.

Pantoprazole (Protonix)

- **intravenous:** 1mg/kg daily

Metoclopramide (Reglan) - a prokinetic agent, 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, 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 Nutrition Team.

Erythromycin

Erythromycin has been used as a prokinetic agent to treat feeding intolerance and reflux in infants. 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 (see dosing below).

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.

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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 300 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 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. 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 is informative only if collected at the proper time relative to the acute presentation. Novel biochemical technologies—such as tandem mass spectrometry—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 inborn errors (e.g., Smith-Lemli-Opitz syndrome, due to a defect in cholesterol biosynthesis; Zellweger syndrome, due to defects in peroxisomal biogenesis; 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 Inborn Errors of Metabolism should receive Developmental referral and ECI (Early Childhood Intervention) referral.

Categories of Inborn Errors

In the overall assessment of a clinical scenario, two general categories of inborn errors 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:

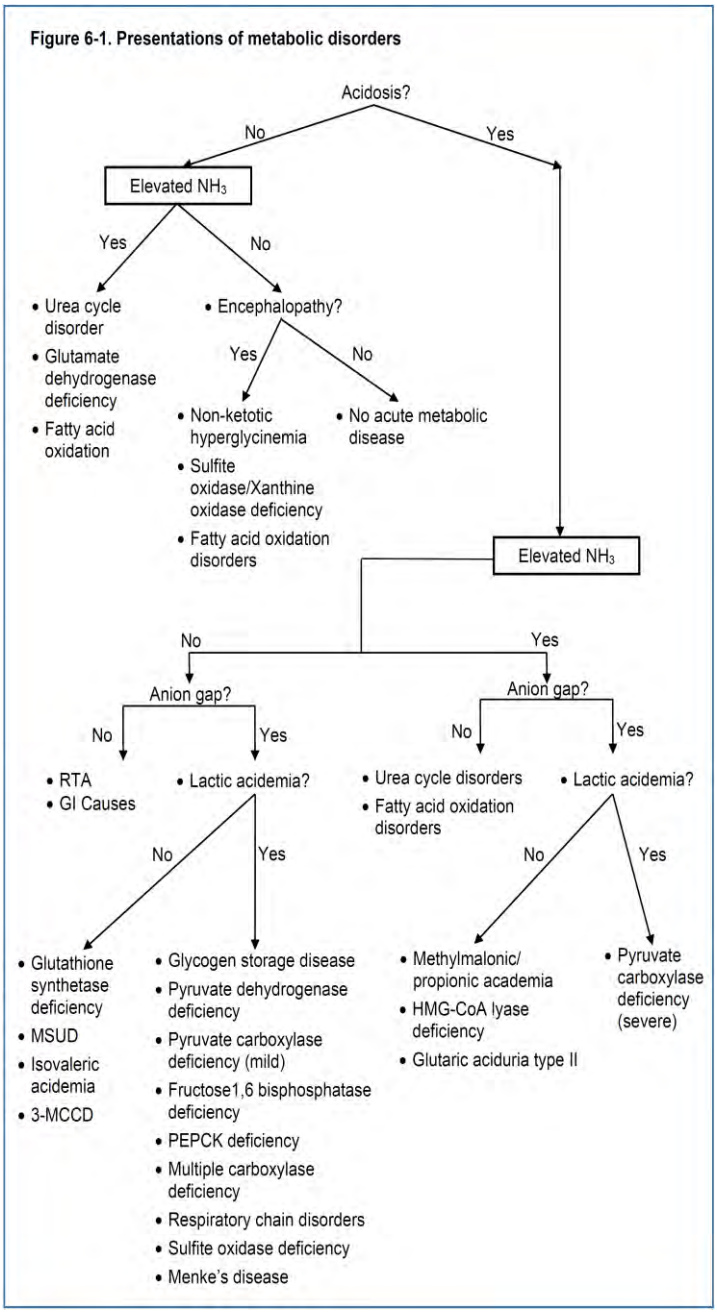
» **Disorders that affect the synthesis or breakdown of complex molecules (e.g., the lysosomal storage disorders) -** this group of disorders tends to have a progressive, somewhat fixed course independent of dietary intake or intercurrent events such as infection. While this class of disorders can present 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.

» **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 amino acidopathies, 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.

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 **(see Figure 6–1).** Suspect an inborn error 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 disorder may precede birth followed by further neurological deterioration post-birth. Inborn errors of metabolism may be categorized by their most prominent neurological, behavioral or other clinical characteristics.

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. 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:

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

Hypoglycemia

Hypoglycemia can be a prominent feature in inborn errors of metabolism 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. Abnormalities in blood chemistries that support the diagnosis of GSD1 include hyperlipidemia, uric acidemia, and lactic acidemia, while patients with GSD3 exhibit elevated ALT and AST, and elevated CPK in most patients. DNA testing can establish the diagnosis of GSD1A and preclude the need for liver biopsy.

Other inborn errors in which hypoglycemia is a prominent feature include:

- fatty acid oxidation disorders (especially MCAD),
- glutamate dehydrogenase deficiency, and
- 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, VLCAD, or CPT2, the typical patient is older. About 20 different enzyme defects are

associated with fatty acid metabolism 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 hyper-ammonemia.

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.

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).

Fetal Hydrops

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

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 and low platelets (HELLP) syndrome and fatty liver of pregnancy in some carrier (heterozygous) mothers, and 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 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)

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

Lyosomal Storage Disorders

- sialidosis
- I-cell disease
- galactosialidosis disease
- 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
- multiple sulfatase deficiency
- Hurler syndrome (MPS type I)
- Morquio syndrome (MPS type IV)
- Sly syndrome (MPS type VII)

Other Metabolic Disorders

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

Hematologic Disorders (associated with hemolysis)

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

Chromosome Abnormalities

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

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)

Clinical Evaluation

Neurologic Status

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 or 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 though, with rare exception, true convulsions are an inconsistent feature of inborn errors of metabolism. Seizures dominate the clinical picture in pyridoxine-dependent and folinic-acid–responsive seizures. 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 are deposited 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.

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 inborn error from non-genetic etiologies can be quite challenging. Biochemical tests for inborn errors 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). Conduction abnormalities may accompany several disorders of fatty acid metabolism.

Laboratory Evaluation

Screening tests that detect a large number of inborn errors 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 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.

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.

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. Elevated arginine is a constant finding in untreated arginase deficiency, although these patients generally are not symptomatic in the newborn period.

Several urea cycle disorders cannot be reliably distinguished by plasma amino acid analysis and require additional tests, including urine orotic acid. 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 and cataracts. 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 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 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. 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 inborn error of metabolism. 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 - an excellent screening test for a large number of inborn errors. 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.

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 inborn errors. 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.

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.

Online Resources

Several websites, including **www.genetests.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 are widely used in practice. Specialist Metabolic-Genetic consultation may helpfully guide investigation.

References

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Treatment

Initial treatment of an infant with a suspected inborn error of metabolism 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 usually can be obtained within 24 hours, while an acylcarnitine profile may take 48 to 72 hours.

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 40 + 2 panel and identifies approximately 96% of patients in Texas. The DNA analysis takes 2 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 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 **Sally Mason, CF Center Coordinator at (832) 822-3933 or skmason@texaschildrenshospital.org.**

Prediagnosis Treatment

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.

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.

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

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 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, 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.

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 to 300 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.

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.

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 urea cycle for protein synthesis to reverse protein catabolism. 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

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 Deficiency (CUD) • Carnitine Palmitoyl Transferase Deficiency1 (CPT1)
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 (GAL) • Sickle Cell Disease (SCD) including HbS/S), Hb S- Beta thalassemia,Hb S/C • Severe Combined ImmunoDeficiency (SCID)

detects a large number of additional inborn errors of metabolism (e.g., many of the disorders of fatty acid oxidation, organic acidurias, and amino acidopathies), often before the onset of symptoms. The recently introduced expanded newborn screening in Texas includes 28 disorders (**Table 6–2**). 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 Health, 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.

Expanded testing is also available commercially in Texas. Information regarding additional metabolic screening is available upon request from the Genetics Service.

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. 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 deletion syndrome. One advantage of FISH is that test results may be obtained in 48-72 hours 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. With a single test, CMA can detect genomic disorders that were previously identified using chromosome analysis or FISH. CMA includes probes for all the known microdeletion/duplication syndromes (more than 65 conditions), pericentromeric regions, and subtelomeric regions. Additionally, CMA includes probes that cover many 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 variants of unknown significance, and counseling regarding the significance of such findings may require parental testing for the variant in question 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 will 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.

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 clinical feature 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, mutations 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"). Thus, whole exome sequencing is a complex test and requires consent prior to ordering the test. In addition, patients and

families should review the consent form with their practitioner so that they are aware of all possible test results (carrier status, paternity identification, etc.) in order to select the information that they would like to receive in the results. 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 a three 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. WES has limitations in that it does not detect trinucleotide repeat disorders such as congenital myotonic dystrophy, large deletions, large duplications, or translocations, hence a high resolution CMA is recommended to increase the chance of finding a deletion not detected by DNA sequencing,

References

The most updated and most commonly recommended CMA is the CMA comprehensive (CMA HR+SNP) v 10.1. See https://www.bcm.edu/research/medical-genetics-labs/test_detail.cfm?testcode=8665 for more details.

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/microL). However, healthy preterm and term newborns can have counts significantly outside these ranges (5th percentile as low as 104,000/microL and the 95th percentile as high as 750,000/microL). The normal platelet count increases in postnatal life in a sinusoidal fashion with two peaks, at 2-3 weeks and 6-7 weeks respectively. At birth, concentrations of many of the hemostatic proteins are low; vitamin K dependent factors (FII, FVII, FIX, FX) and contact factors (FXI, FXII) are about 50% of normal adult values in term infants and are lower in preterm infants. Similarly, concentrations of antithrombin, protein C, and protein S also are low at birth. Despite this apparent functional immaturity, 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.

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 **(see 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,
- the infant's condition at birth, and
- 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:

- a complete blood count (CBC),
- prothrombin time (PT), and
- 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.

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 problem is not an isolated issue, but part of another/systemic disorder. N, ↑, and ↓ represent normal, increased, and decreased respectively.

Adapted from Goorin AM, Neufeld E. Bleeding. In: Cloherty JP, Eichenwald EC, Stark AR (eds). *Manual of Neonatal Care*, 2004. Philadelphia, Lippincot, Williams & Wilkins.

Coagulation Disorders

Hemophilias A and B are the most common inherited bleeding disorders to present in the newborn period. However, other disorders may present rarely. In the case of inherited coagulation disorders, once the diagnosis has been reached, the infant should be managed in conjunction with the Hematology Service. 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.

Amongst acquired coagulation disorders, DIC is the most common. DIC occurs as a secondary event, and may be seen following birth asphyxia, infection, necrotizing enterocolitis, brain injury, homozygous protein C/S deficiency, etc. 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 damage. 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.

Thrombocytopenias

Thrombocytopenia occurs in 1% to 5% of the general newborn population at birth, with severe thrombocytopenia (platelets less than 50 × 109/l) 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 **(see Table 7–2)** 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 **(see TCH NAIT clinical guideline below).** 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 and the thrombocytopenia. Thrombocytopenia is often severe, with affected neonates receiving 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 out- come, and most current guidelines are consensus guidelines rather than evidence-based guidelines **(see Figure 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.

Table 7–2. Causes of neonatal thrombocytopenia

Increased consumption of platelets

- Immune thrombocytopenia
  - » Autoimmune
  - » Alloimmune
- Drug-induced
- Peripheral consumption
  - » Hypersplenism
  - » Kasabach-Merritt syndrome
  - » Disseminated intravascular coagulation
  - » Infection
  - » Drug toxicity
- Procedure-related, following exchange transfusion
- Miscellaneous
  - » Neonatal cold injury
  - » Von Willebrand disease

Decreased production of platelets

- Congenital thrombocytopenias
- Inflitrative disorders
- Infections: bacterial, viral, or fungal
- Drug toxicity

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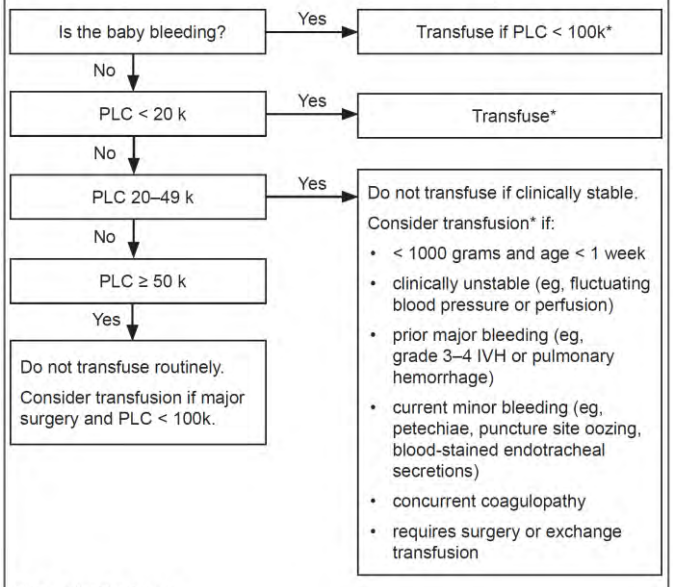
Figure 7–1. Guidelines for platelet transfusion in the newborn



PLC = platelet count

*Use human-platelet-antigen–compatible platelets for infants with suspected or proven neonatal alloimmune thrombocytopenia

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. It is important to recognize the neonate in whom NAIT is a diagnostic consideration to initiate appropriate treatment in these infants, and to request appropriate serologic testing and follow up for patients and their parents.

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) antigen is responsible for **NAIT** in approximately 75 to 90 percent of cases in Caucasians; in Asians, HPA-4 (Yuk/Pen) antigen is the most frequent cause of **NAIT**.

NAIT may be distinguished clinically from other etiologies of neonatal thrombocytopenia by more frequent occurrence of severe thrombocytopenia (usually < 50,000/mm3), and more frequent occurrence of bleeding manifestations regardless of platelet counts. Intracranial hemorrhage has been reported to occur in up to 20% of patients with **NAIT.**

Diagnostic evaluation and treatment for **NAIT** are distinct from other etiologies of neonatal thrombocytopenia, and require prompt collaboration among the treating clinician or neonatologist, 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/mm3) 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. Consider consultation with a pediatric hematologist and a blood bank physician. For some infants, this may necessitate transfer to a tertiary-care facility.

B. Check platelet counts 10 minutes to 1 hour after transfusion. (Since the recovery and the half-life of random donor platelets, presumably antigen positive, are not adequate: carefully monitor the plate- let count.) Repeat transfusion of random donor platelets as needed until maternal washed platelets or antigen negative platelets are available. (Discretion is advised when using random donor platelets in a female Rh-negative infant as this would sensitize the infant to the Rh antigen.)

1. Platelet count is less than 30,000/mm^3 in an uncomplicated, term infant
2. Platelet count is less than 50.000/mm^3 in an uncomplicated, preterm infant (i.e., less than 37 weeks gestation).

(Note: Consider transfusion at a higher platelet count (e.g., less than 100,000/mm^3) in very low birth weight infants (less than1500 grams), who are at high risk for intraventricular hemorrhage (IVH) and other co-morbid conditions.)

D. Administer IVIG (1 gram/kg: may be repeated if no increase in platelet counts following initial dose).

E. Consult with the TCH Blood Bank physician to initiate procedure for maternal platelet collection for transfusion to the infant. Maternal platelets are transfused to the infant AS SOON AS POSSIBLE. 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.

(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 thrombocytopenia infants (head ultrasound vs. CT) even if the infant is asymptomatic.

(**Note:** up to 20% of infants may experience intracranial hemorrhage as a complication of **NAIT**).

3. Perform definitive laboratory testing for **NAIT.**

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 may be needed prior to subsequent pregnancies.
2. Family testing results and counseling about future pregnancies must be discussed and carefully documented.

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Blood Transfusion

Before initial transfusion, written informed consent must be obtained using the Disclosure Panel information outlined by Texas law. After discussion with the attending physician, a note that outlines indications for transfusion should be placed in the patient's chart.

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 40% in association with symptoms or if circulatory insufficiency occurs in the presence of a calculated acute deficit of greater than 10%. 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 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 evidence of impaired tissue oxygenation.
- **Chronic cardiopulmonary disease -** Transfusion may be indicated if signs such as persistent resting tachycardia suggest high cardiac output state specifically related to anemia.

Trigger Levels

A transfusion should be considered at the following hematocrit levels depending on associated clinical conditions:

- less than 35% to 40%: infants receiving mechanical ventilation with high inspired oxygen concentration or high mean airway pressure or who have hypotension or chronic or recurrent bleeding.
- Less than 25% to 30%: signs of anemia such as unexplained tachycardia, frequent apnea, and poor weight gain with adequate nutrition, or unexplained lethargy.
- Less than 20% to 25%: transfusion should be considered independent of signs of anemia.

Transfusion and Risk of Necrotizing Enterocolitis

Evidence relating to the risk of NEC associated with transfusion (TANEC) is limited, primarily retrospective, and conflicting. However, in an effort to enhance consistency in practice amongst our group, we recommend feedings be held in certain clinical scenarios **(see Chapter 13-Feedings and Transfusions Section).**

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

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

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.

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, normally growing premature infant. Efforts should be made to cluster such routine sampling with other laboratory tests.

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 bilirubin and car- bon monoxide (CO). The end-tidal carbon monoxide concentration (ET- COC) is an index of total bilirubin production. Unconjugated bilirubin can cross cell membranes and is potentially neurotoxic. However, such toxicity is avoided by the binding of bilirubin to albumin during trans- port. 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 kernicterus.

The liver converts bilirubin 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 both may 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-gluc-uronidase, 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 post- natal 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:

- **Shortened RBC survival time (about 90 days compared to 120 days for adults) -** Normally this is insignificant but it becomes the major contributor to net bilirubin load in hemolytic disorders.
- **Reduced intrahepatic conjugation of bilirubin -** This usually is related to immaturity of enzyme systems. Although rarely of importance in term infants, it may become a significant factor in a preterm or critically ill infant.
- **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 non-pathologic jaundice (physiologic or breast-milk jaundice). It may become a significant factor in any disease process that delays bowel function and stool passage.

Risk Factors for Severe Hyperbilirubinemia

See Table 7–3.

Table 7–3. Risk factors for severe hyperbilirubinemia

Major risk factors

- Predischarge TSB or TcB level in the high-risk zone **(see Figure 7–2)**
- Jaundice observed in the first 24 hours
- Blood group incompatibility with positive direct antiglobulin test, other known
- hemolytic disease (eg, 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 **(see Figure 7–2)**
- Gestational age 41 weeks or greater
- Exclusive bottle feeding
- Black race*
- Discharge from hospital after 72 hours

*Race as defined by mother's description.

Differential Diagnosis of Jaundice

Increased serum bilirubin results from increased production, increased enterohepatic circulation, or decreased elimination. **Risk of Hyperbilirubinemia is related to total serum bilirubin level, postnatal age, gestational age, and impact of co-existing illnesses.**

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. It is convenient to think of causes of jaundice in relation to timing of occurrence. 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.

Jaundice Appearing on Day 1 of Life

Presumed to be pathologic. Assume hemolytic process and seek specific etiology. Primary causes include:

- Isoimmune hemolysis due to Rh, ABO, or minor blood group abnormalities. Coombs test usually is positive, and 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 kernicterus 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 defects such as spherocytosis, elliptocytosis, G-6- PD deficiency.
- Hemoglobinopathies rarely cause significant jaundice but may exacerbate other problems.

Jaundice Appearing Later in the First Week

- **Non-pathologic jaundice** - In most cases, these are healthy term or late preterm infants who have so-called physiologic or breast-milk– related jaundice in which the enterohepatic circulation of bilirubin persists or is exaggerated. Studies using ETCOC measurements suggest increased bilirubin production also is a contributing factor.
- Highest incidence occurs in breastfed infants and bilirubin levels may peak somewhat later (day 5 or 6) and levels above 10 mg/dL may persist somewhat longer. The upper safe level of bilirubin in these patients is unknown. Although risk of kernicterus is quite low, reported cases have increased in recent years. Specific intervention depends upon total serum bilirubin level and postnatal age.
- Occasionally, sepsis, metabolic disorders, or hypothyroidism manifest during this time period.

Jaundice Persisting or Appearing Past the First Week

- Sepsis, either bacterial or viral.
- Cystic fibrosis or malformations or functional abnormalities of the GI tract leading to delayed passage of meconium and prolonged enterohepatic recirculation of bilirubin.
- Inborn errors of bilirubin metabolism (Crigler-Najjar or Gilbert syndromes).
- Persistent breast milk jaundice.

Cholestatic Jaundice

In these cases, the conjugated and unconjugated bilirubin fractions are elevated and the condition usually is more chronic. **(See Chapter 5- Gastroenterology)** Causes include:

- TPN cholestasis,
- neonatal hepatitis, and
- chronic, nonspecific cholestasis vs. biliary atresia.
- Evaluation

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

A basic workup for pathologic causes of jaundice might include serum 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. The possibility of G-6-PD deficiency as a contributor to neonatal jaundice must be considered. A peripheral blood smear may be useful as well.

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. 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 **(Figure 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 7–4).**

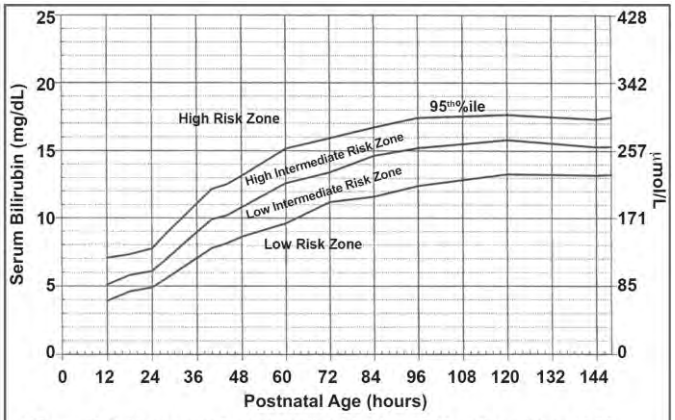

Figure 7–2. Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values. The serum bilirubin level was obtained 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.

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Table 7–4. Hyperbilirubinemia: Age at discharge and follow-up

Age at Discharge (hours)	Follow-up Assessment (age in hours)
< 24	by 72
24-47.9	by 96
48-72	by 120

Management

Because of variations in laboratory methods, it is recommended that all management decisions be based upon total serum bilirubin values. Nearly all data on the relationship between TSB levels and kernicterus or outcome are based on **capillary** TSB values, and data are conflictingon the relationship between venous and capillary TSB. The AAP does not recommend confirming an elevated capillary value with a venous sample because it may delay treatment.

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

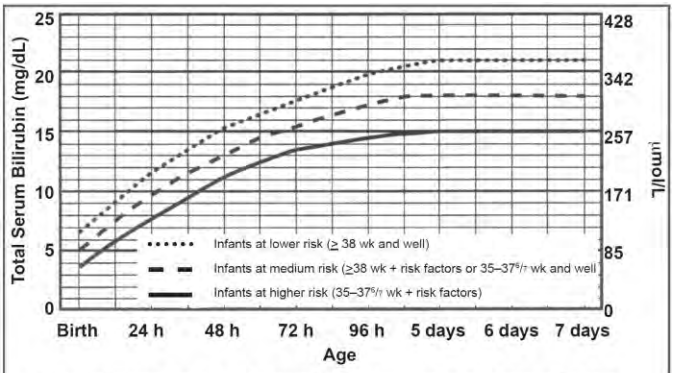
Efficacy of phototherapy is determined by:

- light source (blue-green spectrum is best),
- irradiance or energy output in the blue spectrum, and
- surface area exposed.

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 guide- lines for phototherapy but with TSB not at or near exchange transfusion levels. Use a high-intensity phototherapy device placed less than 18 inches from the patient. This will deliver an irradiance of 18 to 23 micro- Watts/cm^2/nm. In some circumstances, use of an open crib or bassinet may be necessary to allow placing the phototherapy device as close as 12 inches. Measurement of delivered dose is not required but may aid in optimizing treatment.

Intensive phototherapy is used for infants with TSB levels at or near exchange transfusion 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



- 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 35–376/7 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 376/7 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.

Figure 7–3. Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.

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/cm² 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 8–3], 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.

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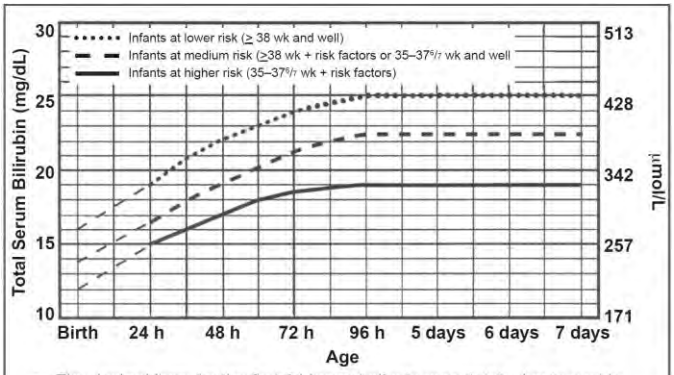
covered only with a disposable cover furnished by the manufacturer. This technique both increases delivered irradiance and recruits additional surface area for light exposure.

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 **Figure 7–3.**

Intravenous Immune Globulin

Administration of intravenous immune globulin (IVIG) to infants with isoimmune hemolytic disease has been shown to decrease the need for exchange transfusion. An infant with isoimmune hemolytic disease whose TSB level rises despite intensive phototherapy or is within 2 to3 mg/dL of the exchange transfusion level should be given intravenous immune globulin (0.5 to 1 g/kg over 2 hours). This dose can be repeated if needed in 12 hours.



- 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 35–37⁶/₇ wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Figure 7–4. Guidelines for exchange transfusion in infants 35 or more weeks' gestation.

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 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 ≥ 38⁰/₇ wk	8.0	0.94
Infants 35⁰/₇–36⁶/₇ wk and well or ≥ 38⁰/₇ wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	7.2	0.84
Infants 35⁰/₇–37⁶/₇ wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.80

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) crossmatched against the mother and compatible with the infant.

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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 nonhemolytic 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.

Risk of kernicterus in healthy term newborns with nonhemolytic 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 **Figure 7–4.**

Table 7-5. Guidelines for Management of Hyperbilirubinemia in Low Birth weight Infants

Total Serum Bilirubin levels (mg/dL) to initiate therapy

	Phototherapy		Exchange Transfusion
	1st week	2nd week	
< 750 grams	≥ 5		> 13
750-999 grams	≥ 5	≥ 7	> 15
1000-1499 grams	7 - 9 *	10 - 12	15 - 16
1500-1999 grams	10 - 12 *	13 - 15	16 - 18
2000-2500 grams	13 - 15 *	14 - 15	18 - 19

* For infants ≥ 1000 grams, in the first 96 hours, consider using the higher risk line in **Figures 7–3 & 7–4** (graph for treatment of jaundice in infants 35 weeks or greater), if line has a lower threshold than the numbers in **Table 7–5** above.

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.

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 **Figure 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.

Management of Hyperbilirubinemia in Low Birth Weight Infants

Currently, there are no AAP recommendations for treatment of hyperbilirubinemia in LBW, VLBW or ELBW infants. Until such recommendations are available, **Table 7–5** summarizes the best practice guidelines for use in Baylor-affiliated nurseries, and have been derived from a review of the literature including relevant controlled trials and expert opinions.

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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 cord clamping or milking of the cord in preterm infants has been associated with improved neonatal outcomes including increased hematocrit, decreased need for transfusion, hemodynamic stability requiring decreased use of vasopressors and decrease in intraventricular hemorrhage. No major differences in neonatal benefits have been observed when delayed cord clamping is compared to milking of the cord. The use of delayed cord clamping in preterm infants < 28 weeks and high risk pregnancies is still being studied.

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.

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.

Hematocrits of blood from venous samples are usually 5%-15% lower than those obtained from capillary samples.

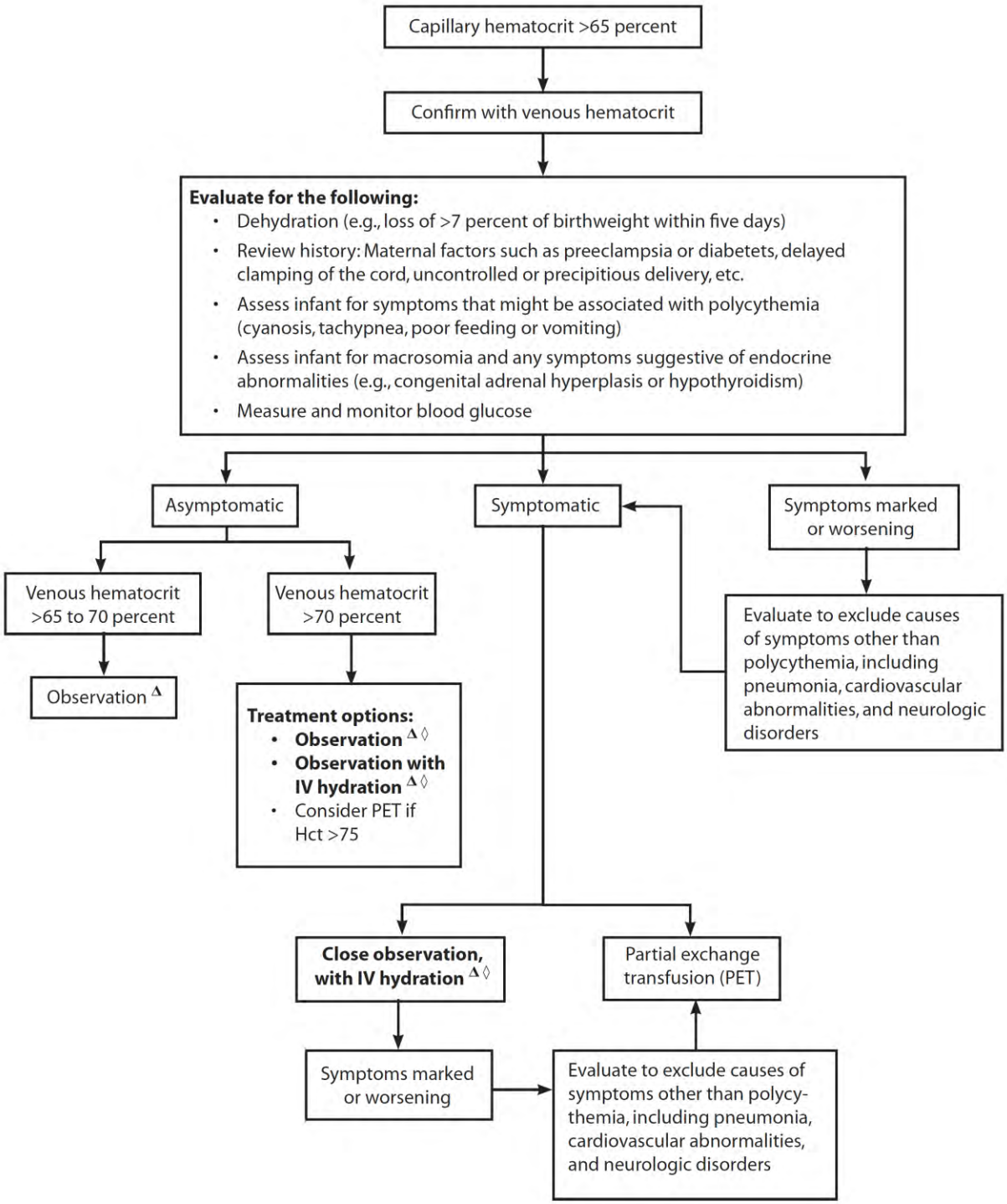
Management

- 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 **(see Figure 7-5).**
- 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 Figure 7-5 for recommended management strategies.**
- If a partial exchange transfusion is done for polycythemia, replace the removed blood with an equal volume of normal saline.
- 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.

Vol (replaced) =

$$\frac{[Hct_{initial} - Hct_{desired}] \times \text{Weight (kg)} \times 80 \text{ mL/kg}}{Hct_{initial}}$$

Figure 7-5. Algorithm for management of neonatal polycythemia



The management approaches outlined in this algorithm are based primarily upon expert opinion. There is insufficient evidence to fully assess the efficacy or safety of partial exchange transfusion (PET), or the clinical indications for this procedure.

Δ Observation consists of: monitor intake, weight, and urine output; follow up blood glucose as indicated based on initial results; monitor for symptoms.

◊ Preferred pathways.

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Bacterial Sepsis

General Points

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 38% of cases.

If an infant is ELBW (less than 1000 grams), has renal dysfunction, or is to be treated for more than 72 hours with gentamicin, serum levels should be monitored **(see Chapter 9 - Medications chapter).**

"Outbreaks" in any NICU may dictate temporary changes in the empirical drug regimens suggested below.

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.

Blood Cultures

Current semi-automated, computer assisted blood culture systems identify bacterial pathogens rapidly, within 24–36 hours. Candida species also will grow in this system, but occasionally can take longer.

Age 0 to 72 Hours (Early-Onset, Maternally Acquired Sepsis)

Indications for Evaluation

Term Infants (infants greater than 37 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, an evaluation (cultures) is done and empirical antibiotics are given to the infant.
- 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.

Preterm Infants (infants less than 37 weeks' gestation)

- Prolonged rupture of membranes (greater than 18 hours), maternal fever (greater than 100.4°F) before or within 24 hours after delivery, chorioamnionitis, 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

Term Infants

- **Infants with signs of sepsis** (e.g., respiratory distress, hypotension, lethargy, apnea, temperature instability, seizures, tachycardia, vomiting, diarrhea, abdominal distention, poor feeding, 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.
- **Healthy-appearing term infants.** Evaluate with a blood culture and initiate non-meningeal doses of ampicillin in combination with gentamicin. 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.**

Preterm Infants

- **Signs of sepsis.** For sepsis with a CBC, obtain 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) and initiate meningeal doses ampicillin in combination with gentamicin. If the infant develops signs of sepsis [see above], or has a positive blood culture, perform another CBC, a LP, and a repeat blood culture.
- 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.

Initial Empirical Therapy

(For doses, see Chapter 9 - Medications chapter.)

If CSF is abnormal or cannot be obtained when a lumbar puncture is performed, if gram-negative organisms are suspected, give cefotaxime at meningeal doses. **If CSF is normal**, administer ampicillin at non-meningeal doses in combination with gentamicin.

If CSF is normal, administer ampicillin at non-meningeal doses in combination with gentamicin.

Duration of Therapy

Infants with signs of sepsis - Ten days of therapy is given if sepsis is proven or strongly suspected; 14 to 21 minimum days depending upon etiologic agent and clinical course, is given if meningitis is proven or strongly suspected. If cultures are negative and the clinical course is not felt to be compatible with sepsis, discontinue antibiotics no longer than 48 hours after therapy initiated.

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.

Late-Onset Infection

Age older than 3 days and continuous Level 1-4 care. Consider maternal and hospital-associated sources for infection. **(See Figure 8–2)**

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 is present**.**

Evaluation

Obtain a CBC and cultures of blood, CSF, and urine (preferably by bladder tap). 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. However, urine culture, preferably by bladder tap, 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.

Initial Empirical Therapy

For doses, **see Chapter 9 - Medications chapter.**

Sepsis without a focus - Administer vancomycin and gentamicin. All BCM-affiliated NICUs have had endemic methicillin-resistant S. aureus strains since 1988, and most coagulase negative staphylococcal isolates (approximately 85%) are methicillin resistant.

Suspected disseminated staphylococcal infection - Administer vacomycin and nafcillin with gentamicin until culture results and antibiotic susceptibilities are known.

NEC (pneumatosis or presumed perforation) - Assuming that CSF is normal, treat initially with ampicillin, gentamicin, and clindamycin. If ileus due to sepsis is suspected, vancomycin may be used in substitution for ampicillin. However, if cultures are negative at 48 hours, vancomycin must be discontinued. Continued empirical therapy with ampicillin, gentamicin, and clindamycin is suggested if treating for NEC.

Meningitis - If suspected or proven, an Infectious Disease consultation and at least 24-hour observation in the Level III NICU are recommended to assist with management. The infant should be empirically treated with ampicillin, gentamicin and, if gram-negative organisms are suspected, cefotaxime at meningeal doses.

Infection of bone, joint, or both - Administer vancomycin, nafcillin and gentamicin; 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 vancomycin and gentamicin. 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.**

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2. Staphylococcal Infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book*: 2012 *Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2012.
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Group B Streptococcus (GBS)

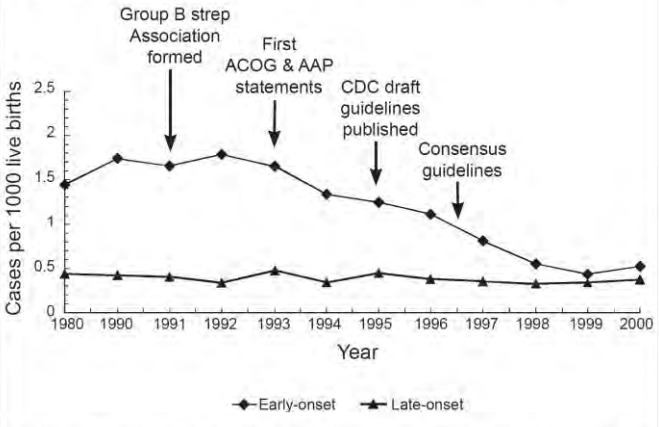
Management of At-risk Infants

- GBS caused approximately 7600 cases of sepsis and approximately 210 deaths per year in the U.S. before 1996. Early onset (0–6 days) infection now constitutes approximately 50% of GBS cases since introduction of routine maternal GBS culture screening and intrapartum antibiotic prophylaxis (IAP). Early-onset GBS infection results from vertical transmission of GBS during labor or delivery. Clinical onset of early onset disease occurs within the first 24–48 hours of birth in more than 95% of babies. It is characterized by septicemia, pneumonia, or

meningitis (approximately 5–8% of cases). GBS commonly is found in the maternal gastrointestinal and genitourinary tracts (15–40%). Antibiotic therapy given during pregnancy or intrapartum does not eradicate GBS from these sites.

- In 2010, the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists endorsed revised CDC guidelines; these guidelines are outlined in the algorithms **(see Figure 8–3 through Figure 8–7)**. These algorithms do not cover all circumstances. **Recommendations in the 2012 edition of the AAP Red Book—are maternal GBS culture-based and include:**
  - » Penicillin, ampicillin, or cefazolin, if initiated 4 hours prior to de- livery, are considered to be adequate prophylaxis. Clindamycin or vancomycin can be used in the mother at high risk for anaphylaxis, but their efficacy in preventing early-onset GBS is not established.
  - » Prophylaxis for women at high risk for penicillin allergy should not receive clindamycin unless the colonizing GBS isolate is known to be clindamycin sensitive (~30% of GBS isolates are resistant)
  - » Prophylaxis regimens for women at low (e.g., cefazolin) or high risk for penicillin allergy
  - » In GBS-colonized women undergoing planned cesarean deliveries, routine intrapartum antibiotic prophylaxis is not indicated if labor has not begun or membranes have not ruptured.
  - » A suggested algorithm for management of patients with threatened preterm delivery
  - » An algorithm for management of newborns exposed to intrapartum antibiotic prophylaxis
- Infants who receive the limited evaluation are triaged to a Level 1 New- born Nursery and are not candidates for short stay.

Figure 8–1. Incidence of early- and late-onset group B streptococcus



Adapted from: Prevention of Perinatal Group B Streptococcal Disease. Revised Guidelines from CDC. *MMWR* 2002;51(RR-11):5.

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Cytomegalovirus (CMV)

General Points

Most neonates congenitally infected by CMV are usually asymptomatic although they may develop hearing loss or learning disability later. About 5% of infants will have profound involvement (intrauterine growth restriction, jaundice [conjugated and unconjugated], purpura, hepatosplenomegaly, microcephaly, brain damage, retinitis). Periventicular calcification in the brain may be seen. Sensorineural hearing loss (SNHL) is the most common result of congenital CMV infection may be the only clinical finding. SNHL may be unilateral or bilateral. CMV infection acquired at birth or shortly thereafter usually is not associated with clinical illness except in preterm infants where acute infection has been associated with lower respiratory tract disease and may be fatal. In infants with negative bacterial evaluation (bacterial cultures negative at 24-48 hours) who are greater than 3 weeks postnatal age and have never been discharged home from the NICU obtain a bag urine sample for CMV PCR. If the PCR is positive, obtain a CMV blood PCR and consult the ID Service.

Evaluation

Virus can be isolated from urine, nasal pharyngeal secretions, or peripheral blood leukocytes. Specimens must be obtained within 3 weeks of birth in order to diagnose a congenital infection. Elevated CMV IgM at birth also is diagnostic but is not always present. Polymerase chain reaction (PCR) can be performed to detect CMV DNA in blood, tissue or CSF. Traditional "TORCH titers" have little value and are not recommended.

Treatment

An Infectious Disease consult should be obtained for all infants with CMV infection. Infants with CNS disease or signs of acute infection are usually treated with ganciclovir for up to 6 weeks. Valganciclovir administered orally to young infants is currently being studied in a clinical trial and may come to be another treatment option.

Figure 8–2. Late-onset Sepsis in Newborn Center Patients, Level 2 and 3

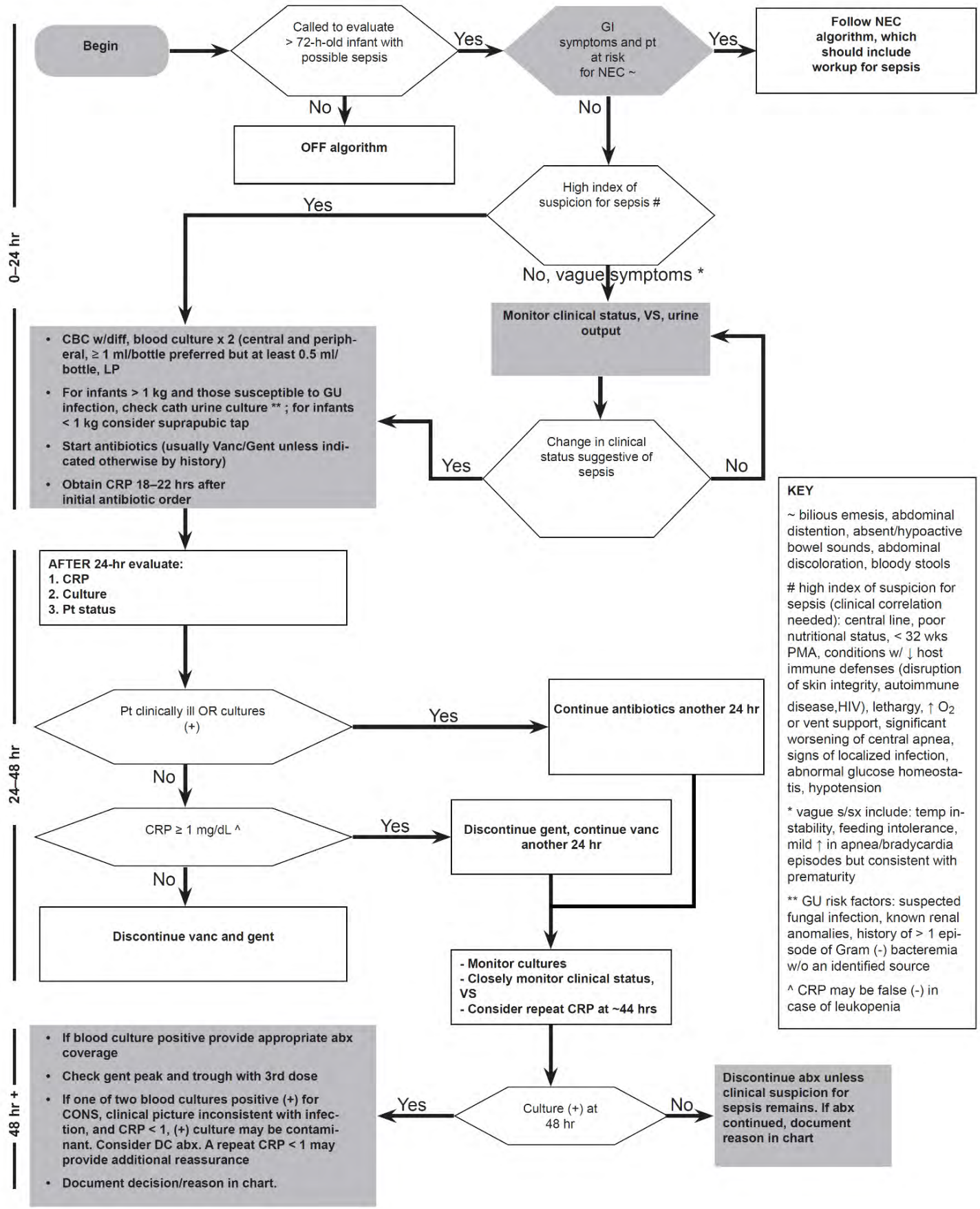


Figure 8–3. Indications and nonindications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcus

Intrapartum antibiotic prophylaxis (IAP) indicated

- Previous infant with invasive GBS disease
- GBS bacteriuria during any trimester of the current pregnancy *
- Positive GBS vaginal-rectal screening culture in late gestation† during current pregnancy *
- Unknown GBS status at the onset of labor (culture not done,incomplete, or results unknown) and any of the following:
  - Delivery at < 37 weeks' gestation †
  - Amniotic membrane rupture ≥ 18 hours
  - Intrapartum temperature ≥ 100.4ºF (≥ 38.0ºC) ¶
  - Intrapartum NAAT** positive for GBS

Intrapartum GBS prophylaxis not indicated

- Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
- GBS bacturiuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
- Negative vaginal and rectal GBS screening culture during in late gestation† during the current pregnancy, regardless of intrapartum risk factors
- Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age

Abbreviation: NAAT = Nucleic acid amplification tests

* Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesareandelivery is performed before onset of labor on a woman with intact amniotic membranes

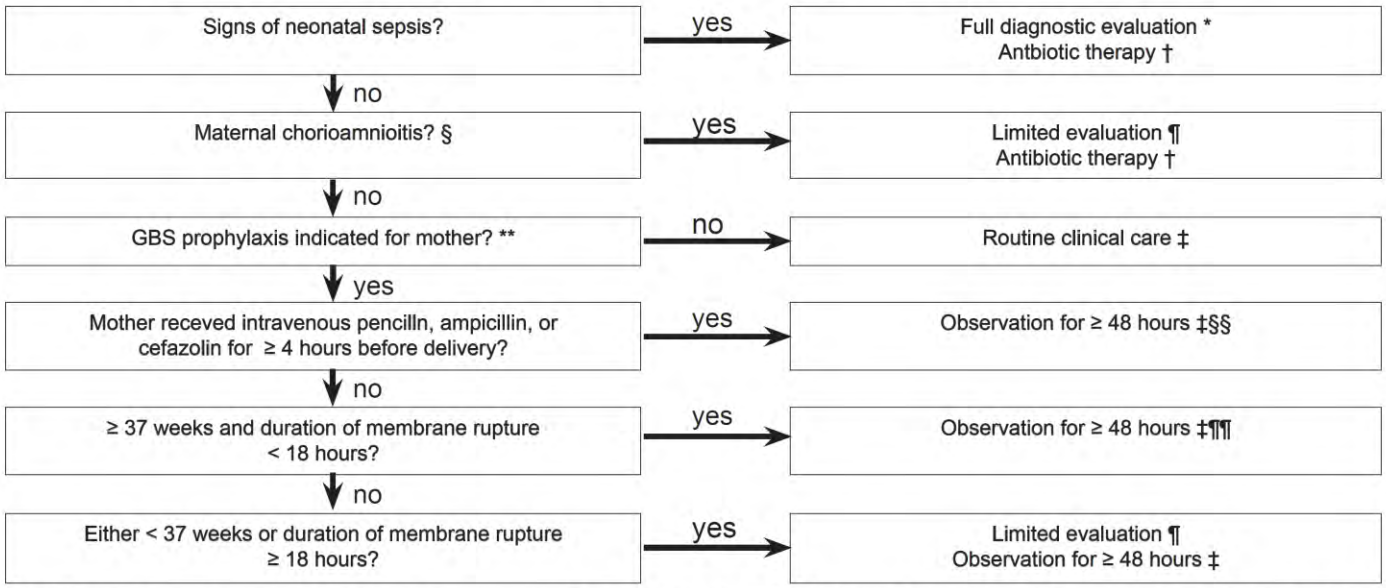
† Optimal timing for prenatal GBS screening is at 35–37 weeks' gestation

§ Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 8–5 and 8–6

¶ If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis

**NAAT testing for GBS is optional and might not be available in all settings. If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at < 37 weeks' gestation, amniotic membrane rupture at ≥ 18 hours, or temperature ≥ 100.4°F (≥ 38.0°C) is present, then intrapartum antiobiotic prophylaxis is indicated.

Figure 8–4. Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected)

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are non-specific.

¶ Limited evaluation includes blood culture (at birth), and CBC with differential and platelets (at birth and/or at 6–12 hours of life)

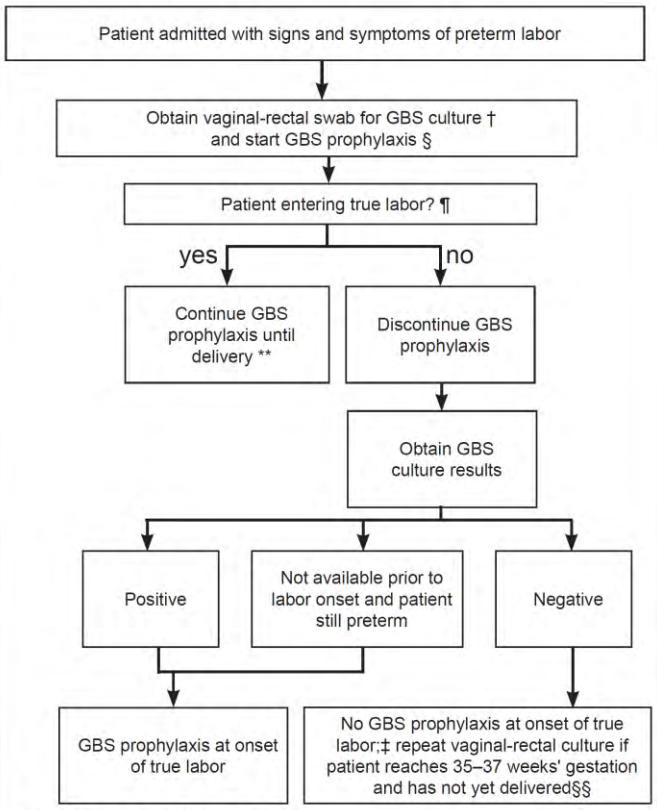
** See table 8–3 for indications for intrapartum GBS prophylaxis

‡ If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated

§§ If ≥ 37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a personwho 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 for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

Figure 8–5. Algorithm for screening for group B streptococcal (GBS) colonization and use of intrapartum prophylaxis for women with preterm* labor (PTL)



* At < 37 weeks and 0 days of gestation

† If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

§ See Figure 8–7 for recommended antibiotic regimens.

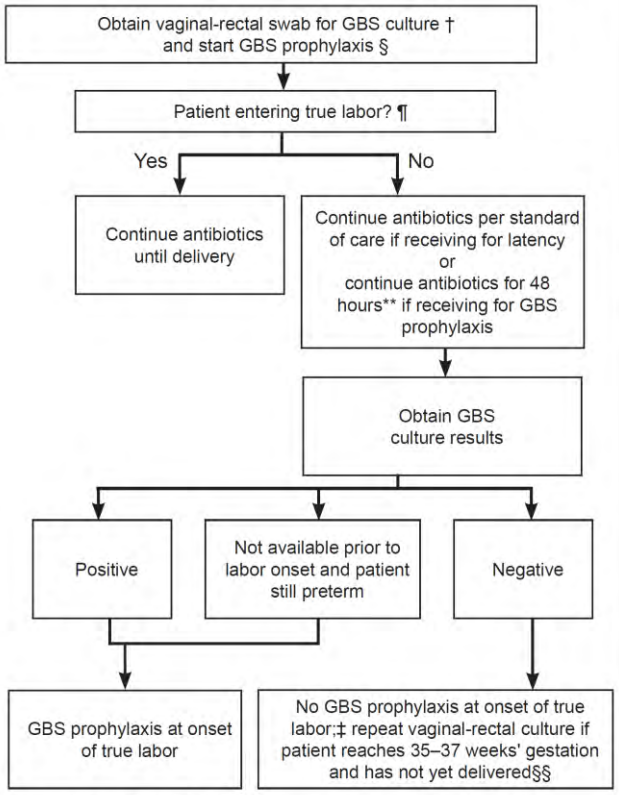
¶ Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis.

** If GBS culture results become available prior to delivery and are negative, then discontinue GBS prophylaxis.

‡ Unless subsequent GBS culture prior to delivery is positive.

§§ A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is readmitted with signs and symptoms of PTL and had a negative GBS screen > 5 weeks prior, she should be re-screened and managed according to this algorithm at that time.

Figure 8–6. Algorithm for screening for group B streptococcal (GBS) colonization and use of intrapartum prophylaxis for women with preterm* premature rupture of membrane (pPROM)



* At < 37 weeks and 0 days of gestation

† If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

§ Antibiotics given for latency in the setting of pPROM that includes ampicillin 2 g intravenously (IV) once, followed by 1 g IV every 6 hours for at least 48 hours are adequate for GBS prophylaxis. If other regiens are used, GBS prophylaxis should be initiated in addition.

¶ See Figure 8–7 for recommended antibiotic regimens.

** GBS prophylaxis should be discontinued at 48 hours for weomen with pPROM who are not in labor. If results from a GBS screen performed on admission become available during the 48-hour period and are negative, GBS prophylaxis should be discontinued at that time.

‡ Unless subsequent GBS culture prior to delivery is positive.

§§ A negative GBS screen is considered valid for 5 weeks. If a patient with pPROM is entering labor and had a negative GBS screen > 5 weeks prior, she should be re-screened and managed according to this algorithm at that time.

Fungal Infection (*Candida*)

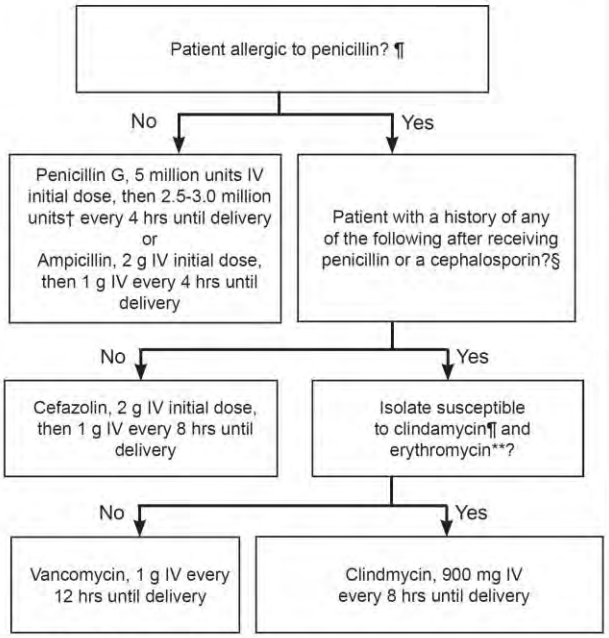
General Points

Infection due to *Candida* species is usually caused by *Candida albicans* and *Candida parapsilosis*. However, in some NICUs the incidence of fungemia and disseminated disease due to other species, such as *C. tropicalis, C. lusitiani, C. krusei,* and *C. glabrata,* also occur. 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 or anatomic site. Candidemia can occur with or without organ dissemination in patients with indwelling central lines. Systemic corticosteroid use as well as prolonged broad-spectrum antibiotics (especially third generation cephalosporins and meropenem) increases 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 infection can be made by isolation of Candida from blood, CSF, infected tissue, or urine obtained by suprapubic aspiration or catheterization (10^4 cfu/mL or greater). Invasive fungal dermatitis, which can be caused by Candida species 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, in addition to abdominal ultrasonography and echocardiogram are indicated (in most cases) in suspected disseminated candidiasis (i.e., all VLBW infants with candidemia). MRI of the brain with contrast is appropriate for evaluation of CNS Candida

Figure 8–7. Recommended regimens for intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal (GBS) disease* premature rupture of membrane (pPROM)



Abbreviation: IV = intravenously.

* Broader spectrum agents, including an agent active against GBS, might be necessary for treatment of chorioamnionitis.

† Doses ranging from 2.5 and 3.0 million units are acceptable for the doses administered every 4 hours following the initial dose. The choice of dose within that range should be guided by which formulations of penicillin G are readily available to reduce the need for pharmacies to specially prepare doses.

§ Penicillin-allergic patients with a history of anaphylaxis, angioedema, respiratory distress, or urticaria following administration of penicillin or a cephalosporin are considered to be at high risk for anaphylaxis and should not receive penicillin, ampicillin, or cefazolin for GBS intrapartum prophylaxis. For penicillin-allergic patients who do not have a history of those reactions, cefazolin is the preferred agent because pharmacologic data suggest it achieves effective intraamniotic concentrations. Vancomycin and clindamycin should be reserved for penicillin-allergic women at high risk for anaphylaxis.

¶ If laboratory facilities are adequate, clindamycin and erythromycin susceptibility testing (Box 3) should be performed on prenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis. If no susceptibility testing is performed, or the results are not available at the time of labor, vancomycin is the preferred agent for GBS intrapartum prophylaxis for penicillin-allergic women at high risk for anaphylaxis.

** Resistance to erythromycin is often but not always associated with clindamycin resistance. If an isolate is resistant to erythromycin, it might have inducible resistance to clindamycin, even if it appears susceptible to clindamycin. If a GBS isolate is susceptible to clindamycin, resistant to erythromycin, and testing for inducible clindamycin resistance has been performed and is negative (no inducible resistance), then clindamycin can be used for GBS intrapartum prophylaxis instead of vandomycin.‡ Unless subsequent GBS culture prior to delivery is positive.

infection. These diagnostic imaging studies should be performed in the late 2nd or third week of therapy since initial evaluation can be misleading early in the course of therapy.

Chemoprophylaxis

Several studies, including 3 multicenter randomized studies, have com- pared the effect of prophylactic intravenous fluconazole versus placebo for six weeks in very low or extremely low birth weight infants. Both colonization with Candida sp. 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 sp.* have emerged. The 2012 Red Book recommends routine fluconazole prophylaxis for infants weighting less than 1000 g at birth in NICU's where the incidence in the NICU is moderate (~5-10%) or high (>10%).

Treatment

Systemic candidiasis requires treatment with amphotericin B deoxycholate (1.0 mg/kg per day over 2 hours). Renal indices (serum BUN and creatinine) as well as serum potassium levels initially must be deter- mined 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. 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 require specific antifungal therapy. Indwelling vascular catheters must be removed as soon as feasible. Consultation with the Infectious Disease Service is suggested for any patient with systemic candidiasis or other invasive fungal infection.

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Gonococcal Disease

Most commonly, infection in the newborn will involve the eyes; other sites of infection septicemia, arthritis, meningitis, or scalp abscess.

Managing Asymptomatic Infants

If the mother has untreated gonorrhea at the time of delivery, the infant should receive a single dose of ceftriaxone (125 mg IM or IV) in addition to receiving eye prophylaxis. For low birth weight infants, the dose is 25 to 50 mg/kg, with a maximum of 125 mg. A single dose of cefotaxime (100 mg IM or IV) is an acceptable alternative.

Managing Symptomatic Infants

In cases of symptomatic neonatal disease, cultures of blood, cerebrospinal fluid, eye discharge, or other sites of infection (e.g., synovial fluid) should be obtained to delineate the extent of infection and determine the antibiotic susceptibility of the organism. Treatment with an extended spectrum (3rd generation) cephalosporin (e.g., ceftriaxone) is recommended.

Recommended antimicrobial therapy for localized infection, including ophthalmia neonatorum, is a single dose of either ceftriaxone (25 to 50 mg/kg IM or IV, not to exceed 125 mg) or cefotaxime (100 mg/kg IM or IV). For disseminated infection, including arthritis or septicemia, give parenteral ceftriaxone (25 to 50 mg/kg IM or IV) once a day for 7 days or, in neonates with hyperbilirubinemia, cefotaxime (50 to 100 mg/kg per day IM or IV) should be administered in 2 divided doses for 7 days. If meningitis is documented, treatment

should be continued for10 to 14 days. Both the mother and her sexual partner should be evaluated and treated appropriately.

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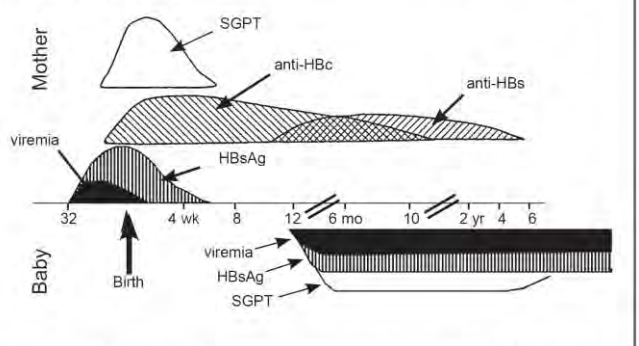
Hepatitis B

Vaccine Use in Neonates

Hepatitis B virus (HBV) may be transmitted vertically from mothers with acute hepatitis during pregnancy or with the hepatitis B surface antigen (HBsAg) carrier state. The risk of an infant with perinatal exposure is 70% to 90%.

- All mothers will 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 hepatitis screening are not otherwise available.
- The results of the maternal HbsAg test should be ascertained before the infant is discharged.

Figure 8–8. Time course of actue 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.

Maternal Screen Status

Positive

- Give Hepatitis B Immune Globulin (HBIG) 0.5 mL IM and Hepatitis B vaccine vaccine (10 mcg/mL) 5 mcg IM as a one-time order. Give concurrently with separate syringes at separate sites according to current dosage guidelines.
- Give to term or preterm infants within 12 hours of birth.
- For preterm 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. **(See Routine Vaccination.)**
- 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. Emphasize to the parents the importance of the follow-up.
- 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 after completion of at least 3 doses of a licensed Hepatitis B vaccine series at age 9 to 18 months.

Unknown

If the report of the maternal screen is not available within 12 hours of age, all infants should receive hepatitis B vaccine (10 mcg/mL) 5 mcg. If the mother is determined to be positive, infants with a birth weight greater than 2 kg should receive HBIG (0.5 mL) as soon as possible, but within 7 days of birth.

Preterm infants who weigh less than 2 kg at birth should be given HBIG (0.5 mL) as well as 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.

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

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 can 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.

Recommended Doses of Hepatitis B Virus Vaccines

Infants whose mothers' status is HBsAg positive, in addition to 0.5 mL HBIG IM

- Recombivax HB vaccine, pediatric formulation, 5 mcg (0.5 mL) IM
- Energix-B, 10 mcg (0.5 mL) IM

Infants whose mothers' status is HBsAg negative

- Recombivax HB vaccine, pediatric formulation, 5 mcg (0.5 mL) IM
- Energix-B, 10 mcg (0.5 mL) IM

Follow-up

The attending physician is responsible for follow-up and to order additional doses of vaccine. If the patient remains hospitalized, the NNP-NNC or physician will order hepatitis B vaccine doses 2 and 3 according to the schedule appropriate for that patient. At BTGH, signed consent must be obtained before administering any vaccine.

References

1. Hepatitis B. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2012

Hepatitis C Virus Infection

Hepatitis C virus is transmitted by perinatal exposure of blood from infected mothers. Serologic testing is recommended for anti-HCV in infants born to women previously identified to be HCV infected because about 5% of those infants will acquire the infection. Maternal coinfection with HIV increases transmission.

The duration of passive maternal antibody in infants is about 18 months. Therefore, testing for anti-HCV should not be performed until after 18 months of age.

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.

Herpes Simplex Virus (HSV)

Newborns of Mothers with Suspected HSV

Neonatal herpes simplex virus (HSV) infection is uncommon, but it may be devastating. The incidence has been estimated at 1/3,000 to 1/20,000 live births. Most infected neonates (70%) are born to women with neither a history of genital herpes nor active lesions. With primary infections 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.

Neonatal HSV can present as:

- disseminated, systemic infection involving the liver and lung predominantly, but also other organs including the central nervous system (CNS),
- localized CNS disease, or
- localized infection involving the skin, eyes, or mouth.

Disseminated HSV has a mean age of onset of 7 days, but can occur at any time between birth and 4 weeks of age. In the 2nd or 3rd week of life, infections most often involve the skin, eye, or mouth or any combination of those sites or the CNS (localized). Symptoms may arise as late as 6 weeks of age, but this is uncommon. 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, or symptoms of sepsis). Mortality and morbidity are high with disseminated or CNS disease, even with treatment. Virtually all HSV infections in neonates are symptomatic. Infection may be caused by either HSV type 1 or type 2. Other viruses (e.g., enterovirus [enterovirus, echovirus and coxsackie A & B virus] adenovirus) also may cause systemic disease that mimics overwhelming bacterial sepsis. Whenever systemic viral infection is suspected, appropriate viral cultures (i.e., skin lesions [e.g., vesicles], rectal, oropharynx, nasopharyngeal, urine, conjunctiva, CSF) should be obtained. CSF should be sent for cell count, glucose and protein, as well as culture. A CBC with differential and platelet count, along with electrolytes and liver and renal function tests should be performed. Polymerase chain reaction (PCR) studies on an aliquot of CSF for HSV DNA are particularly useful in evaluating HSV encephalitis. A whole blood sample for HSV PCR can be helpful in diagnosing HSV viremia or disseminated disease. PCR for enterovirus RNA in CSF can be performed to help distinguish between the 2 etiologies. Serological tests generally are not helpful.

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, a detailed history should be obtained to determine:

- when and how the diagnosis was made,
- the time of the last symptoms, and
- any treatment (if any) given to the mother.

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 that are 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 in the mother or the newborn that might increase disease transmission in infants found to be at risk include:

Maternal

- primary genital infection
- cervical or vaginal rather than vulvar lesions
- status (primary or recurrent) is unknown
- rupture of membranes more than 4 hours

Neonatal

- prematurity (37 or fewer weeks' gestation)
- fetal scalp monitor
- skin trauma or laceration at delivery

Management of At-Risk Infants

- Consultation with the Infectious Disease Service may be considered for **all at-risk infants** to ensure that HSV cultures are properly collected and transported to the Virology Laboratory at Texas Children's Hospital, if necessary, and to determine the need for antiviral treatment.

The infant may be observed in an open crib in continuous rooming in or in contact isolation. Contact precautions should be observed by anyone who handles the infant. (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. Infants with HSV infection should be placed in an isolation room (when available) with contact isolation.

- Breastfeeding is permitted unless breast or hand HSV lesions are present. The mother or 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.
- When an asymptomatic infant is ~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 taken before this time may reflect contamination rather than viral replication. In mothers with active genital herpes that represents a primary infection or the status is unknown, a neonatal blood HSV DNA PCR and ALT also should be obtained. Further, CSF cell count, chemistries, and HSV PCR should be gotten in these infants and acyclovir started. In mothers with known recurrent genital herpes a HSV blood PCR should also be obtained in addition to the cultures, but acyclovir should not be started.
- **After** cultures are obtained, apply trifluridine 1% solution 4 times a day to the eyes for 5 days.
- If HSV cultures are negative at 72 hours, then the infant is a candidate for home follow-up if all the events below can be arranged:
    1. Parent education about early symptoms and signs of HSV infection in the infant (skin lesions, poor feeding, fever, lethargy, etc.).
    2. Parent education regarding the use of the eye medication.
    3. Visiting nurse follow-up at home at 10 to 14 days of life. (BTGH)

Do not promise families discharge unless all 3 events have been arranged. If the events above cannot be accomplished, the infants must be observed in the hospital until the cultures are finalized as being negative or negative for 96 hours after being set up for cell culture, whichever is shorter.

If HSV cultures or blood PCR are positive, or if the infant develops symptoms consistent with HSV disease, CSF cell count, chemistries, and HSV PCR as well as a serum ALT and CBC diff and platelet count should be obtained and treatment started. Also, consultation with the Infectious Diseases and Ophthalmology Services may be considered to assist in the evaluation and management.

Treatment

- In most asymptomatic patients born of mothers with recurrent herpes, only ophthalmologic treatment is advised. However in certain situations, an infant's risk of infection is so great that empiric parenteral antiviral therapy may be warranted even before the onset of overt disease. **This includes all infants whose mothers have active lesions at birth and the infection is primary or the maternal status is unknown.** If the mother is found to have recurrent infection and the HSV PCR and cultures are negative, acyclovir can be stopped. Treat these and culture-positive or symptomatic infants as follows:
- Acyclovir 60 mg/kg per day in 3 divided doses for 14 days given intravenously if the disease is limited to the skin, eyes, or mouth; 21 days if disseminated, blood HSV DNA positive indicating viremia, or involved the CNS. The dose should be decreased in patients with impaired renal function. 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.
    - » In infants born to mothers with **primary HSV** infection, but CSF indices are not indicative of infection, blood and CSF PCR are negative and the serum ALT is normal, treat with intravenous acyclovir for 10 days.
- If ocular involvement, 1-2% trifluridine, 1% iododeoxyuridine, or 3% vidarabine as well as systemic therapy.

- The use of oral acyclovir suppressive therapy for 6 months following treatment of acute neonatal HSV disease has been shown to improve neurodevelopmental outcomes in infants with HSV CNS disease and to prevent skin recurrences in infants with any disease. The dose is 300 mg/m2/dose, administered 3 times daily.
- 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. Disseminated enteroviral infection currently has no treatment, although high dose IVIG has been used, especially if myocarditis is present (ID consult required).

References

1. Herpes Simplex. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2012.
2. Kimberlin DW, Baley J, Committee on Infectious Diseases, Committee on Fetus and Newborn. Executive summary: Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics. 2013;(2):383386.

Human Immunodeficiency Virus (HIV)

Perinatal transmission of HIV accounted for more than 90% of pediatric HIV infections in the U.S. in prior decades; at present it is virtually the only route of acquisition. Zidovudine therapy of selected HIV-infected pregnant women and their newborn infants reduced the risk of perinatal transmission by about two thirds. Present antiretroviral therapy for the pregnant mother with HIV infection is similar to that for non-pregnant adults (www.aidsinfo.nih.gov). The long-term affect of these drugs on a fetus is unknown and long-term follow-up of an infant is recommended. Delivery by elective cesarean section before rupture of the fetal membranes and onset of labor decreases transmission to 2% when a mother receives antiretroviral therapy.

Breastfeeding should be avoided since about 15% of perinatal acquisition of HIV occurs in this manner.

Arrange consultation with the Retrovirology or the Allergy & Immunology Service to assist with the diagnostic evaluation and management.

Treatment of Newborn Infants

- Zidovudine (AZT) should be given as soon as possible after birth to a newborn infant who is born of a mother with HIV infection whether or not she received treatment. 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 12 hours.
- Continue treatment for the first 6 weeks of life.

Dosage

- **ZDV ≥ 35 weeks gestation:** 4 mg per kg body weight per dose given orally twice daily, started as soon after birth as possible and preferably within 6-12 hours of delivery or, if unable to tolerate oral agents, 3 mg per kg body weight per dose intravenously, beginning within 6-12 hours of delivery, then every 12 hours though 6 weeks of age.
- **ZDV < 35 to ≥ 30 weeks gestation:** 2 mg per kg body weight per dose given orally (or if unable to tolerate oral agents, 1.5 mg per kg body weight per dose intravenously), beginning within 6-12 hours of delivery, then every 12 hours. At 15 days postnatal age, increase the dose to 3 mg per kg body weight per dose (or 2.3 mg per kg body weight per dose intravenously) every 12 hours.
- **ZDV < 30 weeks gestation:** 2 mg per kg body weight per dose given orally (or if unable to tolerate oral agents, 1.5 mg per kg body weight per dose intravenously) started as soon after birth as possible and preferably within 6-12 hours of delivery, then every 12 hours. At 4 weeks of age, increase the dose to 3 mg per kg body weight per dose (or 2.3 mg per kg body weight per dose intravenously) every 12 hours.

Additional Antiretroviral Prophylaxis for HIV-Exposed Infants of Women who received No Antepartum Treatment

In addition to ZDV as shown above, administer Nevirapine (NVP), 3 doses in the first week of life (1st dose within 48 hours of birth (birth-48 hours), 2nd dose 48 hours after 1st, 3rd dose 96 hours after 2nd).

- Birth weight 1.5-2 kg: 8 mg/dose PO
- Birth weight > 2 kg: 12 mg/dose PO

References

1. Human Immunodeficiency Virus Infection. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2012.
2. Jennifer S. Read and Committee on Pediatric AIDS. Human Milk, Breastfeeding, and Transmission of Human Immunodeficiency Virus Type 1 in the United States. *Pediatrics* 2003;112:1196–1205
3. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Anti-retroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Department of Health and Human Services, USA. July 31, 2012. http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf Accessed 6/20/2013.

Respiratory Syncytial Virus (RSV)

Infection Prophylaxis

RSV lower respiratory tract infection is the leading cause of hospitalization during the first year of life. 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 infection from RSV; it does reduce the severity of the illness.

Indications for Use of Palivizumab

When palivizumab prophylaxis is given, it should be started immediately before the RSV season begins and continued through the season except for eligible 32-35 week gestation infants. It does not interfere with the response to vaccines. The total number of doses for a season usually is 5, except for eligible 32-35 week gestation infants where a total of 3 doses is recommended. Palivizumab prophylaxis should be considered for:

- Infants and children younger than 2 years old who required medical therapy for chronic lung disease (CLD) within 6 months before the start of RSV season.
- Infants born at less than 32 weeks' gestation (31 weeks, 6 days or less) without CLD who are younger than 6 months of age, and those born at less than 28 weeks' gestation (27 weeks, 6 days or less) who are younger than 12 months of age at the beginning of RSV season.
- Infants born between 32 to 35 weeks' gestation (32 weeks, 0 days through 34 weeks, 6 days) who are less than 3 months of age at the beginning of RSV season or born during the RSV season and who are likely to have an increased risk of exposure to RSV and have at least 1 of 2 risk factors (i.e., a sibling less than 5 years of age: multiple births younger than 1 year of age do not qualify as fulfilling this risk factor or infant attends child care) should receive no more than 3 doses. If the infant reaches the age of 3 months during the RSV season, no further doses of palivizumab should be administered; thus, many infants will receive only one or two doses before they reach 3 months of age. Unless infants 32 to 35 weeks' gestation have additional risk factors, palivizumab is not recommended.
- An exception to the above is in infants with severe neuromuscular disease or congenital abnormalities of the airways. They should receive 5 doses. Every effort should be made to teach families how to control tobacco smoke exposure as high-risk infants should never be exposed to tobacco smoke.
- Infants who are 24 months of age or younger with hemodynamically significant cyanotic and acyanotic heart disease (i.e., receiving medication for the treatment of congestive heart failure, moderate to severe pulmonary hypertension, and cyanotic heart disease).

Palivizumab is **not** recommended to prevent nosocomial RSV infection.

Dosage

Administer the first dose of palivizumab immediately before hospital discharge during the RSV season (typically October through February), 15 mg/kg IM according to package instructions.

References

1. Respiratory Syncytial Virus. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2012.
2. Meissner HC, Long SS, and the Committee on Infectious Dis- eases and Committee on Fetus and Newborn, American Academy of Pediatrics. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003;112:1447–1452.
3. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003;112(6 Pt1):1442–1446.

Rotavirus

Rotavirus infection is highly contagious and is transmitted by the fecal-oral route. In Houston, it occurs only in late winter and spring. It causes diarrhea, emesis, fever and may rarely cause abdominal distention in premature neonates, as well as NEC. 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.

There are currently 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 of age and 14 weeks 6 days. 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).

Syphilis, Congenital

Evaluation

Evaluation and therapy of any infant thought to have congenital syphilis is primarily based on maternal history. All mothers are serologically screened for syphilis (RPR) at delivery. If the RPR is positive, a TP-PA is done. 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), maternal name, 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 being:**

- 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 is evaluated and treated as outlined below.

Assessment

Symptomatic Infants or Infants Born to Symptomatic Mothers

Full evaluation including CBC with diff/platelets, CSF cell count, protein concentration, VDRL, x-ray of long bones; 10 to 14 days therapy; report the case. Follow-up 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 single dose, IM benzathine PCN 50,000 units/kg/dose as a single dose if mother treated during pregnancy, or if mother was treated before pregnancy and infant follow-up is uncertain. If the RPR is > fourfold of the maternal titer, consider giving 10 days of intravenous therapy. No treatment needed for infants if mother was treated before pregnancy maternal titers are low and stable, and infant follow-up is certain. Follow-up by private pediatrician or by arrangement with ID service.
- **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 either 10 days of therapy or a single dose of IM benzathine PCN 50,000 units/kg/dose as a single dose (most experts recommend IV therapy). If any part of the evaluation is abnormal, not done, and uninterpretable or if follow-up is uncertain, the 10-day course is required. Follow-up by private pediatrician or by arrangement with ID service.
- **If evaluation is abnormal,** treat the baby with 10 days of IV penicillin. Follow-up by a private pediatrician or 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 penicillin (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, CBC, 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 every 12 hours for the first 7 days of life then every 8 hours for the next 3 days; total 10 days of treatment. For neurosyphilis, use the same dose divided every 6 to 8 hours. 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. Cannot be used for neurosyphilis.

ID Consultation

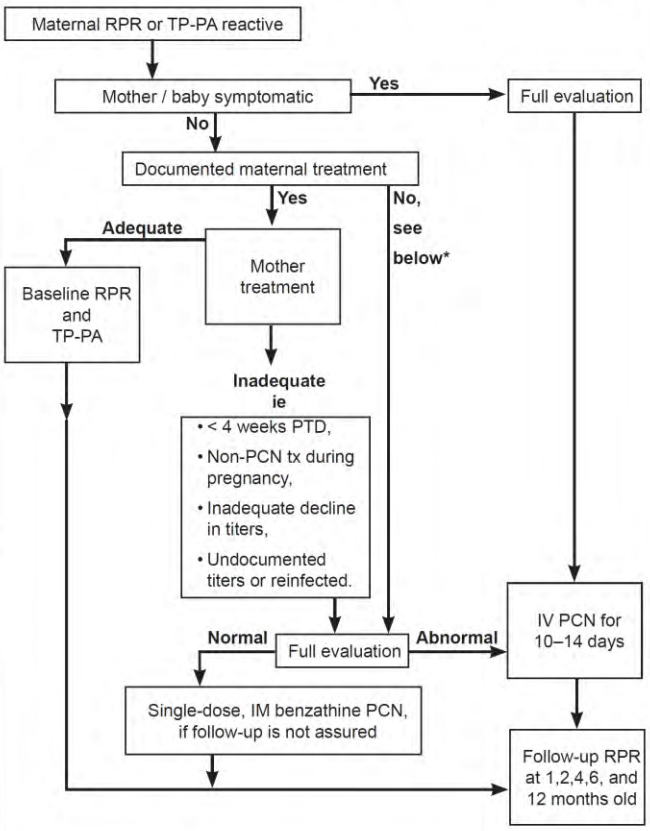
Neurosyphilis or severe symptomatic syphilis warrants an ID consult. Mothers who are HIV positive or have AIDS may

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 at 3, 6, and 12 months of age. 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.

Figure 8–9. Algorithm for evaluation of positive maternal RPR



*Management of infant born to a mother who **did not receive treatment and whose evaluation is *normal***: administer **either** 10–14 days of IV PCN (if follow-up can not be assured) **or** single dose, IM benzathine PCN at the discretion of the Neonatology Attending.

Table 8–1. 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 in 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.

References

1. Syphilis. In: Pickering LK, Baker CJ, Kimberlin DK, Long SS, eds. *Red Book: Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL. American Academy of Pediatrics;2012.
2. Zenker PN, Berman SM. (CDC). Congenital syphilis: trends and recommendations for evaluation and management. *Pediatr Infect Dis J* 1991; 10:516–1522.

Tuberculosis

Newborns of PPD-Positive Mothers

These guidelines pertain only to term, healthy newborns. They are nursed in the Level 1 setting.

- Mothers who have been screened (by history, prenatal records, and CXR) by the OB service and deemed non-infectious are allowed contact with their infants.
- Mothers with documentation of adequate management for TB disease or infection (prenatal records or TB Control records) and found to be noninfectious are not separated from their infants.
- 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) 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 PPDs, chest x-ray, chemoprophylaxis, follow-up, etc.
- When the mother is found to be non-infectious and the newborn is ready for discharge, discharge is not delayed pending screening of household contacts and family members.
- Consult Pediatric Infectious Disease for all cases where the newborn may need treatment or follow-up.

While congenital tuberculosis is rare, in utero infection can occur via the maternal blood stream. In a baby with suspected infection the following should be performed: a tuberculin skin test (TST), chest radiograph, lumbar puncture, and appropriate cultures of blood, urine and CSF collected. Immunologic based testing that measure ex vivo interferon- gamma production from T-lymphocytes in response to stimulation is not recommended to replace the TST even though most TSTs in newborns are negative. The placenta should always be examined and cultured.

Consult Pediatric Infectious Disease for all cases where the newborn may need treatment or follow-up.

References

1. Tuberculosis. In: Pickering LK, Baker CJ, Kimberlin DK, Long SS, eds. *Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2012.

Varicella-Zoster Virus (VZV)

Exposure in Newborns

Approximately 90% to 95% of women of childbearing age have antibody to varicella-zoster virus (VZV). Thus, infection during pregnancy is rare, occurring in only 0.7 of 1,000 pregnancies. The incubation period (exposure to onset of rash) usually is 14 to 16 days (range 10 to 21). Most neonatal transmission of VZV is vertical; however, intrauterine infection may occur albeit rarely.

Clinical Syndromes Varicella Embryopathy

Varicella embryopathy occurs during the 1st or early 2nd trimester. Clinical signs include cutaneous scarring of the trunk (100%), limb hypoplasia, encephalitis with cortical atrophy (60%), low birth weight (60%), and rudimentary digits, chorioretinitis or optic atrophy, cataracts or microphthalmia, and clubfoot (30% to 40%). The risk of defects in a woman having a first trimester VZV infection is approximately 2.3%.

Note: Infants with intrauterine infection do not require varicella-zoster immune globulin (VariZIG).

Perinatal Exposure

Classically, a mother's exposure to varicella occurs in the last 2 to 3 weeks of pregnancy. Neonatal disease generally occurs during the first10 days of life. **Timing is critical.**

- 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 or less before delivery or within 48 hours of delivery 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.

Varicella-Zoster Immune Globulin (VariZIG) and Intravenous Immune Globulin (IVIG)

VariZIG does not prevent varicella, though it might help to modify the clinical disease. If VariZIG is not available, IVIG may be used.

Indications for VariZIG

- 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 (28 or more weeks' gestation) whose mother has no history of chickenpox
- Exposed premature infants (less than 28 weeks' gestation or 1000 grams or less) regardless of maternal history

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.

VariZIG is not indicated for normal, term infants exposed to varicella including those whose mothers develop varicella more than 2 days postnatally.

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.

Dosing

To be most effective, VariZIG should be administered within 96 hours of exposure, ideally within 48 hours. 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. The FDA has extended the window of passive immunization after varicella exposure 4 to 10 days.

Indications for IVIG

However, if VariZIG is not available within 96 hours of exposure, intra- venous immune globulin (IVIG) can be used. 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. The indications for IVIG are the same as those for VariZIG. Any patient receiving IVIG should subsequently receive varicella vaccine, provided that the vaccine is not counter indicated. 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 (intravenousor oral acyclovir, oral valacyclovir, oral famciclovir) should be instituted immediately 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. An Infectious Disease Service consult is recommended.

Routine Immunization of Hospitalized Infants

For current recommended immunization schedules and current updates see http://www.cdc.gov/vaccines/schedules.

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 receive 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.

References

1. Varicella-Zoster Infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. 2012 *Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2012.
2. Centers for Disease Control and Prevention (CDC). FDA approval of an extended period for administering VariZIG for postexposure prophylaxis of varicella. *MMWR Morb Mortal Wkly Rep* 2012;61:212.

Medication Dosing

Usual dosing ranges of medications for newborns are detailed in **Table 9–1**

Managing Intravenous Infiltrations

(See Extravasation Guidelines – Texas Children's Hospital Formulary)

Infiltration of intravenous (IV) fluids and medications can be associated with damage to the skin and underlying tissue. Hypertonic solutions, dopamine and calcium 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.
- Discontinue peripheral IV if any of the following are observed: redness, blanching, edema, capillary refill greater than 3 seconds at the site, or difficulty irrigating the IV.
- Notify the physician after discontinuation of the peripheral IV if the site is edematous, red, blanched, or dark in color.
- Elevate the involved extremity.
- If the site is on the scalp, elevate the head of the bed.
- 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. Dilute 0.1 mL of hyaluronidase (200 units/mL) in 0.9 mL of normal saline for final concentration of 20 units/ml or order 5 single dose syringes from the pharmacy (20 units/mL). After skin preparation with providone-iodine and allowing the skin to dry for 1 minute, inject 0.2 mL (20 units/mL), subcutaneously or intradermally, into the leading edge of 5 separate extravasation sites with a 5- or 27-gauge needle. Needle should be changed after each 0.2 mL injection if injecting from a single syringe. Best results can be obtained if used within 1 hour of extravasation injury.

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 (PCA = gestational plus postnatal age). The recommendations in **Table 9–2** provide general guidelines for selection of initial antibiotic doses and intervals based upon categories of postmenstrual age 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.

Serum Antibiotic Level

The elimination half-life of gentamicin ranges from 3 to 11 hours. The elimination half-life of amikacin ranges from 4 to 7 hours. Measurement of serum levels is necessary when treatment is anticipated for longer than 48 hours or if renal dysfunction is present. Peak levels are obtained 30 minutes after the IV infusion is complete; a trough level is done immediately before the dose. Because aminoglycosides have potential for renal toxicity, measurement of BUN and creatinine and a urinalysis is recommended. Peak and trough levels should be drawn before and after the third dose and weekly during therapy. 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 10 and 20 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 not be performed until vancomycin has been administered for at least 72 hours or until after 3 doses, and 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

Table 9–1. Usual dosing ranges

Medication	Dose
***Adenosine**	IV: Initial: 0.05 mg/kg by rapid push over 1-2 seconds; flush with saline before and after use. Administer in a central catheter or at a peripheral IV site as proximal as possible to trunk (not in lower arm, hand, lower leg, or foot). If not effective within 2 minutes, increase dose by 0.05 mg/kg increments every 2 minutes to a maximum dose of 0.25 mg/kg or until termination of supraventricular tachycardia.
Albumin 25%	IV: 0.5-1 gram/kg per dose, over 2-4 hrs
Albuterol / levalbuterol metered dose	Acute exacerbation Inh: 2-4 puffs every 20 minutes for 3 doses, then 2-4 puffs every 2-4 hours for 24-48 hours as needed (albuterol preferred in patients without history of arrhythmias)
Bicarbonate, sodium	IV, code situation: 2 mEq/kg per dose at 1 mEq/kg per min (0.5 mEq/mL; 4.2% solution) (Use in this situation discouraged) IV, alkalization: 1-2 mEq/kg per dose over 30 min
Calcium chloride, 10%	IV: 20 mg/kg per dose at 50 mg per min
Calcium gluconate	IV: 100 mg/kg per dose (concentration: 100 mg/mL)
Captopril	PO: Initial: 0.01-0.1 mg/kg per dose every 8-24 hours; titrate dose up to 0.5 mg/kg per dose given every 6-24 hours. Lower doses (~1/2 of those listed) should be used in patients who are sodium and water depleted due to diuretic therapy.
Cardioversion (synchronized)	0.5 to 1 J/kg initially; If not effective, increase to 2 J/kg. Sedate if possible, but do not delay cardioversion.
Cosyntropin Low Dose Stim Test	IV: 1 mcg IV push once: Check cortisol levels before the dose and at 30 minutes and 60 minutes after the dose.
Dopamine	IV, continuous infusion: 2.5-20 mcg/kg per min
Dobutamine	IV, continuous infusion: 2.5-20 mcg/kg per min
Epinephrine (1:10,000)	IV: 0.1-0.3 mL/kg per dose (0.01-0.03 mg/kg) max 1 mL (0.1 mg) ET: 0.5 to 1 mL/kg per dose (0.05-0.1 mg/kg) IV continuous infusion: 0.1-1 mcg/kg per minute; titrate to desired effect
Fentanyl	IV: 1-2 mcg/kg per dose IV continuous infusion: Initial IV bolus: 1-2 mcg/kg, then start at 0.5-1 mcg/kg per **hour**; titrate by 1 mcg/kg per hour
Furosemide	IV, IM: 0.5-2 mg/kg per dose, every 12-24 hrs PO: 1-4 mg/kg per dose, every 12-24 hrs IV continuous infusion: 0.1-0.4 mg/kg per hr
Glucose, 10%	IV2 mL/kg per dose at 1 mL per min
Ibuprofen lysine	IV: For treatment of PDA: 10 mg/kg once, then 5 mg/kg q 24 for 2 doses (Base doses on birth weight)
Indomethacin	IV: For prophylaxis in neonates ≤ 26 6/7 weeks gestation or <800 grams birth weight: 0.1 mg/kg q 24 hours for 3 doses (Base doses on birth weight; administer within 12 hours of birth).
***Lidocaine**	IV: 1 mg/kg per dose, over 2 min for ventricular arrhythmia, not for SVT
Lorazepam	IV, anxiety and sedation: 0.05 mg/kg per dose (range 0.02-0.1 mg/kg) every 4-8 hrs IV, status epilepticus: 0.05 mg/kg per 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.
Midazolam	IV: 0.05-0.15 mg/kg per dose, over at least 5 minutes every 2-4 hours
***Milrinone**	IV: 0.375-0.75 mcg/kg per min as a continuous infusion; titrate dose to effect. Avoid in severe obstructive aortic or pulmonic valvular disease.
Morphine sulfate	IV, IM, SQ: 0.05-0.1 mg/kg per dose every 4-8 hrs; IV, continuous infusion: Initial bolus 0.05-0.1 mg/kg, then start at 0.01 mg/kg per **hour**; titrate by 0.01 mg/kg per hour
Naloxone (0.4 mg/mL)	IV, IM: 0.1 mg/kg per dose; repeat every 2-3 minutes if needed. **All pain relief will also be reversed.**
Pancuronium bromide	IV: 0.05-0.1 mg/kg per dose, every 1-2 hrs as needed; adjust dose as needed based on duration of paralysis required IV, continuous infusion: 0.02-0.04 mg/kg per **hour**
Phenobarbital	IV, loading dose: 15-20 mg/kg loading dose, then 5-10 mg/kg per dose at 20-minute intervals until the seizure is controlled or a total dose of 40 mg/kg is reached. IV, PO, maintenance dose: 3-4 mg/kg/DAY once daily; assess serum concentrations; increase to 5 mg/kg/DAY if needed (usually by second week of therapy)
Prostaglandin E (5 or 20 mcg/mL)	IV, continuous infusion: 0.05-0.1 mcg/kg per minute; adjust as needed to lowest effective dose (0.01–0.4 mcg/kg per minute)
Ursodiol	PO, cholestasis: 30-45 mg/kg per day given in 2-3 divided doses
Vecuronium	IV: 0.1 mg/kg per dose every 1-2 hours as needed; maintenance: 0.03-0.15 mg/kg per dose IV, continuous infusion: 0.06-0.09 mg/kg per hour

All drugs involve possible hazards. **The ordering physician must be aware** of specific indications, contraindications, and possible side effects of any medication.
*Use of these drugs must be discussed with the attending neonatologist before instituting therapy.

Table 9–2. Guidelines for initial antimicrobial doses and intervals based on categories of postmenstrual age
Antibiotic dosing based on Red Book® dosing guidelines when available

Amikacin:		
Weight-directed dosing: IV:		
Body weight <1 kg:		
PNA ≤14 days:	15 mg/kg	every 48 hrs
PNA 15-28 days:	15 mg/kg	every 24-48 hrs
Body weight 1-2 kg:		
PNA ≤7 days:	15 mg/kg	every 48 hrs
PNA 8-28 days:	15 mg/kg	every 24-48 hrs
Body weight >2 kg:		
PNA ≤7 days:	15 mg/kg	every 24 hrs
PNA 8-28 days:	15 mg/kg	every 12-24 hrs
PNA >28 days:	15-30 mg/kg/**DAY**	divided every 8 hrs
Meningitis: IV:		
Note: Use smaller doses and longer intervals for neonates <2 kg		
PNA ≤7 days & ≥2 kg:	15-20 mg/kg	every 12 hrs
PNA >7 days & ≥2 kg:	30 mg/kg	every 8 hrs
PNA >28 days:	20-30 mg/kg/**DAY**	divided every 8 hrs
Ampicillin:		
Bacteremia, Group B strep(presumed or proven)/Early onset sepsis: IM, IV**:**		
Note: Treatment of bacteremia without a defined focus should be for at least 10 days		
Body weight ≤2 kg:		
PNA ≤7 days:	100 mg/kg	every 12 hrs
PNA 8-28 days:	50 mg/kg	every 8 hrs
Body weight >2 kg:		
PNA ≤7 days:	100 mg/kg	every 12 hrs
PNA 8-28 days:	50 mg/kg	every 6 hrs
Meningitis, Group B streptococcal: IV:		
PNA ≤7 days:	100 mg/kg	every 8 hrs for 14 days
	some experts have also recommended 75 mg/kg every 6 hrs	
PNA >7 days:	75 mg/kg	every 6 hrs for 14 days
PNA >28 days:	75 mg/kg	every 6 hrs
General dosing, susceptible non-GBS infection: IM, IV:		
Body weight <1 kg:		
PNA ≤14 days:	50 mg/kg	every 12 hrs
PNA 15-28 days:	50 mg/kg	every 8 hrs
Body weight 1-2 kg:		
PNA ≤7 days:	50 mg/kg	every 12 hrs
PNA 8-28 days:	50 mg/kg	every 8 hrs
Body weight >2 kg:		
PNA ≤7 days:	50 mg/kg	every 8 hrs
PNA 8-28 days:	50 mg/kg	every 6 hrs
PNA >28 days mild/mod:	50-100 mg/kg/**DAY**	divided every 6 hrs
PNA >28 days severe:	100-150 mg/kg/**DAY**	divided every 6 hrs
Amoxicillin:		
UTI, prophylaxis (hydronephrosis, vesicoureteral reflux): PO**:**		
Oral:	10 to 15 mg/kg	once daily
Ceftazidime:		
General dosing, susceptible infection (non-CNS): IM, IV:		
Body weight <1 kg:		
PNA ≤14 days:	50 mg/kg	every 12 hrs
PNA 15-28 days:	50 mg/kg	every 8-12 hrs
Body weight 1-2 kg:		
PNA ≤7 days:	50 mg/kg	every 12 hrs
PNA 8-28 days:	50 mg/kg	every 8-12 hrs
Body weight >2 kg:		
PNA ≤7 days:	50 mg/kg	every 12 hrs
PNA 8-28 days:	50 mg/kg	every 8 hrs
PNA >28 days mild/mod:	90-150 mg/kg/**DAY**	divided every 8 hrs
PNA >28 days severe:	200-300 mg/kg/**DAY**	divided every 8 hrs
Meningitis: IV**:**		
PNA ≤7 days:	100-150 mg/kg/**DAY**	divided every 8-12 hrs
PNA >7 days:	150 mg/kg/**DAY**	divided every 8 hrs
PNA >28 days:	150 mg/kg/**DAY**	divided every 8 hrs
Clindamycin:		
General dosing, susceptible infection: IM, IV, PO:		
Body weight <1 kg:		
PNA ≤14 days:	5 mg/kg	every 12 hrs
PNA 15-28 days:	5 mg/kg	every 8 hrs
Body weight 1-2 kg:		
PNA ≤7 days:	5 mg/kg	every 12 hrs
PNA 8-28 days:	5 mg/kg	every 8 hrs
Body weight >2 kg:		
PNA ≤7 days:	5 mg/kg	every 8 hrs
PNA 8-28 days:	5 mg/kg	every 6 hrs
PNA >28 days mild/mod:	20 mg/kg/**DAY**	divided every 8 hrs
PNA >28 days severe:	40 mg/kg/**DAY**	divided every 6-8 hrs

Gentamicin:		
Postmenstrual Age-Based Dosing: IM, IV:		
≤29 weeks:		
PNA 0-7 days:	5 mg/kg	every 48 hrs
PNA 8-28 days	4 mg/kg	every 36 hrs
PNA ≥28 days:	4 mg/kg	every 24 hrs
30-34 weeks:		
PNA 0-7 days:	4.5 mg/kg	every 36 hrs
PNA ≥8 days:	4 mg/kg	every 24 hrs
35-43 weeks:		
All:	4 mg/kg	every 24 hrs
≥44 weeks:		
All:	2.5 mg/kg	every 8 hrs
Nafcillin:		
General dosing, susceptible infection (non-CNS): IM, IV:		
Body weight <1 kg:		
PNA ≤14 days:	25 mg/kg	every 12 hrs
PNA 15-28 days:	25 mg/kg	every 8 hrs
Body weight 1-2 kg:		
PNA ≤7 days:	25 mg/kg	every 12 hrs
PNA 8-28 days:	25 mg/kg	every 8 hrs
Body weight >2 kg:		
PNA ≤7 days:	25 mg/kg	every 8 hrs
PNA 8-28 days:	25 mg/kg	every 6 hrs
PNA >28 days mild/mod:	100-150 mg/kg/**DAY**	divided every 6 hrs
PNA >28 days severe:	150-200 mg/kg/**DAY**	divided every 4-6 hrs
Meningitis: IV**:**		
PNA 0-7 days:	75 mg/kg/**DAY**	divided every 8-12 hrs for 14-21 days
PNA 8-28 days:	100-150 mg/kg/**DAY**	divided every 6-8 hrs for 14-21 days
PNA >28 days:	200 mg/kg/**DAY**	divided every 6 hrs for 14-21 days
Penicillin GK:		
General dosing, susceptible infection (non-CNS): IM, IV:		
Body weight <1 kg:		
PNA ≤14 days:	25,000-50,000 units/kg	every 12 hrs
PNA 15-28 days:	25,000-50,000 units/kg	every 8 hrs
Body weight ≥1 kg:		
PNA ≤7 days:	25,000-50,000 units/kg	every 12 hrs
PNA 8-28 days:	25,000-50,000 units/kg	every 8 hrs
PNA >28 days mild/mod:	100,000-150,000 units/kg/**DAY**	divided every 6 hrs
PNA >28 days severe:	200,000-300,000 units/kg/**DAY**	divided every 4 hrs
Meningitis, Group B streptococcal: IV**:**		
PNA 0-7 days:	250,000-450,000 units/kg/**DAY**	divided every 8 hrs
PNA 8-28 days:	450,000-500,000 units/kg/**DAY**	divided every 6 hrs
PNA >28 days:	450,000-500,000 units/kg/**DAY**	divided every 6 hrs
Vancomycin:		
Weight-based dosing: IV:		
PNA <7 days:		
<1,200 g:	15 mg/kg	every 24 hrs
1,200 to 2,000 g:	10-15 mg/kg	every 12-18 hrs
>2,000 g:	10-15 mg/kg	every 8-12 hrs
PNA ≥7 days:		
<1,200 g:	15 mg/kg	every 24 hrs
1,200 to 2,000 g:	10-15 mg/kg	every 8-12 hrs
>2,000 g:	10-15 mg/kg	every 6-8 hrs
PNA >28 days mild/mod:	40-45 mg/kg/**DAY**	divided every 6-8 hrs
PNA >28 days severe:	45-60 mg/kg/**DAY**	divided every 6-8 hrs
Zidovudine:		
HIV infection, treatment: Use in combination with other antiretroviral agents; standard neonatal doses may be excessive in premature infants; PO, IV:		
Oral:		
GA <30 wks:	2 mg/kg	every 12 hrs
at 4 wks of age,	increase to 3 mg/kg	every 12 hrs
at >8-10 wks of age	increase to 12 mg/kg	every 12 hrs
GA ≥30 & <35 wks:	2 mg/kg	every 12 hrs
at PNA 15 days,	increase to 3 mg/kg	every 12 hrs
at >6-8 wks of age	increase to 12 mg/kg	every 12 hrs
GA ≥35 wks:	4 mg/kg	every 12 hrs
at >4 wks of age	increase to 12 mg/kg	every 12 hrs
Weight-directed dosing: PO:		
4-<9 kg:	12 mg/kg	every 12 hrs
IV: Use IV route only until oral therapy can be administered		
GA <30 wks:	1.5 mg/kg	
at 4 wks of age	increase to 2.3 mg/kg	every 12 hrs
at >8-10 wks of age	increase to 9 mg/kg	every 12 hrs
GA ≥30 & <35 wks:	1.5 mg/kg	every 12 hrs
at PNA 15 days	increase to 2.3 mg/kg	every 12 hrs
at >6-8 wks of age	increase to 9 mg/kg	every 12 hrs
GA ≥35 wks:	3 mg/kg	every 12 hrs
at >4 wks of age	increase to 9 mg/kg	every 12 hrs

Table 9–3. Intravenous Medication Infusion Chart			
Drug	**Dose**	**Infusion Time**	**Comments**
Acyclovir	20 mg/kg per dose	60 minutes	Incompatible with TPN
Amikacin	15 mg/kg per dose	30 minutes	Trough: just before dose (goal < 10) Peak: 30 minutes after dose infused (goal is dependent upon indication: 15-40)
Amphotericin B	1 mg/kg per dose	2-6 **hours**	Compatible with dextrose only; Incompatible with TPN & IL
Ampicillin	75-150 mg/kg per dose Px: 25 mg/kg per dose	15 minutes	Must use reconstituted product within 1 hr; Incompatible with TPN & IL
Caffeine citrate	Load: 20 mg/kg per dose Maint:5-10 mg/kg per dose	30 minutes 10 minutes	May need to give in two divided doses for older PMA patients
Calcium chloride	20 mg/kg per dose	60 minutes	Peripheral line: 20 mg/ml; Central line: 100 mg/ml
Calcium gluconate	100 mg/kg per dose	30 minutes	Peripheral line: 50 mg/ml; Central line: 100 mg/ml
Cefotaxime	50-75 mg/kg per dose	30 minutes	
Ceftazidime	30-50 mg/kg per dose	30 minutes	
Chlorothiazide	2-4 mg/kg per dose	30 minutes	Incompatible with TPN & IL
Clindamycin	5-13 mg/kg per dose	30-60 minutes	
Dexamethasone	0.25-1 mg/kg per dose	10 minutes	
Fentanyl	1-2 mcg/kg per dose	5 minutes	Rapid administration can cause chest wall rigidity
Fosphenytoin	2.5-4 mg/kg per dose	15 minutes	Monitor **phenytoin** trough just before dose (Goal: 10-20 mcg/mL) Incompatible with TPN & IL
Furosemide	0.5-2 mg/kg per dose	10 minutes	
Gentamicin	2.5-5 mg/kg per dose Synergy: 1-1.5 mg/kg per dose	30 minutes	Trough: just before dose (Goal < 1.5) Peak: 30 min after dose infused (Goal is dependent upon indication: 5-12)
Hydrocortisone	2.5-50 mg/m2 per dose 1 mg/kg per dose	30 minutes	
Ibuprofen	5-10 mg/kg per dose	15 minutes	Use birth weight for dosing. Incompatible with TPN & IL
Indomethacin	0.1 mg/kg per dose	30 minutes	Use birth weight for dosing. Incompatible with TPN & IL
Lorazepam	0.05-0.1 mg/kg per dose	5 minutes	Incompatible with IL
Midazolam	0.05-0.15 mg/kg per dose	5 minutes	Incompatible with TPN & IL
Morphine	0.05-0.1 mg/kg per dose	5 minutes	Histamine-related infusion reactions: Max concentration: 5 mg/mL
Nafcillin	25-50 mg/kg per dose	60 minutes	
Phenobarbital	Load:10-20 mg/kg per dose Maint: 2-6 mg/kg per dose	30 minutes 10 minutes	Start maintenance dose 12-24 hours after loading. Draw trough just before dose (Goal 20-40 mcg/mL) Incompatible with TPN & IL
Potassium Chloride	0.5-1 mEq/kg per dose MAX: 1 mEq/kg per dose	Max:1 mEq/kg per **hour**	Peripheral line: 0.08 meq/mL Central line: 0.3 meq/mL
Ranitidine	0.5-1.5 mg/kg per dose	5 minutes	
Rifampin	5-10 mg/kg per dose	30-180 minutes	Compatible with dextrose only May discolor body fluids to a red-orange color Incompatible with TPN & IL
Sodium Bicarbonate	1-2 mEq/kg per dose	Max: 1 mEq/kg per **hour**	Final concentration before administration should be 4.2%; Incompatible with TPN
Vancomycin	15-20 mg/kg per dose	60 minutes	Trough: just before dose (Goal: 10-20)

Metabolic Management 10

Fluid and Electrolyte Therapy

Water Balances

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. **(See Table 10-1)**

Table 10-1. 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 10-2** 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.

Table 10-2. Suggested Total Fluid requirements (ml/kg/day)*

Birth Weight (g)	Day 0-1	Day 2	>Day 4
<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 replacement fluid requirements vary widely depending upon environmental conditions, body weight, and gestation.

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 D5W plus added electrolytes in a composition similar to the fluid being lost **(See Table 10-3).**

Table 10–3. Composition of GI fluids

	Gastric (mEq/L)	Small bowel (mEq/L)
Na	H + equiv = 130–140	100–140
K	10–15	10–30
Cl	140	50–60
HCO_3	0	40–75

Short-term Intravascular Fluid Therapy (Day 1-3)

Goals of therapy include:

- Prevent hypoglycemia.
- Provide protein-sparing carbohydrate calories at basal metabolism rate (30-35 kcal/kg per day).
- Provide protein-sparing amino acids in appropriate VLBW infants (see Nutrition Support chapter)
- Limit negative fluid balance to 1-2% of birth weight per day.

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
(a) Fluid prescription = $D_{10}W$ + 2 mEq NaCl + 2 mEq KCl/100 mL to run at 8.3 mL/hour

Glucose Monitoring

Plasma glucose concentration should be monitored in all infants receiving intravenous (IV) glucose infusions. For most infants, daily monitoring is recommended until plasma glucose concentration is stable. **For known high risk patients (or those receiving insulin infusions) more frequent monitoring is necessary.**

At birth, the umbilical cord glucose is less than that in the mother (up to 1/3 lower level). Postnatal plasma glucose levels diminish and reach a nadir by 1-2 hours of age with mean values in the range of 50-60 mg/dL. Values may fall as low as 30 mg/dL in some asymptomatic infants. Healthy term or near term neonates should exhibit mean plasma glucose values > 60 mg/dL after 48 hours of life.

In certain categories of high risk infants, the blood glucose may not rise appropriately postnatally or may fall to subnormal levels.

These include hypoglycemia – high risk categories:

- Prematurity
- IUGR
- IDM
- LGA
- Sepsis
- Disorders producing hyperinsulinism
- Specific metabolic disorders

  Infants in these high risk groups should receive glucose screening between 30 minutes and 2 hours of life. Management strategy is that of assuring a progressive rise in postnatal plasma glucose values to > 45 mg/dL.

(**For detailed discussion of Transient Neonatal Hypoglycemia and Persistent Hypoglycemia see Chapter 3 - Endocrinology)**

Hyperkalemia

Hyperkalemia is a medical emergency that requires close observation of the patient, continuous cardiac monitoring, and measurement of serial potassium levels.

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 digoxin)
- 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 over 10 minutes. 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.**
- If the patient is acidotic, give sodium bicarbonate 1 to 2 mEq/kg IV over 10 to 20 minutes; 1 mEq/kg of sodium bicarbonate will lower potassium by 1 mEq by driving potassium ions into the cells. If the infant has a 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 effective). 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 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 bolus over one hour per pharmacy protocol with 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. 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.**

Hypocalcemia

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, 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.

Other Factors

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).

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. In particular, 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.

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. Immediately add maintenance Ca gluconate to the IV solution (500 mg/kg per day).

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 hours twice daily until the serum Mg normalizes (greater than 1.5 mg/dL).

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 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. 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. **(See Oral Therapy section below for dosing instructions.)**

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. (See 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, Good Start® 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. Good Start® 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 started with calcium gluconate tablets, 250 mg/kg/day divided into 4-6 doses daily (~25 mg/kg/day elemental calcium).

If calcium gluconate tablets are not available or infant is not responding well to calcium gluconate, use calcium lactate tablets. Start with 192 mg/kg/ day divided into 4-6 daily doses (~25 mg/kg/day elemental calcium). If this is tolerated for 3 days, the dose may be doubled, if necessary, to provide up to 50 mg/kg/day elemental calcium.

- Pt. may be discharged on Similac® PM 60/40 or Good Start® 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. 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.

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 1.60 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 of 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 severe 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.

Use of Sodium Bicarbonate in Acute Cardiopulmonary Care

Treatment of acidosis in neonates using sodium bicarbonate has been common for many years. However, evidence that correction of acidosis with sodium bicarbonate improves outcome of cardiopulmonary dysfunction remains lacking. Several lines of evidence suggest a much more limited role for this agent.

1. 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.
2. No human studies have demonstrated a beneficial effect of bicarbonate on survival or outcome following CPR. The NRP no longer recommends use of buffers during neonatal resuscitation.
3. Effect of bicarbonate infusion on blood pH, if any, is transient.
4. No studies have demonstrated increased survival or reduced morbidity in neonates with respiratory distress receiving sodium bicarbonate.
5. 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 acid such as lactate. None of these underlying disorders is corrected by sodium bicarbonate. The underlying mechanism itself should be the target of therapeutic intervention.
6. 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.

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 cardiology 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.

Persistent Metabolic Acidosis

Infants with chronic buffer loss or a persistent base deficit are a different clinical category. Examples include renal failure, GI losses from an ileostomy or chronic TPN use in VLBW babies. These infants have persistent metabolic acidosis without marked elevation in lactate levels.

Many, especially those ≤ 1500g, benefit from addition of acetate to their TPN or, uncommonly, to base supplementation 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.

Encephalopathy

A diagnosis of neonatal encephalopathy may be considered when an infant has both a change in mental status and an abnormal neurological examination. Alterations in mental status include hyperalertness, drowsiness, stupor, or even coma. Common neurological findings include abnormal tone (increased or decreased), seizures, non-habituating primitive reflexes, tremors, apnea, weak suck, and sometimes a bulging fontanel. The modified Sarnat classification **(see Table 11–1)** is the tool most frequently used to describe the severity of encephalopathy and is most appropriate for infants with hypoxic-ischemic encephalopathy (HIE).

Table 11–1. Modified Sarnat Criteria for Defining Encephalopathy

Category	Mild	Moderate	Severe
Level of Consciousness	Hyperalert	Lethargic	Stupor or coma
Spontaneous Activity	Normal	Decreased	No activity
Posture	Mild distal flexion	Strong distal flexion	Decerebrate/ extension
Tone	Normal	Hypotonia	Flaccid
Primitive Reflexes:			
Suck	Weak	Weak/absent	Absent
Moro	Strong	Incomplete	Absent
Autonomic System:			
Pupils	Dilated	Constricted	Deviated, Non-reactive
Heart Rate	Tachycardia	Bradycardia	Variable
Respiration	Normal	Periodic Breathing	Apnea

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: A clinical and electroencephalographic study. *Arch Neurol* 1976;33(10):696-705. Only newborns with moderate-to-severe encephalopathy should receive therapeutic hypothermia.

Neonatal encephalopathy may be seen in infants with:

- 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), or
- HIE.

The cause of the encephalopathy is not always immediately known, and automatically ascribing it to hypoxia-ischemia is not appropriate. However, certain peripartum scenarios (placental abruption, severe feto-maternal hemorrhage, maternal hypotension/shock, prolonged labor, multiple births, chorioamnionitis, placental insufficiency, IUGR) may place a newborn at increased risk for hypoxia-ischemia. Infants with hypoxic-ischemic injury severe enough to cause neurologic sequelae usually are severely depressed at birth (Apgar score ≤ 3 at 5 minutes of life), exhibit a significant acidosis (pH < 7 in cord arterial blood), and have evidence of injury to other organs (pulmonary, renal, hepatic, cardiac, bowel, bone marrow) along with the encephalopathy. Up to 10% of infants with HIE may not exhibit obvious multi-organ injury, even though encephalopathy may be severe.

Evaluation

Evaluation of an infant presenting with encephalopathy includes an in depth history and a complete neurologic examination; sequential neurologic examinations should be performed to assess what often is an evolving encephalopathic picture. The maximum Sarnat stage reached by an infant can provide prognostic information. The initial neurologic evaluation also includes initiation of continuous video EEG at admission (continues through rewarming) and MRI at 4–5 days of life. A head ultrasound (HUS) should also be performed to rule out severe intracranial hemorrhage and should be performed 8–12 hours after initiation of cooling. Additional evaluation includes CBC with differential and platelets, lumbar puncture, blood culture, blood glucose, calcium, magnesium and electrolytes. Depending upon the history and presentation, additional indicated studies may include blood ammonia level, serum and CSF lactate levels, serum and CSF amino acids, urine organic acids, and troponin I level. Evaluation of the placenta may indicate that infectious or clotting issues are involved in the etiology of the encephalopathy. If a hypoxic-ischemic etiology is strongly suspected, baseline hepatic and renal assessment, as well as an echocardiogram can be useful. If the infant's primary problems are hypotonia, respiratory depression, or both, spinal cord injury and neuromuscular diseases need to be considered.

Intervention/Therapies

Usual care for neonatal HIE is supportive intensive care which includes correcting metabolic and electrolyte disturbances, stabilizing pulmonary and hemodynamic instability, treating seizures, and monitoring other organ systems for dysfunction. Eleven international multicenter randomized clinical trials including 1,505 infants have addressed the safety and efficacy of therapeutic hypothermia as a therapy for HIE in newborns ≥35 weeks' gestation. According to the Cochrane review, therapeutic hypothermia if begun within 6 hours of birth, 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,

also found 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 NICHD concluded that therapeutic hypothermia, if offered, needs to be performed using a rigorous set of criteria and a published protocol.

Therapeutic hypothermia is available in the TCH NICU.

Treatment Criteria for Whole Body Cooling

1. ≥35 weeks' gestation, AND
2. Biochemical evidence of a hypoxic-ischemic event:
   a) pH ≤7.00 or base deficit ≥16 mmole/L on cord gas or within first hour of life (in any blood sample),

   OR

   b) if no blood gas, or pH 7.01–7.15, or base deficit between 10 and 15.9 mmole/L: presence of an acute perinatal event and an Apgar score <5 at 10 minutes of age or need for resuscitation for ≥10 minutes,

   AND
3. Evidence of moderate-to-severe encephalopathy – seizures or abnormalities in 3 of 6 Sarnat criteria for moderate or severe encephalopathy (level of consciousness, spontaneous activity, posture, tone, primitive reflexes [suck or Moro], and autonomic nervous system [pupils, heart rate, or respiration]). Mark "severe" encephalopathy if there are more signs and symptoms in the severe vs the moderate column. If the signs and symptoms are equally distributed between severe and moderate columns, the severity is based on the level of consciousness **(see Table 11-1).**

Cooling should be initiated within 6 hours of birth (including passive cooling). Passive cooling should be initiated at the referral hospital after the infant has been determined to be a candidate for therapeutic hypothermia, by having all heat sources removed from the infant. It is critical to tell the referring care providers to monitor temperature every 15 minutes, and if the temperature goes <33.5^{0}C, to turn on the radiant warmer until the transport team arrives to prevent overcooling. Active servo-controlled therapeutic hypothermia (with continuous rectal temperature) will be used during transport from the referral hospital to the TCH NICU unless infants are transferred from hospitals within the Texas Medical Center (since infants from nearby hospitals may be better served by getting to TCH as soon as possible to receive the definitive therapy instead of taking the time to initiate active cooling). For inborn infants, if the determination is made that a newborn is a candidate for therapeutic hypothermia, then passive cooling should be initiated and the infant transported to the TCH NICU.

In the TCH NICU cooling and rewarming is done according to specific protocols (Refer to nursing bedside manual for complete details of process). 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. Pediatric Neurology Service should be contacted for initiation of continuous bedside EEG. It is desirable to have arterial and central venous access during cooling, if possible. Low-dose morphine should be used to prevent agitation or shivering that occurs during therapeutic hypothermia.

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. Infants receiving whole body cooling will receive a Developmental Pediatrics consult and evaluation prior to discharge. Follow-up post hospitalization will include Neurology clinic visit with a brain MRI at 1 year of age, and TCH Meyer Developmental Center clinic visits at 6 months, 1 year, and 18 months of age. At 18 months, a full Bayley examination will be performed.

TCH Total Body Cooling Protocol

All supplies needed for therapeutic hypothermia are located in the TCH Swing Unit. Please refer to bedside manual for complete details of cooling process.

- Have cooling blanket ready on the radiant warmer (or use cooling blanket from transport)
- Core body temperature measured by esophageal temperature probe with placement confirmed by CXR to be located at 2/3 the distance of the esophagus
- Therapeutic hypothermia for 72 hours
- All external heat sources turned off
- Desired patient temperature is set at 33.5°C with goal temperature 33.5 ± 0.1°C
- Vital signs and urine output recorded every hour
- Total fluid goal on day 1 of 40–45 ml/kg/day (do not give fluid boluses simply for low urine output)
- NPO during cooling and rewarming
- Record initial and daily Sarnat stage (dot phrase: ".Sarnat") in the History and Physical (EPIC) and daily progress notes
- Neurologic assessment every hour until goal patient temperature achieved, then every 4 hours
- Continuous video EEG initiated immediately on admission
- Morphine drip (load with 0.1 mg/kg and then begin at 0.01 mg/ kg/hr and adjust dose to limit shivering (>0.03 mg/kg/hr is rarely needed) for the whole 72 hours of cooling
- Cranial ultrasound (with resistive index) at 8–12 hours after initiation of cooling
- Reposition infant every 2 hours while cooled
- Recommended labs to be drawn during cooling (or more often as needed):
  - » Glucose: on admission, then every hour x 6 hours, then every 12 hours x 2, then daily x 4 days

- » CBC with differential and PLT: on admission, then daily x 3 days
- » Obtain blood culture on admission
- » PT, PTT, fibrinogen: on admission, then daily x 3 days
- » Chem10, ionized calcium: on admission, then daily x 3 days
- » Arterial blood gases: on admission, then every 6 hours x 4, then every 12 hours x 2, and then daily x 3 days (or more frequently as needed)
- » LFTs: on admission and then daily for 3 days
- » Use order set: IP NEO THERAPEUTIC HYPOTHERMIA ADMISSION (EPIC)
- » Strongly consider infection as a cause of encephalopathy and obtain a blood culture on admission and begin antibiotics
- » Use NEO IP HIE H&P for Admission History and Physical (EPIC)
- » Rewarming begins after 72 hours to increase temperature 0.5°C every hour until goal temperature of 36.5°C
- » Schedule neonatal head MRI (including spectroscopy) for day 4–5 (NO CONTRAST)

Outcomes

The outcome of neonatal encephalopathy depends upon the etiology. In infants with encephalopathy due to a metabolic disorder, outcome will be related to the specific disorder. Similarly, outcome of encephalopathy related to an infectious etiology will depend upon the specific infection. If encephalopathy is due to hypoxic-ischemic injury, outcome is good if the infant has an EEG and a neurologic exam that are normal by 7 days of age. Outcomes also can be related to maximum Sarnat stage reached which is an indication of the severity of the neonatal encephalopathy. 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 severe neurodevelopmental disability at 18 months, and the benefits noted at 18 months persist to early school age.

Infants receiving whole body cooling should be referred to the TCH Meyer Developmental Center for long-term follow up.

Seizures

Definition

An epileptic seizure is defined as abnormal electrical activity in the brain that may or may not produce physical signs and symptoms which may include convulsive activity, small jerks or twitches, thought disturbances or a combination of such symptoms. The type of observed during seizures depends on the location and extent of the abnormal activity in the brain, its cause, the patient's age and general state of health.

Incidence

Seizures are frequent during the neonatal period. The incidence varies between 1–5/1000 neonates. It has been noted that premature infants are at increased risk compared to term infants.

Background and Pathogenesis

Acute symptomatic seizures are due to a specific provoking condition and are one of the commonest types of neonatal seizures. Therefore, a key factor in treating neonatal seizures is the accurate diagnosis and treatment of the underlying etiology.

Seizures may potentially exacerbate pre-existing brain injury through the following mechanisms:

Hypoventilation/apnea – resultant hypoxia and ischemia or a combination of both may cause brain injury by precipitating cardio- pulmonary collapse and hypercapnia may increase intracranial pressure by increasing cerebral blood flow.

Signs and Symptoms

Increased blood pressure – increase in the intracranial pressure.

Hypoglycemia – increased consumption secondary to anaerobic metabolism.

Increased neurotransmitter release (Excitatory amino acids) – may damage neurons.

At least some of the adverse outcomes above may be prevented by appropriate management implemented in a timely fashion and by controlling seizures.

Diagnosis

Neonatal seizures are classified as epileptic and non-epileptic. Epileptic seizures occur when there is an abnormal electrical discharge and can include tonic, clonic, and myoclonic seizures. Non-epileptic seizures may be subtle and are often associated with pedaling and posturing movements related to brainstem release phenomena. It may be difficult to differentiate epileptic from non-epileptic seizures at the bedside, particularly among premature infants. Eye deviation, blinking, fixed stare, repetitive mouth and/or tongue movements, apnea, pedaling, tonic posturing of limbs can be manifestations of seizures, immature reflexes or simply the sequelae of other illnesses.

The most common etiologies of neonatal seizures are listed in **Table 11-2.** The initial evaluation includes a sepsis work up including a lumbar puncture, metabolic studies (blood glucose, ionized calcium, magnesium, phosphorus, electrolytes, ammonia and lactate) and screening for maternal drug exposure. Ideally, an EEG should be obtained to document the presence/absence of epileptiform activity prior to the initiation of any anticonvulsant therapy; however, there may be occurrences where the clinical events are obviously epileptic in nature that warrant immediate treatment and may not require an EEG. The content and extent of additional laboratory tests (serum amino acids, urine organic acids) will depend upon the results of the initial evaluation, findings on physical examination, perinatal history and response to treatment. Imaging studies are important if intracranial processes are suspected. Head ultrasound can detect major intracranial hemorrhages and structural abnormalities, but may

not detect superficial cortical hemorrhage, such as subarachnoid bleeding. CT brain scan is helpful in detecting gross abnormalities, hemorrhagic lesions and calcifications, whereas MRI is the study of choice for the delineation of infarctions and more subtle white or gray matter abnormalities.

Table 11-2. 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
	Hypocalcaemia
	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

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 – bolus of 2 ml/kg of D10W followed by IV glucose infusion to stabilize the blood glucose level.

Hypocalcemia – (see Chapter 10 for management of late onset seizures due to 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 follows zero order kinetics and has greater protein binding compared to phenobarbital, 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 management of neonatal seizures is listed below:

- **Phenobarbital:** 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. The desired phenobarbital level is 20–40 mcg/L. Be aware of respiratory depression associated with administration of phenobarbital that may warrant intubation.
- **Lorezepam**: given as an initial intravenous bolus of 0.1 mg/kg. An additional intravenous bolus dose of 0.1–0.15 mg/kg can be given 15–30 minutes later, while awaiting other AEDs
- **Fosphenytoin:** (20 mg/kg) given intravenously at a rate of 0.5-1 mg/kg/min.
- **Levetiracetam:** 10 mg/kg/day divided twice daily; increase dosage by 10 mg/kg over 3 days to 30 mg/kg/day; additional increases up to 45-60 mg/kg/day.

If an infant continues to exhibit seizure activity, a neurology consultant should decide the need for and the type of additional therapy. Vitamin B6 (pyridoxine) should be considered for refractory seizures. It should be noted that there are no randomized clinical trials evaluating the efficacy or safety of levetiracetam (Keppra®). However, Keppra® has a well-tolerated safety profile that includes low protein binding and no drug-to-drug interactions and is currently being explored as an AED in neonatal seizures. No long-term outcomes studies exist at this time. Despite this, a recent survey conducted by the Child Neurology Society indicated that it is used frequently to treat neonatal seizures.

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, anticonvulsant therapy 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 the medications 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 recommend that ongoing treatment be limited to 1 agent, if possible, and be administered for the shortest possible time period. It would be an infrequent occurrence that AEDs would need to be continued beyond discharge from the NICU.

Cerebral Hemorrhage and Infarction

Periventricular, Intraventricular Hemorrhage (PIVH)

Periventricular, intraventricular hemorrhage (PIVH) is 1of 2 major neuropathologies of prematurity and is a major cause of death in pre- mature 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 fibrinolyic 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. 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 under- stood, 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.

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

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. **(NICHD Workshop-Pediatrics 2007;120:609 and Stroke 2008;39:2644).**

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 (Stroke 2008;39:2644 and Chest 2008;133:887s).**

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 **(see references above).**

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 a particular 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

(See Normal Newborn chapter, section on Dermatologic: Extracranial Swelling.)

Skull Fractures

(See Normal Newborn chapter, section on Neuromusculoskeletal.)

Subgaleal Hemorrhage

(See Normal Newborn chapter, section on Dermatologic: 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, sub- arachnoid, 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 intra- cranial pressure (full fontanel, hypertension, bradycardia, and irregular breathing) close observation for signs of herniation is warranted, and a neurosurgical consult obtained in the event that decompression is needed.

Brachial Palsies and Phrenic Nerve Injury

(See Normal Newborn chapter, section on Neuromuscular.)

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 include 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.

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.

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 recent randomized trial of prenatal vs. postnatal repair of myelomeningocele demonstrated that prenatal surgery reduced the need for shunting and improved motor outcomes at 30 months when surgery was performed <26 weeks' gestation. The trial was stopped for efficacy of prenatal surgery. However, the prenatal surgery was associated with maternal risks (placental abruption, spontaneous rupture of membranes, uterine dehiscence) and fetal risks (preterm delivery, RDS and apnea). This surgery is currently available in the TCH Fetal Center.

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 particular 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 the majority of 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.

Meningomyelocele – mortality is 10–15%; 74% of survivors will be able to ambulate; 73% will exhibit an IQ >80.

Drug-exposed Infants

Nursery Admission

Infants with intrauterine exposure to drugs other than marijuana or cocaine (babies with a positive urine drug screen or whose mothers have a history of drug use) should be admitted to the Level 2 NICU. Infants with intrauterine exposure only to marijuana or cocaine are admitted to the Level 1 nursery, but should be treated the same as all other drug- exposed babies. Common indications for toxicology testing in the neonate include: no or limited maternal prenatal care, placental abruption, preterm delivery, intrauterine growth restriction and cardiovascular accident of mother or child. First line workup for suspicion of drug-exposed infants should begin with a meconium drug screen with the first stool as it reflects drug exposure that occurred throughout the third trimester of pregnancy. Meconium toxicology screen is the most comprehensive and reliable test in the newborn period

with results returning in 1-4 days. Urine screen (15–20 mL) can also be done; however, it only reflects exposure in the previous 48 hours.

Observation of drug-exposed infants for any indications of withdrawal is essential. A scoring system such as the Neonatal Abstinence Syndrome (NAS) **(Finnegan 1975; Zahorodny 1998)** can be used to document signs and symptoms, lending consistency to the patient observations and providing a tool to guide treatment decisions.

Maternal Drug and Alcohol History

A thorough history of maternal drug and alcohol use during pregnancy is essential to management of the newborn infant. If a history is not avail- able (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, synthetic narcotics (pentazocine, hydromorphone, methadone), diet pills, etc.
  - » **over-the-counter** – dextromethorphan, bromides, etc.
- Pattern of use (amount, frequency, duration of drug use, with detailed history especially during last trimester of pregnancy).
- Treatment (involvement in drug treatment or voluntary detoxification during pregnancy).

General

At-risk asymptomatic infants need to be observed for 5 days. 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.
- Infant is AGA or LGA and ≥37 weeks' gestation.
- No dysmorphic features.

Breastfeeding

Breastfeeding is contraindicated with maternal use of cocaine, diazepam, lithium and possibly phenothiazines, but it is not contraindicated with commonly used stimulants, sedatives or narcotics.

Discharge

The unit social worker and drug abuse counselors will assess the mother and the home situation. 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.

Treatment of Withdrawal

Non-pharmacologic Measures

Conservative measures are instituted with the onset of early signs of withdrawal (e.g., tremors, irritability, and increased activity). Supportive measures include swaddling or containment, peaceful sensory environment, frequent small feedings if vomiting/diarrhea present, massage, rocking or rhythmic movement and nonnutritive sucking.

Pharmacological Measures

Pharmacological therapy is indicated, if non-pharmacologic measures fail to control clinical signs and symptoms of withdrawal, including irritability that interferes with normal sleep patterns, vomiting or diarrhea, hyperactivity/hyperreflexia, hyperthermia, seizures. Treatment decisions should be guided by scoring of withdrawal signs and symptoms using a tool such as the NAS **(See Table 11–3)**. An average of daily scores or trending of scores rather than a single score should be used. NAS is done every 4 hours and then averaged every 24 hours.

- Scores <8 indicate that symptoms are controlled.
- Scores > 12 or 13 require immediate treatment.

After medication is discontinued, the infant needs to be scored for recurring signs/symptoms of withdrawal for 24–48 hours before hospital discharge. Pain assessment should be continued during opioid weaning. If risk factors for pain are present and/or an infant has elevated pain scores or exhibits physical and/or behavioral signs of pain, opioid weaning is deferred and pain is managed.

For opiate withdrawal – neonatal morphine solution (oral) initiated at 0.05 mg/kg every 4 hours (0.3 mg/kg/day) and increased by 0.02–0.03 mg/kg as often as every 4 hours until the signs and symptoms of withdrawal improve (maximum 0.8 mg/kg/day). After signs and symptoms of withdrawal have been stabilized for 3 days, consider weaning (decreasing the daily dose by 10% of the original dose each time). Treatment decisions should be guided by scoring of withdrawal signs and symptoms using a tool such as the NAS (see above). To guide medication changes, use an average of daily scores or trending of scores rather than a single score.

After medication is discontinued, observe 24–48 hours before discharge.

Sedative-hypnotic withdrawal – treat with phenobarbital 5–8 mg/kg/ day in 2 divided doses. After symptoms are controlled, taper by stepwise reduction (25% of the original dose) over 1–2 weeks.

Opioid Withdrawal Guidelines

Opioid tolerance and dependence may occur in neonates with in utero exposure or in neonates who received analgesic therapy postnatally. If risk factors for pain are present 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.

Opioid Weaning Options

Conversion to methadone should only be considered in patients who are not dependent upon their opioid for pain or sedation and who require long-term weaning.

Three opioid weaning options (based on duration of opioid therapy and/or dosage during therapy):

Table 11–3. Neonatal abstinence scoring system

	Date		time												Comments
	Weight		am						pm						
System	Signs and Symptoms	Score	7	8	9	10	11	12	1	2	3	4	5	6	
Central Nervous System Disturbances	Excessive high-pitched (or other) cry (cry face)	2													
	Continuous high-pitched (or other) cry (cry face)	3													
	Sleeps less than 1 hour after feeding	3													
	Sleeps less than 2 hours after feeding	2													
	Sleeps less than 3 hours after feeding	1													
	Hyperactive moro reflex	2													
	Markedly hyperactive moro reflex	3													
	Mild tremors disturbed	1													
	Moderate-severe tremors disturbed	2													
	Mild tremors undisturbed	3													
	Moderate-severe tremors undisturbed	4													
	Increased muscle tone	2													
	Excoriation (specific area)	1													
	Myoclonic jerks	3													
	Generalized convulsions	5													
Metabolic , Vasomotor, & Respiratory Disturbances	Sweating	1													
	Fever less than 101 (99–100.8 F / 37.2–38.2 C)	1													
	Fever greater than 101 (38.4 C and higher)	2													
	Frequent yawning (greater than 3–4 times / interval)	1													
	Mottling	1													
	Nasal stuffiness	1													
	Sneezing (greater than 3–4 times / interval)	1													
	Nasal flaring	2													
	Respiratory rate greater than 60 / min	1													
	Respiratory rate greater than 60 / min with retractions	2													
Gastrointestinal Disturbances	Excessive sucking	1													
	Poor feeding	2													
	Regurgitation	2													
	Projectile vomiting	3													
	Loose stools	2													
	Watery stools	3													
	Total score every 2 to 4 hours														
	Signature of scorer(s)														

Use of Neonatal Abstinence Scoring Sheet

Neonatal abstinence score sheet. Check sign or symptom observed at various time intervals and add scores for total at each evaluation. (Modified from Finnegan LP, Kaltenbach K: The assessment and management of neonatal abstinence syndrome. In Hoekelman RA, Nelson N, editors: Primary pediatric care, ed 3, St Louis, 1992, Mosby.)

Staff will begin tool at the most appropriate time and to choose the best scoring intervals, if necessary.

Baseline scores should be taken prior to weaning or a minimum of 2 hours after admission or both.

Scoring interval is every 4 hours.

Scoring for infants demonstrating scores 8 or higher automatically becomes ever 2

Pharmacologic intervention is needed when the total abstinence score is 8 or higher for 3 consecutive scorings or when the average of 3 scores is 8 or higher.

Immediate action is needed for scores of 12 or higher.

All observations are scored within the scoring interval and not at one particular time. (Water stools seen 2 hours earlier would be scored at the next scoring interval.)

Reflexes should be elicited only when infant is awake.

Count respirations for a full minute.

Prolonged crying is scored whether or not it is high-pitched.

NAS monitoring can be stopped 48 hours after opioid has been discontinued if NAS scores continue to be between 0 and 7.

Short-term opioid therapy (<5 days)

- Therapy can be discontinued without weaning. Intermediate opioid therapy (5 days to 2 weeks)
  - » Wean 10% of original dose every 2–3 days if NAS score ≤ 7.
  - » Stop NAS monitoring 48 hours after opioid has been discontinued if NAS scores continue ≤7.

Long-term opioid therapy (longer than 2 weeks and/or maximum fentanyl > 4 mcg/kg/hour or morphine >0.1 mg/kg/hr)

- » Wean opioid as described under intermediate weaning option, **OR**
- » Start methadone.

- 0.1 mg/kg/dose IV q 8 hours if current dose is <0.1 mg/kg/hr morphine or 5 mcg/kg/hr fentanyl.
- 0.2 mg/kg/dose IV q 8 hours if current dose is >0.1 mg/kg/hr morphine or 5 mcg/kg/hr fentanyl.
- Decrease the opioid infusion by 33% of the original dose after the second dose of methadone.
- Decrease the opioid infusion by the same amount (33% of original dose) after the third dose of methadone.
- Discontinue the opioid infusion after the fourth dose.
- Change dosing interval to every 12 hours when NAS score is 7 or less for 2–3 days.
- Wean by 10% decrements of the maximum dose (in mg/kg/dose) every 2–3 days if NAS score ≤7.

Example:

A 4 kg patient's original dose of methadone = 0.8 mg IV q12h (0.2 mg/kg/dose)

- **10% of 0.2mg/kg/dose = 0.02 mg/kg/dose**
- **0.2 mg/kg/dose – 0.02 mg/kg/dose = 0.18 mg/kg/dose**
- **0.18 mg/kg/dose × 4 kg = 0.72mg PO q12h**

Use this 10% of maximum dose as your weaning factor for the remainder of the wean.

- Discontinue when dose is 0.05 mg/kg/day and NAS score ≤7.
- Stop NAS monitoring 48 hours after methadone has been discontinued if NAS scores continue ≤7.
- Delay hospital discharge until at least 3 days after methadone has been discontinued.

When an infant is tolerating enteral feedings, treatment with an oral opioid (morphine or methadone) should be considered. The conversion factor for IV to PO methadone is 1:1. The conversion factor for IV to PO morphine ranges from 1:1 to 1:2.

Additional Considerations

Methadone

- Infant receiving scheduled phenobarbital, phenytoin or rifampin, may be need higher doses, because of the induction of liver enzymes leading to a decrease in plasma levels.
- Methadone should be used with caution in infants with severe hepatic impairment due to limited availability of data on clearance.
- Administer 50–75% of normal dose for infants with severe renal impairment (CCR < 10 mL/minute/1.73 m2).
- Infants receiving fluconazole, erythromycin or amiodarone may need lower dose due to an increased narcotic effect.

Pain Assessment and Management

The goal of pain management is to minimize procedural, post-operative or disease-related pain. **(Table 11–4)**

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 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 in an effort 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).

Table 11–4. Suggested management of procedural pain in neonates at Baylor College of Medicine affiliated hospital NICUs

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. Copyright © 2002 Section of Neonatology, Baylor College of Medicine. All rights reserved.

- 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 1procedure = 0.6 mL.**
  - » Infants 35 weeks or more corrected age: 1 mL/dose every 2 minutes up to 3 doses, maximum dose for 1procedure = 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.

Morphine Sulfate

- **Intermittent IV dose –** 0.05–0.1 mg/kg over 5 to 10 minutes every 3–4 hours
- **Intermittent PO dose** – 0.2–0.5 mg/kg every 4–6 hours
- **Continuous IV infusion dose** – loading dose is 100–150 mcg/kg (0.1–0.15 mg/kg) over 1 hour followed by a continuous infusion of 10–20 mcg/kg/hr (0.01–0.02 mg/kg/hr).

Fentanyl Citrate

- **Intermittent IV dose –** 1–2 mcg/kg/dose over 5–10 minutes every 2 hours
- **Continuous IV infusion dose** – 1–5 mcg/kg/hr

While opioid-induced cardiorespiratory side effects are uncommon, neonates should be monitored closely during opioid therapy to prevent adverse effects. **Longer dosing intervals often are required in neonates less than 1 month of age due to longer elimination half-lives and delayed clearance of opioids as compared with adults or children older than 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. **(See section Opioid Weaning Guidelines in this chapter.)**

Acetaminophen is a non-steroidal anti-inflammatory drug commonly used short-term for mild to moderate pain in neonates. Intermittent dose is based on weight as follows:

- 1.5–1.9 kg 20 mg orally every 12 hours
- 2–2.9 kg 30 mg orally every 8 hours
- 3–3.9 kg 40 mg orally every 8 hours
- 4–5.2 kg 60 mg orally every 6 hours

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 11–4.**

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Normal Newborn 12

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 can occur in the mother's room with intermittent assessment by nursing personnel.**

Routine Care

Bathing

A newborn's first bath usually is given at 3 to 6 hours of life when stability through the transitional period has been demonstrated. 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 only mild, non-perfumed soaps. Skin folds, such as behind the ear, in the neck, and in the groin, should get extra attention. The skin should be patted dry after bathing. Hair should be shampooed at least twice a week with baby shampoo.

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 separates from the abdomen on average 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. Epiphora (excess tearing) usually does not occur until after the first 3 weeks of life. Although the usual cause of epiphora is a blockage of the nasolacrimal ducts, the possibility of congenital glaucoma is an important consideration in the differential diagnosis. Less commonly, tearing can result from dacryocystitis. 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; **these babies should be referred to ophthalmology for follow-up.** The bulbar and palpebral conjunctivae are normally moist and pinkish. Redness or exudate is abnormal and often indicates infection.

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Eye Prophylaxis and Vitamin K Administration

The incidence of gonococcal disease is an estimated 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. **Failure of the physician, nurse, or midwife to provide ocular prophylaxis constitutes a Class B misdemeanor on their part.** 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 also 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 fed for several days,
- infants with intestinal malabsorption defects, or
- infants whose mothers are on anticonvulsant medications, specifically phenytoin.

VKDB in the newborn can manifest as bruising, persistent bleeding from a needle puncture site, bleeding from the circumcision site, gastrointestinal bleeding or possibly intracranial bleeding, which obviously carries the risk of long term neurological sequelae.

VKDB is classified according to when it presents:

1. Early VKDB: occurs within 24 hours of birth. Seen almost exclusively in newborns whose mothers took vitamin K inhibiting drugs during pregnancy.
2. Classic VKDB: 24 hours to 7 days of age.
3. Late VKDB: 2- 24 weeks of age.

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 regarding the need for vitamin K to prevent VKDB and the potential devastating consequences, including death. 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.

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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) encourages practitioners to "promote, protect, and support" the practice of breastfeeding. Breast-fed infants have significantly fewer respiratory, middle ear, and gastrointestinal infections than formula-fed infants. Additionally, breast-fed babies are less likely to develop allergic and autoimmune disorders and may become more intelligent children and adults. Breastfeeding has also been associated with a decreased incidence of Sudden Infant Death Syndrome (SIDS). Physicians should encourage all mothers to breastfeed and must be able to educate new mothers on methods of breastfeeding.

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 a lactation consult 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 (Contact person: Connie Gascamp, R.N.)

Methods and Practices

A newborn should be put to the breast as soon after delivery as possible. The AAP recommends the initiation of breastfeeding within the first hour after birth. If the mother is unable to breastfeed immediately after delivery, donor breast milk may be available in some hospitals for baby's first feedings. Breastfeeding should occur at a frequency of **8-12 times per day (**or more**)** for a duration of at least 10 to 15 minutes on each breast or until the infant is satisfied. This high-frequency breastfeeding will be necessary until a good milk supply is established. Breastfeeding is a supply-and-demand phenomenon; frequent feedings promote a more plentiful milk supply. Water supplements should not be given to newborns. Using a pacifier during the early period may decrease breastfeeding success. However, the use of pacifiers at sleep time has been associated with a decreased incidence of SIDS; therefore, the AAP recommends delaying pacifier use only until a good milk supply has been established (~ 3 to 4 weeks).

Assessment of Breastfeeding

Infant signs of effective breast feeding include:

- Maintains deep latch on to breast.
- Long jaw movements observed
- Some swallowing heard/observed

Assess all breast-fed newborns for adequate hydration status within a 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)
  - » About 8 breastfeeds (may be less)
  - » 1 urine/1 stool or more
- 24-48 hours:
  - » Frequent STS
  - » About 8 breastfeeds
  - » 2 urine/2 or more stools
- 48-72 hours:
  - » 8-12 breastfeeds
  - » 3 urine/3 or more stools.

Most babies have 1 wet diaper for each day of life up to day 6, at which time expect about 6 wet diapers per day. The breast fed infant usually has 1 stool with each feeding, however, stooling patterns are variable and should not be exclusively used as an indicator of effective breast feeding. The stools of breast-fed babies differ from those of formula-fed babies. Breast-milk stools are yellow and 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.

Table 12–1. Tongue Range of Motion
Circle "Yes", "No" or "Unable to Assess" for each assessment item and record totals below

Look	**Rounded tongue tip?** Stimulate tongue movement by running finger pad along lower and upper gum ridge and/or brushing lips in downward motion ***Observe tongue tip as rounded without evidence of cleft, notch, tension or distortion with movement***	**YES**	**NO**	Unable to Assess
Look	**Over lower lip?** Stimulate tongue protrusion using finger to brush downward from tongue tip to lower lip **Tongue tip protrudes over lower lip without difficulty**	**YES**	**NO**	Unable to Assess
FEEL	**Motion of tongue wave-like?** Insert pinky finger pad-side up to junction of hard and soft palate; feel the tongue movement on finger during suck bursts ***Complete, rhythmic peristalsis with each suck; begins with tip elevation to mid-blade to posterior tongue; NO AREA FLAT***	***YES***	***NO***	Unable to Assess
FEEL	**Sustains tongue over lower gum line firmly cupping finger?** Insert pinky finger pad-side up to junction of hard and soft palate, feel the tongue movement on finger during suck bursts ***Actively cups consistently over lower gum ridge; forms central groove; can also visually inspect by lowering bottom lip***	**YES**	**NO**	Unable to Assess
SWEEP	**Obstruction free finger sweep?** Insert finger pad facing down directly on mouth floor just behind lower gum ridge; sweep finger in lateral motion ***Sweep should be unobstructed by lingual frenulum insertion points or length***	**YES**	**NO**	Unable to Assess
SWEEP	**Slack and elastic lingual frenulum?** Insert finger pad facing down resting midline on lower gum; advance finger directly to frenulum to palpate elasticity ***Feels loose (slack) and elastic; yields easily to pressure without tension or tightness***	**YES**	**NO**	Unable to Assess
Two or more "NO" items may indicate a restrictive range of motion and potential feeding difficulties	**TOTAL FOR EACH ITEM**			

Ankyloglossia

Ankyloglossia, commonly known as tongue-tie, is a congenital oral anomaly characterized by an abnormally short or tight lingual frenulum which restricts the mobility of the tongue. Ankyloglossia in the newborn has a reported incidence as high as 4.8% and is more common in males. Often, when a thorough family history is obtained, a history of ankyloglossia is discovered either as an actual diagnosis, or as a possible diagnosis in family members with a history of speech impediments or difficulty breastfeeding.

Per the AAP Section on Breastfeeding, "Tongue-tie is a significant clinical entity which, when symptomatic, should be treated as early as possible." Several published studies have shown frenulotomy to be an effective means to resolve breastfeeding difficulties associated with ankyloglossia. In infants with suspected ankyloglossia, collaboration between the baby's nurse, the lactation team, and the pediatrician should occur to help identify candidates for frenulotomy. Lactation consultants in our institutions utilize an objective tool when assessing babies with feeding difficulties and suspected ankyloglossia. **(See Table 12–1).**

References and Suggested Reading:

1. Geddes Dt, Langton DB, Gollow I, Jacobs LA, Hartmann PE, Simmer K. Frenulotomy for breastfeeding infants with ankyloglossia: effect on milk removal and sucking mechanism as imaged by ultrasound. *Pediatrics* 2008:122(1):e188-94.
2. Buryk M, Bloom D, Shope T. Efficacy of neonatal release of ankyloglossia: a randomized trial. *Pediatrics* 2011;128:280–288.

Supplementation: Healthy Term Newborns

A mother who plans to breastfeed should be encouraged to feed her baby on demand and avoid formula supplementation. If medically indicated, babies can be supplemented with expressed breast milk (EBM) or pasteurized donor human milk. If these are not available, standard infant formulas should be used.

Indications for supplementation: infant issues

- Asymptomatic hypoglycemia unresponsive to appropriate and frequent breastfeeding
- Significant dehydration (10% weight loss or greater, 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
- Breastfeeding jaundice associated with hyperbilirubinemia
- Breast milk jaundice associated with hyperbilirubinemia where a diagnostic interruption of breastfeeding may be helpful.

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 DBM (donor breast milk) is first choice, then formula.
Method: spoon, cup, supplemental nutrition system (SNS), bottle: determined in consultation with mother.
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

The AAP recommends exclusive breastfeeding for 6 months. Exclusive breastfeeding for more than 6 months has been associated with increased risk of iron deficiency anemia at 9 months of age. It is recommended that exclusively breastfed term infants receive an iron supplementation at 1mg/kg/day,

starting at 4 months of age and continued until appropriate iron-containing complimentary foods have been introduced The AAP also recommends a daily intake of vitamin D for infants of 400 IU/day Breastfeeding infants can achieve this with a daily dose of 1 mL of a vitamin D supplement (i.e., D-Vi-Sol®) beginning in the first few days of life. Breastfed term infants who are < 2500 g birthweight need a daily iron supplement in addition to vitamin D. **(See Chapter 13, Nutrition Support).** For a lactating mother on a normal diet, the need for vitamin supplementation is not well documented. Some vegetarian diets are deficient in B12, and B12 deficiency has been documented in breastfed infants of vegetarian mothers. Thus, continued intake of prenatal vitamins may be helpful for lactating vegetarian women.

Weight Loss

Infant weight loss during the first several days after birth is expected. 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 recent study of exclusively breast fed infants demonstrated a weight loss of 7% to be at the 50th%ile for vaginally delivered infants, and a 9% weight loss to be 50th%ile for infants delivered by c-section **(Flaherman, et. al. Early Weight Loss Nomograms for Exclusively Breastfed Newborns, *Pediatrics*, 2015.)**.

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 electric breast pump can facilitate this. If neither nursing nor pumping milk is possible in the workplace, the mother should be encouraged to continue nursing when at home with her infant and to supplement feedings with an iron-containing formula during working hours. If good breastfeeding has been established, the mother's body usually will adjust to the new schedule.

Contraindications to Breastfeeding

(See also Nutrition Support chapter.)

Very few contraindications to breastfeeding exist. These include:

- Infants with classic galactosemia
- Mothers who are positive for human T-cell lymphotrophic 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
- Maternal illicit drug use

Maternal Medications

Additionally, breastfeeding is generally not recommended for mothers receiving medication from the following classes of drugs: amphetamines, chemotherapy agents, ergotamines, and statins.

Useful resources for determining the safety of maternal medications while breastfeeding include:

1. LactMed: an internet source with comprehensive information regarding the safety of maternal medications and breastfeeding. This website can be accessed at http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
2. "Medications in Mothers" by Dr. Thomas Hale.
3. Additional information on this topic can be accessed via Dr. Hale's website at http://www.infantrisk.com

Feeding, Formula and EBM

Although breast milk is the ideal food during infancy, under certain circumstances an infant may need to be bottle fed either with expressed breast milk (EBM) or formula.

Some 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.

Bottle-feeding has some advantages and disadvantages. Nonetheless, a physician should not use the advantages of bottle-feeding to dissuade a mother from breastfeeding.

Advantages - Mothers may wish to bottle feed with expressed milk to allow other family members to bond with the infant and so that the quantity of milk the infant receives is known. Fewer feedings may be needed with formula feedings since formula takes longer to digest than breast milk.

Disadvantages - Formula has fewer nutritive and immune properties than human milk; it is more expensive (formula and supplies); and, preparation is time-consuming.

Expressed Breastmilk Storage

EBM may be safely stored at different temperatures for a variety of time frames **(see Table 12-2).** To thaw frozen EBM, place the frozen EBM in a refrigerator overnight or in a bowl of warm water. After thawed, it can only be refrigerated for 24 hours before use. Milk left in the feeding container after a feeding should not be reused.

Formula Preparations

In the newborn nursery, an iron-fortified, 19-20-calorie-per-

Table 12–2. Expressed breastmilk storage

Temperature	Duration
Room temperature (up to 77ºF or 25ºC)	6 to 8 hours
Insulated cooler bag with ice packs	24 hours
Refrigerator (39°F or 4°C)	5 days
Freezer compartment within a refrigerator (5ºF or -15ºC)	2 weeks
Freezer compartment of refrigerator/freezer with separate door (0ºF or -18ºC)	3-6 months
Deep freezer (-4ºF or -20ºC)	6-12 months

ounce bovine milk-based formula is suitable for most term babies. 19 cal/oz formula is not recommended for use in babies less than 37 0/7 weeks gestation.

Several types of formula are available:

- **Ready-to-Feed** - No preparation is required. This is the most convenient, but also the most expensive, preparation.
- **Concentrate** - Mix equal parts of formula concentrate and water. Use prepared formula within 2 hours of preparation if left at room temperature. 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.

Feeding During the First Weeks

Term newborns start by feeding approximately 0.5 ounce per feed and increase gradually. Infants usually will take 2 to 3 ounces of formula 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 usually is best. Supplemental iron and vitamins are generally not needed for term infants receiving iron-fortified formula, unless the infant is SGA. **(See Chapter 13, Nutrition Support).**

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.

Screening - Hearing

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 new- born 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. Universal hearing screening using a physiologic assessment tool, is required by The Texas Department of State Health Services (DSHS) for babies born in our hospitals. The rate of abnormal newborn hearing screens (i.e., the refer rate for diagnostic hearing testing after completion of screening) should be less than 4%. After a screening referral, confirmation of hearing loss should occur by 3 months of age with appropriate intervention initiated no later than 6 months of age.

All newborns should have a hearing screen before discharge, once screening criteria are met:

- ≥34 weeks
- off phototherapy (if screening takes place in a separate room, or if baby is placed in an isolette for phototherapy)
- in open crib
- not endotracheally intubated (trach OK)
- clinically stable

Newborns who remain hospitalized after birth should be screened by 3 months of age. Infants readmitted to the hospital (well baby or NICU) should be re-screened when there are conditions associated with potential hearing loss such as:

- Hyperbilirubinemia requiring exchange transfusion
- Culture + sepsis/bacterial meningitis

If the initial screen is abnormal and confirmatory testing indicates hearing loss, then appropriate consultation (e.g., ENT) should be sought. High risk infants should be screened with auditory brainstem response (ABR) instead of an otoacustic emissions (OAE). A urine CMV culture should be obtained on all newborns who unilaterally or bilaterally fail the ABR.

References and Suggested Reading

1. American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs. *Pediatrics.* 2007;Oct;120(4);898-921.
2. Stehel EK. Shoup AG, Owen KE, Jackson GL, Sendelbach DM, Boney LF, Sanchez PJ. Newborn hearing screening and detection of congenital cytomegalovirus infection. *Pediatrics.* 2008;May;121(5);970-975.

Screening - Blood

Glucose Screening of at Risk Infants

Babies at risk for hypoglycemia include those who are LGA, SGA, preterm, and infants of diabetic mothers (IDM). **See Chapter 10, Metabolic Management**, for a detailed explanation regarding glucose screening and management of these babies.

State Newborn Screening, Blood Spots

Texas Department of State Health Services (DSHS) requires newborn blood screening for 29 various disorders. If diagnosed early, outcomes for babies with these disorders are much improved. The various disorders screened for include: cystic fibrosis, congenital hypothyroidism, galactosemia, hemoglobinopathies (e.g., sickle hemoglobin disease and thalassemia), congenital adrenal hyperplasia, biotinidase deficiency, inborn errors of metabolism (amino acidemias, organic acidemias, and disorders of fatty acid oxidation) and screening for Severe Combined Immune Deficiency (SCID). Specimens are collected on all newborns at 24 to 48 hours of age, regardless of feeding status or prematurity. A second newborn screen is repeated at one to two weeks of age. Blood transfusions can cause invalid results. The first screen should be collected prior to the first transfusion if possible. Transfused newborns must be retested two to four weeks following transfusion. **(Refer to Genetics chapter for evaluation of abnormal results.)**

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 Attendings are routed to the Newborn and Infant Screening Service (NBISS) (832- 824-1093).

Screening – Critical Congenital Heart Disease (CCHD)

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 in order 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.

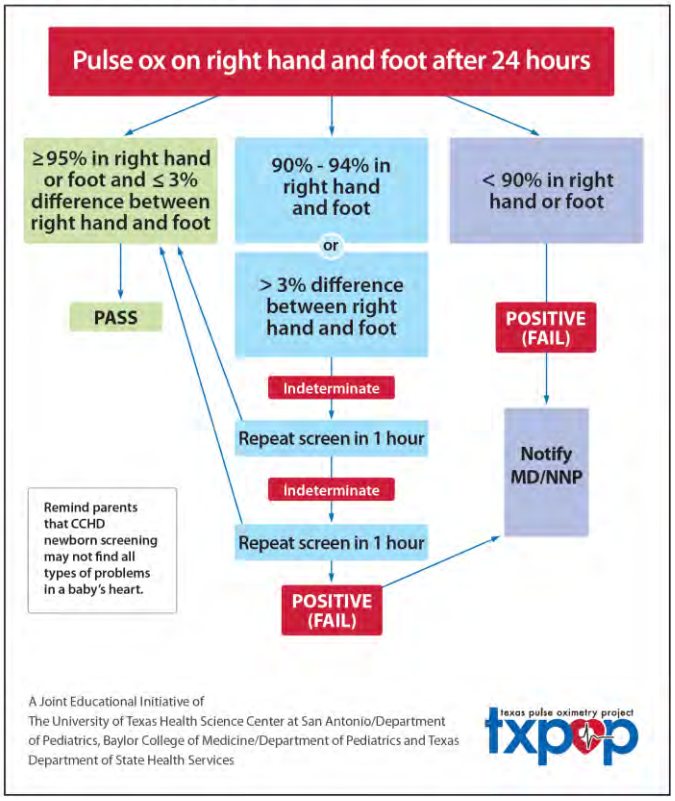
Newborn screening with pulse oximetry has been shown to be useful for the detection of the seven heart defects that cause CCHD. These seven defects represent 17–31% of all congenital heart defects.

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.

Figure 12-1. Newborn Screening Algorithm for Critical Congenital Heart Disease



Screening should occur after 24 hours of age and before hospital discharge. Screening is done by obtaining, and comparing pre and post ductal oxygen saturations via pulse oximetry. **(see Figure 12–1. CCHD screening algorithm)**. Infants with a positive screen (fail) require prompt attention for further evaluation.

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.

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 should be well-documented. 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 **(see previous section on 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. Any infant who does not pass stool in the first 48 hours of life requires further evaluation. Over several days, the stool transitions to 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

The AAP and the Advisory Committee on Immunization Practices of the CDC recommend administration of the first Hepatitis B vaccine (HBV) during the newborn hospitalization. **(See Chapter 8, Infectious Diseases, for details regarding HBV).**

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 (**see Chapter 2, Cardiopulmonary**).

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, ausculatory 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 is characterized as 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 said to be crescendo. The murmur is best heard at the cardiac base and over the left scapula. The murmur most 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:

- the rapidly falling pulmonary vascular resistance,
- the difference in the diameters between the main pulmonary branch and the left and right pulmonary branches, and
- the relatively 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 over normal semilunar valves, 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 grade 2 to 3 murmurs 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.

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% of cases 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). No conclusive evidence supports a correlation between natal or neonatal teeth and some somatic conditions or syndromes.

The decision to keep or extract a natal or neonatal tooth should be evaluated in each case. In deciding, some factors to

consider include:

- implantation and degree of mobility,
- interference with breastfeeding,
- possibility of traumatic injury, and
- whether the tooth is part of normal dentition or is supernumerary

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. One approach for the workup of natal teeth is to:

1. obtain a radiograph of the mandible to delineate whether the tooth is a primary tooth or a supernumerary tooth; a supernumerary tooth should be extracted,
2. consider a consultation with a pediatric dentist or oromaxillofacial service,
3. consider the clinical implications of the tooth (see above; e.g., interference with breastfeeding, etc.), and
4. arrange follow-up of natal or neonatal teeth that are not extracted.

Dermatology

Birthmarks

The majority of birthmarks noted in the newborn period are not of medical significance and warrant only close observation.

Common benign birthmarks include:

- **Salmon patches** (a.k.a. macular stain, nevus simplex, "stork bite", "angel's kiss") - are the most common vascular malformations, are of capillary origin, and almost always fade without need for intervention.
- **Mongolian spots** - are the most common form of cutaneous hyperpigmentation seen in neonates and are caused by dermal melanocytosis. 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** - 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 may 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 hypopigmented (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 - may be 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
  - » 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.

Reference

1. Zywicke HA, Rozzelle CJ. Sacral Dimples. *Pediatr Rev.* 2011;Mar;32(3);109-113.

Ear Tags and Pits

Preauricular ear pits and tags may be familial. They are twice as common in females as 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.

Isolated preauricular pits or tags accompanied by one or more of the following warrants a renal ultrasound:

- other malformations or dysmorphic features
- a family history of deafness, OR
- a maternal history of gestational diabetes.

In the absence of these findings, renal ultrasonography is not indicated.

References

1. Wang RY, Earl DL, Ruder RO, Graham JM Jr. Syndromatic ear anomalies and renal ultrasounds. *Pediatrics* 2001; 108(2): e32–e38.
2. Kohelet D, Arbel E. A prospective search for urinary tract abnormalities in infants with isolated preauricular tags. *Pediatrics* 2000;105(5): e61-e63.
3. Lizama M, et al. Association of isolated preauricular tags and nephrourological anomalies: case-control study. *Pediatr Nephrol* (2007) 22:658-660.
4. Firat Y, et al. Isolated preauricular pits and tags: is it necessary to investigate renal abnormalities and hearing impairment? *Eur Arch Otorhinolaryngol* (2008) 265: 1057-1060.

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 butterfly adhesive strips. Deeper wounds, especially if bleeding, should be sutured by Surgery. Consider a Plastic Surgery consult if the laceration is located on the face. Keep the affected areas clean to minimize risk of infection.

Nipples, Extra

Incidence of supernumerary nipples is 2 to 3 per 1000 live births. They are especially 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 after14 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 not tender or warm. 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.

Extracranial Swelling

Caput Succedaneum

Caput succedaneum is a vaguely demarcated area of edema over the presenting portion of the scalp during a vertex delivery. The soft tissue swelling extends across suture lines and may be associated with petechiae, purpura, and ecchymoses. Usually no specific treatment is indicated and resolution occurs within several days.

Cephalohematoma

A cephalohematoma is a subperiosteal collection of blood. The area of hemorrhage is sharply demarcated by periosteal attachments to the surface of one cranial bone and will not extend across suture lines. Spontaneous resorption usually occurs by 2 weeks to 3 months and may be associated with

calcium deposits. When calcium deposits occur, a bony swelling will result that may persist for several months (rarely up to 1.5 years). Incision or aspiration of the cephalohematoma is contraindicated. Cephalohematomas are considered to be benign but may occasionally be associated with complications such as skull fractures (rare), jaundice, infection, and anemia.

Subgaleal Hemorrhage

Subgaleal hemorrhage is a form of extracranial bleeding that occurs just under the scalp and may become massive and life-threatening. The source of the bleeding is thought to be from rupture of emissary veins with blood accumulating between the epicranial aponeurosis of the scalp and the periosteum.

Cause and Appearance

The occurrence of subgaleal hemorrhage (SGH) is highest with vacuum extraction deliveries, but can also occur with spontaneous vaginal delivery. 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. Clinically this lesion may present with ill-defined borders, be firm to fluctuant, and may have fluid waves. The anatomic limits of this potential space include the orbital margins frontally back to the nuchal ridge and laterally to the temporal facia. The potential for massive blood loss into this space contributes to the high mortality rate associated with this lesion. **(See Table 12–3.)**

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 either in a Level II unit or the NICU, with frequent vital signs, serial FOC measurements, serial hematocrits, and close observation for signs of hypovolemia. The infant's FOC will increase 1 centimeter with each 40 mL of blood deposited in the potential space. Treatment includes volume resuscitation initially with normal saline, followed by packed red cells as needed for ongoing bleeding, as well as fresh frozen plasma if a coagulopathy develops. If SGH is suspected (and the infant is stable) a head CT will be helpful in distinguishing SGH from other forms of extracranial swelling. Neurosurgical consultation should be obtained for symptomatic infants.

Table 12–3. Features of extracranial swelling

	Condition		
Feature	**Caput succedaneum**	**Cephalohematoma**	**Subgaleal hemorrhage**
Location	crosses sutures	distinct margins sutures are limits	crosses sutures football-helmet–like
Findings	firm edema vaguely demarcated	initially firm; distinct margins; fluctuant >48	diffuse, shifts dependently, fluid-like
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**

Hospital Discharge

Early 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.

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 **(See Chapter 7-Hematology, Jaundice section),**
- gastrointestinal obstruction,
- ductus-dependent congenital heart defects,
- bacterial and viral sepsis including HSV, and
- 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.

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 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.
- Mother has adequate knowledge of normal feeding and voiding patterns, general infant care and can recognize jaundice.
- 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.

Infants of group B streptococcus-positive mothers are not eligible for early discharge with one exception. Newborns $\geq$ 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 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. Use of the Newborn Follow-Up Clinic at Ben Taub is recommended for all infants discharged early.

Reference

1. Benitz WE, Committee on Fetus and Newborn. Hospital stay for healthy term newborn infants. *Pediatrics*. 2015. May;135(5)948-53.

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. Non displaced fractures may have minimal or no findings on the first day exam. 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. 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.

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. Obtain Orthopedics consult.

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). Radiologic and electro diagnostic studies may be indicated. 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 with the 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, perinatally, or during infancy and child- hood. 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. The etiology of DDH is unknown, but appears to involve physiologic factors (i.e., ligamentous laxity) and mechanical factors (i.e., intrauterine positioning).

Risk Factors for DDH include:

- Firstborns: due to the confines of the primigravida uterus.
- Breech positioning: DDH is associated in as many as 23% of breech presentations. 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.

Additionally, careful hip examination should be performed for babies with musculoskeletal anomalies related to tight intrauterine "packaging", such as torticollis and metatarsus adductus.

Table 12-4. 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

Assessment and Management

Diagnostic clues to DDH include:

- asymmetrical number of thigh skin folds,
- uneven knee levels (Galeazzi sign),
- discrepancy in leg length
- limitation of hip abduction,
- positive Barlow test (a "clunking" sensation when the femur – at a 90-degree angle to the examining surface – is dislocated posteriorly when light, downward pressure, is applied to the knee).
- 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 Barlow and/or Ortolani test, or other findings suggestive of DDH, obtain a Pediatric Orthopedic consultation. Repeated hip exams should be limited for babies with suspected DDH.

In the Ben Taub nurseries, physical therapy is consulted for placement of the Pavlik harness in babies with suspected DDH, and Pediatric Orthopedic consultation is obtained as an outpatient (i.e., Shriner's Hospital). In high-risk groups (girls with a positive family history and girls delivered breech), future imaging is indicated despite a normal examination. This may be done by either hip ultrasound at 6 weeks of age or plain film radiographs at 4 to 6 months of age.

References

1. American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Developmental Dysplasia of the Hip. Clinical practice guideline: early detection of developmental dysplasia of the hip. *Pediatrics* 2000;105(4):896–905.
2. Phillips, W. Clinical features and diagnosis of developmental dysplasia of the hip. In: UpToDate, Post DW (Ed), UpToDate, Waltham, MA, 2014.

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.

Reference

1. Hahn JS, Sanger T. Neonatal movement disorders. *Neo Reviews.* 2004;5;e321-e326.

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, primigravida 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 hindfoot 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 usually conservative as 90% + will resolve without intervention.

Calcaneovalgus feet is a common newborn positional deformity in which the hindfoot 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, etc.

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.

Reference

1. Chaweerat R, Kaewpornsawen K, Wongsiridej P, Payakkaraung S, Sinnoi S, Meesamanpong Ss. The effectiveness of parent manipulation on newborns with postural clubfoot: a randomized controlled trial. *J Med Assoc Thai*. 2014 Sept; 97 Suppl 9:S68-72.

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.

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 a concern, or the umbilical cord was not cut in a sterile fashion, tetanus immune globulin (250 IU, IM) should be given as soon as possible.

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 drug abuse
- 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.

Umbilical Artery, Single

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 associated congenital malformations. The finding of other associated anomalies is not specific for any one organ system. Further investigation is recommended

The finding of other associated anomalies is not specific for any one organ system. Further investigation is recommended only when another major anomaly is found.

Urology

Urinary Tract Dilation (UTD)

Introduction

Advances in ultrasonography make possible an earlier and more accurate prenatal diagnosis of urinary tract abnormalities. Prenatal diagnosis of fetal urinary tract dilation 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 ultrasonagraphic 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. **(See 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. 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 one month of age.** The second ultrasound is performed at 1-6 months. **If concern exists for an obstructive uropathy, such as PUVs, it is reasonable to do follow-up imaging sooner.**

Delay in discharge of the infant with his/her mother should be avoided. Therefore, if outpatient follow-up cannot be ensured, and/or concern exists for significant urinary tract pathology, postnatal imaging can be done prior to 48 hours. 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 (see reference below). 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. Consultation with Urology is recommended.

References and Suggested Reading

1. Nguyen, HT, et. al. Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system). *J Pediatr Urol.* 2014 Nov;10, 982-99.
2. Nguyen HT, et. al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. *J Pediatr Urol*. 2010 Jun;6(3):212-31.
3. Braga LH, et. al. Antibiotic prophylaxis for urinary tract infections in antenatal hydronephrosis. *Pediatrics*. 2013 Jan;131(1):e251-61.

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 nurseries 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. **(See Chapter 11-Neurology, Pain Assessment and Management section).**

Contraindications

Circumcision is contraindicated in medically unstable infants and those with genital anomalies or bleeding problems. Infants with a family history of bleeding disorders should have appropriate screening laboratory tests before the procedure. In premature newborns, the recommendation is to delay

should be given to delaying circumcision in boys with bilateral cryptorchidism. **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. Petroleum jelly should be applied to the area for 3 to 5 days. 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

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. Parents should teach their son how to do this himself when he is able.

Cryptorchidism (Undescended Testes)

Undescended testes represents 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, Uultrasonography 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, so management after discharge includes monthly follow-up. However, testicular descent is extremely unlikely after 6 months of age. 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.

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 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 glandular or coronal hypospadias, 10% are penile, and 3% penoscrotal and 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).

Patients with severe hypospadias, urinary tract symptoms, family history of urinary reflux, or associated multiple congenital anomalies are most likely to have significant abnormalities and to need uroradiographic studies. Mild hypospadias (glandular to penile) without associated genital abnormalities or dysmorphic features is very unlikely to have identifiable endocrinopathy, intersex problem, or chromosomal abnormality. Severe hypospadias is associated with about a 15% risk of such problems. Hypospadias occurs in certain rare syndromes, many of them with poor prognosis. The differential diagnosis includes female neonates with congenital adrenal hyperplasia, other intersex disorders, syndromes, and idiopathic causes.

Assessment

Evaluation of hypospadias should include:

- history of possible maternal progestin or estrogen exposure,
- family history of hypospadias, endocrine or intersex disorders,
- genital examination to evaluate the hypospadias (urethral meatus, chordee, scrotal folds),
- ultrasound assessment for absence of gonads and presence of a uterus (**See Chapter 3, Endrocrinology)** if a disorder of sexual differentiation is suspected,
- evaluation for gross abnormalities of the kidneys (if the hypospadias is severe),
- identification of possible somatic abnormalities, and
- measurement of stretched penile length.

Further diagnostic studies should be done depending on the risk for endocrine or intersex disorders. Ideally, surgical repair of hypospadias is done late in the first year of life. Obtain a Urology consult. Genetics and Endocrine consults should be considered when other problems are present or suspected.

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.

Nutrition Pathway for High-risk Neonates

In this chapter, all term and premature infants admitted to the NICU or Level 2 nurseries are considered high-risk neonates. Differentiation is made between high-risk, very low birth weight infants and healthy preterm infants as needed.

Human milk is the preferred nutrition for virtually all infants. A healthy infant should be put to the breast within one hour of delivery. Support mothers who want to nurse or provide milk for their infants. **(For breastfeeding guidelines, see Enteral Nutrition section of this chapter.)**

Initial Orders After Delivery

Initiate intravenous fluid with 5% to 10% dextrose to provide an initial glucose infusion rate of 4.5 to 6 mg glucose/kg per minute).

- Infants 23-24 6/7 weeks GA, initiate at 100 mL/kg/day at birth with 5 % dextrose
- Infants 25-26 6/7 weeks GA, initiate at 80 mL/kg/day at birth with 10% dextrose
- Use 10% dextrose if born at 1000 grams or greater birthweight

Initial TPN: Neonatal Early & Starter Solutions

(See Tables 13-1, 2, 3, and 4)

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 at an appropriate volume based on body weight and clinical condition. (**See Table 13-4 for recommended nutrient composition.)**

Neonatal Starter Solution

The standard starter solution only contains glucose, amino acids, calcium and water. No changes can be made to this solution. Parenteral nutrition should be ordered to include phosphorus within the first 24 hours after birth. Vitamins and trace minerals are automatically added by the pharmacy. (**See Table 13–5**)

- Begin TPN upon admission for infants < 1500 grams, for infants with major congenital cardiac disease (any requiring a prostaglandin infusion or pressor support), and for infants with congenital bowel abnormalities such as gastroschisis or omphalocele.
- Use standard starter solution when TPN room is closed (1 pm to10 am) Starter solutions will provide 3% amino acids.
- Limit starter solutions to a maximum of 100 mL/kg. Provide any additional fluid needed as a piggyback IV Fluids (IVF).

Table 13–1. Parenteral nutrient goals

		Initiation Nutrient Needs*	Goals for Growth
Energy	kcal/kg	42 - 57	90–110
Protein	g/kg	2 - 3	3.5-4 (preterm)[a] 1.5–3 (term)
Fat	g/kg	0.5 - 2[b]	3
Glucose	mg/kg minute	4.5–6	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 their tolerance will vary by gestational age, birth weight and clinical condition.

[a] Infants with GI diseases, surgery, other protein-losing state, or long- term TPN may require 4 g/kg per day of protein

[b] 5 mL/kg of 20% IL = 1 g fat/kg

[c] Standard starter and peripheral TPN provides 1.2 mmol/100mL calcium gluconate and central TPN 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 TPN within 24 hours of life.

[e] Peripheral TPN provides 1.2 mmol/100mL potassium phosphate and central TPN 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

- Initiate calcium and phosphorus once TPN can be written. In infants < 1000 g BW, limit calcium gluconate to 1.0 mmol/100mL at 100 ml/kg/day or 1.0 – 1.2 mmol/kg/day in the first 72 hours of life as tolerated. Add phosphorus (either as potassium phosphate, or sodium phosphate in a 1:1 mmol ratio to calcium within 24 hours after birth and as early as can be provided with routine TPN.

Table 13–2. TPN calculations

GIR (mg/kg per min)	% Dextrose (g/100 mL) × Volume (mL/kg per 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

Table 13-4. Early neonatal solutions (0 to 48 hours of age)

	Standard Starter [1]	Early TPN [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 TPN room is closed (1 pm to 10 am) contains no cysteine, phosphorous, trace minerals or vitamins. No changes.

[2] Early TPN should be ordered with GIR of 4.5-6 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.

- Initiate intravenous lipids when TPN is started. Initiate lipids on infants < 27 0/7 weeks at birth during the daytime.
- Infants < 1000 g BW or < 27 0/7 weeks gestational age (GA), should initiate lipids via infusion pump at 0.1 mL/hour over 12 hours due to the syringe size required to include adequate priming. Check a TG (triglyceride) level at approximately 4 and 12 hours after initiation of therapy. If TG level is initially > 250 mg/dL, stop the infusion and repeat TG level in 12 – 24 hours or sooner as clinically indicated. Advance as tolerated if TG is < 250 mg/dL. If a rate of 0.1 mL/hour is not tolerated after several attempts, please discuss with our clinical pharmacy specialists the use of special lower volume syringes that can be run at < 0.1 mL/ hr.
- Infants ≥ 1000 g birthweight or ≥ 27 weeks GA who are SGA or IUGR, have received postnatal steroids or have presumed sepsis, IL should start at 1 g/kg per day with serum TG monitoring before advancement.
- Infants ≥ 1000g birthweight or ≥ 27 weeks GA who are AGA and are not receiving postnatal steroids or believed to be septic, IL may be initiated at 2 g/kg/ per day. Monitoring of TG is generally not needed with every advancement of lipids in this group of infants.
- At 24 hours of age or whenever the first daytime ability to write TPN (which can be within hours of birth) transition to standard parenteral nutrition. Sodium chloride, and potassium chloride, are generally not indicated.
- Magnesium should not be omitted from TPN unless serum Mg level is > 3.9 mg/dL and then serum Mg level should be followed carefully. Add Mg when < 3.0 mg/dL.

Enteral Nutrition

- Infants, especially VLBW/LBW infants, should start feeds as soon as possible (within 6 to 12 hours of birth) if medically stable. For ELBW infants, consider starting feeds on the first day of life if medically feasible.
- Medical stability will usually be described as not being intubated and not requiring pressors except low dose dopamine (See below).
- 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 < 1500 grams (AAP 2012). The use of donor milk may be considered for all infants but infant formula is also an appropriate backup for infants > 1500 g birthweight.
- Initiation of enteral feedings and advancement rates should be individualized, based on a patient's weight, age, and medical stability. Low dose pressors, including dopamine (usually 5 mcg/kg/min or less) are compatible with initial trophic feeds. Umbilical catheters do not preclude trophic feeding. Trophic feeds are typically continued for 3 days, but 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. If infant has feeding intolerance consider feeds every 3 hours but given on a pump over 30 minutes. Due to fat loss in tubing, it is preferred not to give continuous feeds unless severe feeding intolerance.**(See Tables 13–6a, 6b, 6c, 6d and 6e)**

Table 13–5. Components of standard central total parenteral nutrition (TPN) for premature

Component	per 100 mL	Comments	Intakes at 130 mL/kg per day[1]
Glucose	12.5%		16 g/kg per day
Amino acids	2.8%	TrophAmine	3.6 g/kg per day
NaCl	2.6 mEq	= 2.6 mmol Na	3.4 mEq/kg per day
KH_2PO_4-- K_2HPO_4	1.75 mmol P	= 54 mg P	2.3 mmol/kg perday; 71 mg/kg per day
		= 2.5 mEq K+	3.2 mEq/kg per day
Calcium gluconate	1.75 mmol Ca	= 70 mg Ca	2.3 mmol/kg; 91 mg/kg per day
$MgSO_4$	0.5 mEq Mg	= 6 mg Mg	7.8 mg/kg per day
KCl	0.2 mEq	K from KCl	0.26 mEq/kg per day
Lipid		1 to 3 g/kg per day	3 g/kg per day; 15 mL/kg per day
Cysteine	30 mg/g amino acids;	always add proportional to amino acids	
Heparin	1 unit/mL		

Trace elements – Pediatrace (mcg/kg per day)	<2500 g	>2500 g
Zinc	250[2]	250[3]
Copper	20	20
Iodine	1	1
Manganese	1	1
Selenium	2	2
Fluorine	57	57

Vitamins (Infuvite Pediatric)[4]	<2500 g	>2500 g	
Vitamin A (IU)	920 per kg	2300 per day	(690 mcg)
Vitamin D (IU)	160 per kg	400 per day	(10 mcg)
Vitamin E (IU)	2.8 per kg	7 per day	(7 mg)
Vitamin K (mcg)	80 per kg	200 per day	
Vitamin C (mg)	32 per kg	80 per day	
Thiamin B_1 (mg)	0.48 per kg	1.2 per day	
Riboflavin B_2 (mg)	0.56 per kg	1.4 per day	
Pyridoxine (mg)	0.4 per kg	1 per day	
Niacin (mg)	6.8 per kg	17 per day	
Pantothenate (mg)	2 per kg	5 per day	
Biotin (mcg)	8 per kg	20 per day	
Folate (mcg)	56 per kg	140 per day	
Vitamin B_{12} (mcg)	0.4 per kg	1 per day	

[1] Use intakes to calculate parenteral nutrient concentrations during fluid restriction.

[2] Preterm infants require 400 mcg/kg per day of zinc. Provide supplementation as indicated.

[3] Term infants require 250 mcg/kg per day of zinc initially; when >3 months of age, 100 mcg/kg per day is recommended. Adjust TPN accordingly.

[4] Vitamins (Infuvite Pediatric): 2 mL/kg per day for infants <2500 g or 1 vial (5 mL) for infants 2500 g or greater

Providing Oral Care with Mother's Own Colostrum/Breast Milk

Purpose

Colostrum is rich in cytokines, growth factors and immune cells that provide bacteriostatic, bacteriocidal, 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.[1-5]

Procedure

NICU staff, but preferably parents, should initiate oral care using colostrum or expressed breast milk 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.

References:

1. Rodriguez NA, Meier PP, Groer MW, Zeller JM. Oropharyngeal administration of colostrum to extremely low birth weight infants: theoretical perspectives. *J Perinatol* 2009;29(1):1-7.
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3. Lee J, Kang HE, Woo HJ. Stability of orally administered immunoglobulin in the gastrointestinal tract. *J Immunol Methods* 2012;384(1-2):143-7.
4. Seigel JK, Smith PB, Ashley PL, Cotten CM, Herbert CC, King BA, et al. Early administration of oropharyngeal colostrum to extremely low birth weight infants. *Breastfeed Med* 2013;8(6):491-5.
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Total Parenteral Nutrition (TPN)

TPN refers to intravenous nutrition (including glucose, amino acids, lipids, vitamins, and minerals) to provide a total nutrition source for an infant.

TPN Goals

(See Table 13–1, 13–5)

- Use the same components whether giving peripheral or central TPN mixtures. Begin with the standard solution as specified in Table 13–5 and advance volume as tolerated to a maximum of 130 mL/kg per day, which will meet most nutrient requirements. In critically ill infants who require substantial volume infusion of medications or who need frequent adjustment of electrolytes, consider concentrating TPN constituents into a smaller volume as medically feasible.

Table 13–6a. Suggested feeding schedules [1,2]

BW (g)	Initiation Rate	When to Advance	Advancement Rate
<1250	15-20 mL/kg per day See advancement for <1250 g	Maintain for 3 days.	10-20 mL/kg per day
1250–1500	20 mL/kg per day	If feeds tolerated, may advance after 24-48 hours.	20 mL/kg per day
1500–2000	20 mL/kg per day	If feeds tolerated, may advance after 24-48 hours.	25-40 mL/kg per day
2000–2500	25–30 mL/kg per day	Advance daily.	25-40 mL/kg per day
Stable > 2500	50 mL/kg/day or ad-lib with minimum. Cardiac babies: 20 mL/kg per day	Cardiac babies may need 20 mL/kg for a longer period of time.	25-40 mL/kg per day

[1] Individualize initiation and advancement rates based on patient's weight, age and clinical status.
[2] Feedings for infants < 1500 grams are usually best given on a pump for 30–60 minutes.

Carbohydrate

- Provides the main energy source for an infant.
- Limit dextrose to 12.5% when administered by peripheral line.
- Generally initiated at a glucose infusion rate (GIR) of 4.5 to 6 mg glucose/kg per minute. Some ELBW infants may only tolerate 3.5-4.5 mg glucose/kg per minute of glucose in the first day of life
- Generally advance by 1-2 mg glucose/kg per minute if blood glucose <130-150 mg/dL
- Advance glucose usually to a goal GIR of 11-12 mg glucose/kg per minute
- If glucose persistently >280-300 mg/dL, reduce GIR to 3.5 mg glucose/kg per minute prior to initiating insulin.

Amino Acids

- All infant TPN solutions routinely use the amino acid solution TrophAmine®, which promotes plasma amino acid concentrations similar to the breastfed infant. Premasol® may also be used.
- Current recommendations are 3.5 - 4 g protein/kg per day (preterm infants) and 1.5-3 g protein/kg per day (term infants). Infants with poor growth, gastrointestinal disease, surgery, or other protein- losing states require up to 4 g protein/kg per day.
- Provide a maximum of 3 grams of protein/kg/day for infants 23-24 6/7 GA for the first 3 days of life.
- The amino acid cysteine is always added at 30 mg/g amino acids, which improves Ca and P solubility.

Intravenous Lipid (IL)

IL provides essential fatty acids and is a calorie-dense energy source.

- 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. Intralipid, at 0.5 to 1 g (2.5 to 5 mL) per kilogram per day, will provide minimum requirements.
- Use a continuous infusion at a constant rate. Initiate per protocol. **(see Initial TPN: Neonatal Early and Starter Solutions)**
- Advance infants < 1000 g BW or < 27 0/7 weeks gestational age, by 0.5-1g/kg/day if TG is < 250 mg/dL. Monitor after each advancement.
- Infants that are SGA, IUGR, on steroids, or those believed to be septic may require serum triglyceride (TG) monitoring before every advancement targeting values <250 mg/dL.
- Monitoring of TG is generally not needed with every advancement in infants not listed above.
- Advance as tolerated to a goal of 3 g/kg/day (15 mL/kg/day)

Some infants may persistently have TGL values of 200-400 mg/dL. IL should be provided at 0.5 g/kg/day daily despite these values. If values are above 400 mg/dL, hold IL, recheck TGL, and resume IL at 0.5 g/ kg/d (2.5 mL/kg/day) when < 400 mg/d

Lipid limiting strategy (LLS) for Parenteral Nutrition Associated Liver Disease. There is increasing evidence that, limiting the intralipid infusion rates to 1 g/kg/day in infants with Parenteral Nutrition Associated Liver Disease (PNALD) and a conjugated bilirubin > 1.5 mg/dL may be beneficial. Some VLBW infants may require 2 g/kg/day of lipids for growth. Consultation with the nutrition service should be obtained. It is not necessary to decrease prophylactically the intralipids infusion rate in the absence of any evidence of cholestasis. When lipid limiting strategy is initiated, caregivers at TCH and other BCM affiliated nurseries should discuss the potential need of Omegaven® in the future with either Dr. Premkumar or Dr. Hair. **(See Chapter 5-Gastroenterology-Cholestasis Section)**

Vitamins and Minerals

- M.V.I. Pediatric is provided as a standard dose based on weight **(see Table 13–5).**
- Limit peripheral calcium and phosphorous to 1.2 mmol /100 mL.
- Since solubility of Ca and P is a concern, never reduce the amino acids to less than 2.4% without reducing the Ca and P. At 2.4% amino acids, up to 2 mmol of calcium gluconate and potassium phosphate may be provided per 100 mL. Usual additions of acetate (1 to 2 mEq/100 mL) should not affect solubility. Do not remove P from TPN for more than 48 hours without also adjusting Ca and following serum ionized calcium.
- 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, 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 TPN 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. (**See Chapter 10-Metabolic Management-Hypocalcemia and Hypercalcemia Sections)**

Table 13-6b. BW ≤ 750 g Feeding Guidelines

Day of Life	Kcal/oz EBM[1] or Donor EBM	Feeding Volume (mL/kg/day)	TPN (mL/kg/day)	Lipids (mL/kg/day)	Total Fluid[2] (mL/kg/day)
1	20	15-20[3]	100[4]	2.5[5]	130
2	20	15-20[3]	100	2.5-5	140
3	20	15-20[3]	100	5-10	140
4	20	40	95	10-15	150
5	20-26 (add Prolact + 6)[6]	60	75	15	150
6	20-26 (Prolact + 6)	80	55-70	15 or Off Lipids	150
7	20-26 (Prolact + 6)	100	50	0	150
8	24 (add Similac HMF)[7]	100	50	0	150
	or 26 (Prolact + 6)	120	Off TPN	0	120
9	24 (Similac HMF)	120	Off TPN	0	120
	26 (Prolact + 6)	140	0	0	140
10	24 (Similac HMF)	140	0	0	140
	26 (Prolact + 6)	150-160	0	0	150-160
11	24 (Similac HMF) or 26 (Prolact + 6) [8,9]	150-160	0	0	150-160

1 EBM = expressed breast milk

2 Anticipated total fluids include TPN, lipids, TKO's, medications and flushes. Volume available for TPN 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. **See Table 10-2 in Metabolic Chapter**

4 Standard starter used when TPN room closed (1PM – 10AM).

5 For infants <1000 gram birth weight or <27 weeks gestation, see IL initiation protocol.

6 Add Prolact +6 to EBM at 60 mL/kg.

7 If Prolacta is unavailable use Similac HMF Hydrolyzed Protein Concentrated Liquid. After 1 day of 100 mL/kg of enteral feeds, fortify EBM with 4 packets of Similac HMF Hydrolyzed Protein Concentrated Liquid to reach 24 kcal/oz

8 Add poly-vi-sol and fer-in-sol after parenteral nutrition is discontinued for infants consuming EBM + Prolacta and fer-in-sol after parenteral nutrition is discontinued for infants consuming EBM + Similac HMF. The infant should be at least 14 days of age for iron supplementation.

9 Provide iron supplementation at 2-3 mg/kg for infants < 1500 g birthweight.

Table 13-6c. BW 751-1250g Feeding Guidelines

Day of Life	Kcal/oz EBM[1] or Donor EBM	Feeding Volume (mL/kg/day)	TPN (mL/kg/day)	Lipids (mL/kg/day)	Total Fluid[2] (mL/kg/day)
1	20	15-20[3]	80[4]	2.5-5[5]	80-110
2	20	15-20[3]	80-100	5-10	120-130
3	20	15-20[3]	90-100	10-15	120-130
4	20	40	95	15	150
5	20-26 (add Prolact + 6)[6]	60	75	15	150
6	20-26 (Prolact + 6)	80	55-70	15 or Off Lipids	150
7	20-26 (Prolact + 6)	100	50	0	150
8	24 (add Similac HMF)[7]	100	50	0	150
	or 26 (Prolact + 6)	120	Off TPN	0	120
9	24 (Similac HMF)	120	Off TPN	0	120
	26 (Prolact + 6)	140	0	0	140
10	24 (Similac HMF)	140	0	0	140
	26 (Prolact + 6)	150-160	0	0	150-160
11	24 (Similac HMF) or 26 (Prolact + 6)[8,9]	150-160	0	0	150-160

1 EBM = expressed breast milk

2 Anticipated total fluids include TPN, lipids, TKO's, medications and flushes. Volume available for TPN 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. **See Table 10-2 in Metabolic Chapter**

4 Standard starter used when TPN room closed (1PM – 10AM).

5 For infants <1000 gram birth weight or <27 weeks gestation, see IL initiation protocol.

6 Add Prolact +6 to EBM at 60 mL/kg.

7 If Prolacta is unavailable use Similac HMF Hydrolyzed Protein Concentrated Liquid. After 1 day of 100 mL/kg of enteral feeds, fortify EBM with 4 packets of Similac HMF Hydrolyzed Protein Concentrated Liquid to reach 24 kcal/oz

8 Add poly-vi-sol and fer-in-sol after parenteral nutrition is discontinued for infants consuming EBM + Prolacta and fer-in-sol after parenteral nutrition is discontinued for infants consuming EBM + Similac HMF. The infant should be at least 14 days of age for iron supplementation.

9 Provide iron supplementation at 2-3 mg/kg for infants < 1500 g birthweight.

Table 13-6d. BW 1251-1500 g Feeding Guidelines

Day of Life	Kcal/oz EBM[1] or Donor EBM	Feeding Volume (mL/kg/day)	TPN (mL/kg/day)	Lipids (mL/kg/day)	Total Fluid[2] (mL/kg/day)
1[3]	20	20	70[4]	10	80
2	20	40	65	15	100-120
3	20-26 (add Prolact + 6)[5]	60	55	15	100-120
4	20-26 (Prolact + 6)	80	50	Off Lipids	150
5	20-26 (Prolact + 6)[5]	100	50	0	150
6	24 (add Similac HMF)[6]	100	50	0	150
	or 26 (Prolact + 6)[5]	120	Off TPN	0	120
7	24 (Similac HMF)	120	Off TPN	0	120
	26 (Prolact + 6)	140	0	0	140
8	24 (Similac HMF)	140	0	0	140
	26 (Prolact + 6)	150-160	0	0	150-160
9	24 (Similac HMF) or 26 (Prolact + 6)[7,8]	150-160	0	0	150-160

1 EBM = expressed breast milk

2 Anticipated total fluids include TPN, lipids, TKO's, medications and flushes. Volume available for TPN 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).

4 Standard starter used when TPN room closed (1PM – 10AM).

5 Add Prolact +6 to EBM at 60mL/kg.

6 If Prolacta is unavailable use Similac HMF Hydrolyzed Protein Concentrated Liquid. After 1 day of 100 mL/kg of enteral feeds, fortify EBM with 4 packets of Similac HMF Concentrated Liquid to reach 24 kcal/oz.

7 Add poly-vi-sol and fer-in-sol after parenteral nutrition is discontinued for infants consuming EBM + Prolacta and fer-in-sol after parenteral nutrition is discontinued for infants consuming EBM + Similac HMF. The infant should be at least 14 days of age for iron supplementation·

8 Provide iron supplementation at 2-3 mg/kg for infants < 1500 g birthweight and at 2 mg/kg for infants 1500 to 2500 g birthweight

Table 13-6e. BW 1501-2000 g Feeding Guidelines

Day of Life	Kcal/oz EBM/Donor EBM[1] or premature formula	Feeding Volume (mL/kg/day)[2]	IVF (mL/kg/day)	Total Fluids[2] (mL/kg/day)
1	20-24[3]	20	60	80
2	20-24	50	30	100
3	20-24	80	30	100
4	20-24	110	Off IVF	110
5	24 (Similac HMF)[4,5]	110	0	110
6	20-24	130	0	130
7	20-24	150	0	150
8	20-24	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.

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 ≥100 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 <1800-2000 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 for infants 1500 to 2500 g birthweight

Trace Elements

The pharmacy adds trace elements as a standard dose based on weight. **(See Table 13–5)**

- The trace element solution is prepared as 2 components. Only the zinc (Zn) can be modified. Zn doses can be independent of other trace elements.
- In infants with significant secretory losses of Zn (e.g., those with gastrointestinal diseases or surgery), increase the Zn concentration by 400 mcg/kg per day for preterm infants and 100 to 250 mcg/kg per 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 > 1.5 mg/dL) it is recommended to reduce trace minerals in the TPN. 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 with cholestasis while on TPN (to monitor copper and zinc levels, send 5 mL of blood in tall dark blue tube without additives). In the presence of cholestasis without either jejunostomy or ileostomy, trace minerals (including copper and manganese) should be provided 3 times per week (Monday, Wednesday and Friday), and parenteral zinc 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 checked when medically feasible.

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 **(See Table 13-5).**

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 per day) if the infant is expected to be on TPN exclusively for longer than 14 days.

Volume Restricted TPN (Extracorporeal Membrane Oxygenation (ECMO) or Total Body Cooling)

Infants with severe cardiopulmonary disease or those requiring ECMO or total body cooling should be provided at least 2 g/kg/day of protein with an attempt to provide 2.5-3 g/kg/d as soon as feasible. Use of volume to provide protein is of greater importance in this setting than providing more than 1 g/kg/d of lipids 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 TPN based on blood levels. Recommended goal parenteral nutrition composition for ECMO given in **Table 13–7a. Recommended goal parenteral nutrition composition** for cooling given in **Table 13-7b**.

Table 13-7a. Volume Restricted Goal TPN for ECMO 70mL/kg + 15 mL fat (3 grams/kg)[1]

Nutrient	Order/100mL	Amount/kg	Goal Intake/kg
Dextrose	22%	15.4 g (10.7 mg/kg/min)	16 g (11-12 mg/kg/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	0.2 mEq	
		96 kcal(PN + IL)	90-110 kcals

[1] Order electrolytes as needed. Order vitamins and trace minerals.

Table 13-7b. Volume Restricted TPN for Total Body Cooling- 40 mL/kg + 5 mL fat (1 gram/kg)[1]

Nutrient	Order/100mL	Amount/kg	Goal Intake/kg
Dextrose	25%	10 g (6.9 mg/kg/min)	16 g (11-12 mg/kg/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)	90-110 kcals

[1] Order electrolytes as needed. Order vitamins and trace minerals.

Managing Slow Growth in TPN-nourished Infants

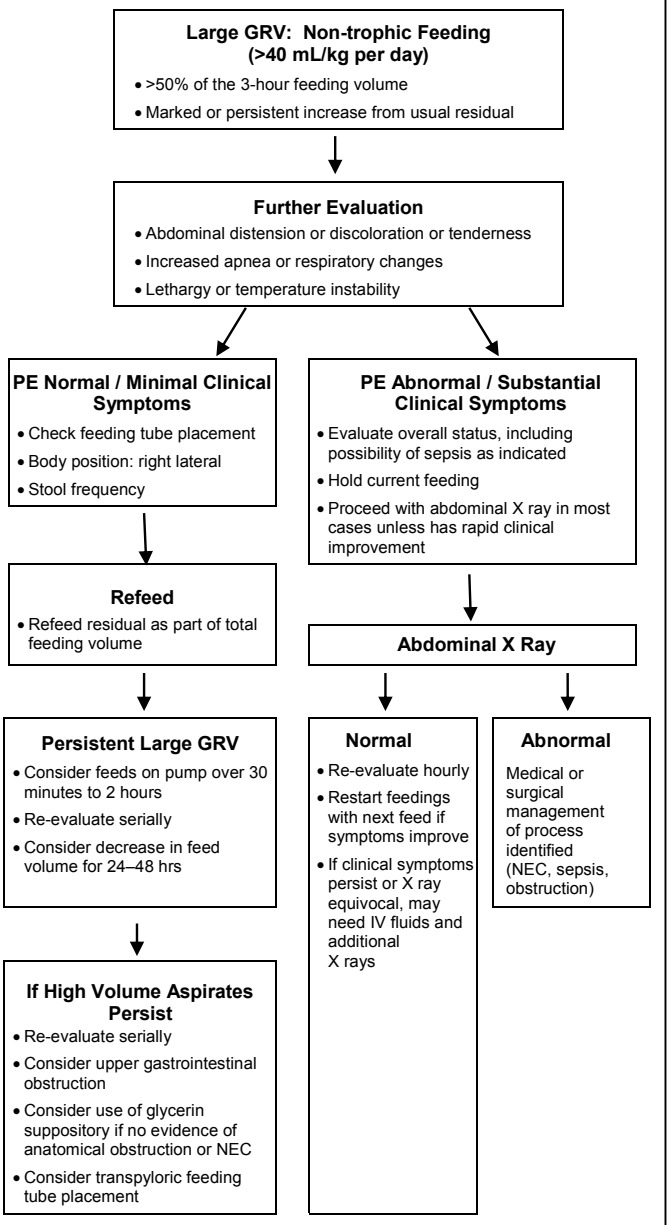
- Treat abnormalities that are unrelated to nutrition that might affect growth, such as metabolic acidosis, hyponatremia, increased work of breathing, cold stress, anemia, use of steroids, and infection.
- Assure that intake is within recommended levels. Adjust TPN as appropriate.
- Generally, the unbalanced addition of carbohydrate is not recommended to increase total calorie intake.

Stop Parenteral Nutrition

- Stop IL when feeds are greater than or equal to 80 mL/kg per day.
- Stop TPN when feeds are greater than or equal to 100 mL/kg per day except in infants with intestinal failure.

Figure 13-1. Feeding tolerance algorithm

Check gastric residual volume **(GRV)** every 3 hours for infants receiving > 40 mL/kg of feedings or infant appears ill. There is no strong evidence for the evaluation of residuals in most VLBW infants. Evaluate infant if residuals exceed 50% of the feeding volume or the infant has other systems of feeding intolerance.



Enteral Nutrition

Human milk is recommended for nearly all infants **(see exceptions in Human Milk section of this chapter**). Unless feeding intolerance necessitates a slower pace, follow the schedules in **Tables 13–6a, 6b, 6c, 6d, 6e and Figure 13–1**. Volumes are approximate. Nutrient components of human milk & fortified human milk are listed in **Table 13-10a**. When infant formula is used, it should be selected based on the infant's gestation, birth weight and/or medical condition **(see Tables 13-8, 13–9 and 13-10b).** The volume of full feedings that enables a good growth rate (15-20g/kg per 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 fortified human milk (24-26 kcal/oz).
  - » 150 mL/kg per day of high protein preterm formula (24 kcal/oz).
  - » 160-170 mL/kg per day premature transitional formula (22 kcal/oz).

  Infants of PMA 34 weeks or greater,
  - » 180 to 200 mL/kg per day of unfortified human milk or term formula (20 kcal/oz).
  - » Cue-based feeding with a minimum of 150 mL/kg per day may be used.
- **Energy intakes** of 100 to 130 kcal/kg per day will meet the needs for term and premature infants.
- **Protein intakes** of 3.5 to 4 g/kg per day will meet the needs for premature infants. Protein intakes of 1.5 g/kg per day will meet the needs of healthy term infants. Illness or surgery increases the need to 2-3 g/kg per day for the term infant.

Table 13–8. Milk Selection[1]

Milk	Indication
Human milk*	Milk initiation for all infants and single milk source for infants >1800-2000 g and >34 weeks' PMA [2]
Human milk + Prolacta [3,4,5]	Birth weight < 1250 g
Human milk + bovine milk-based fortifier [4,5,6]	Birth weight > 1250 g and < 34 wks PMA
Premature infant formula with iron [4]	Birth weight < 1800-2000 g or < 34 wks PMA
Term formula with iron [7]	Birth weight >1800-2000 g or > 34 wks PMA, and able to consume at least 180mL/kg per day
Premature transitional formula with iron	Premature infants post discharge with birth weight < 1800 g [8]

PMA = postmenstrual age

*Consider donor human milk supplementation of mother's milk for infants < 1500 g.

[1] See **Table 13–9** 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, premature infant formula or fortified human milk should not be fed ad lib.

[5] For infants < 1250 g BW, if Prolact+ 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 HMF when an infant has tolerated at least 100 mL/kg per day unfortified milk or if unfortified human milk has been used at >50 mL/kg per day for 5 to 7 days. Add 4 vials of HMF per 100 mL milk, thereafter.

[7] The neonatology section recommends use of term 20 kcal/oz formula for premature infants when term formula is indicated.

[8] 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.

Table 13-9 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, galacto-oligosaccharides	concentrated human milk protein	human
Donor human milk cream fortifier (pasteurized)	caloric fortifier	none	none	human milk cream
Human milk fortifier bovine milk-base	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 corn maltodextrin, lactose	nonfat milk and whey protein concentrate or enzymatically hydrolyzed whey protein isolate	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 g, on limited volume intake or history of osteopenia or poor growth	corn syrup solids, lactose	nonfat milk and whey protein concentrate	20–25% MCT oil, soy oil, coconut oil, high oleic sunflower and/or safflower oil, DHA, ARA
Special Use				
Alfamino®	cow's milk protein allergy, multiple food allergies, malabsorptive conditions, short bowel syndrome	corn syrup solids, potato starch	100% synthetic 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) or fat malabsorption	sucrose, modified tapioca starch, corn maltodextrin	casein hydrolysate with added amino acids	33% MCT oil, high-oleic safflower, soy oils, DHA, ARA
Elecare®	intolerance to intact protein (cow's milk) or hydrolyzed protein, severe food allergies, malabsorption, short-bowel syndrome, GI tract impairment	corn syrup solids	100% synthetic 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	calcium caseinate, sodium caseinate	84% MCT oil, soy oil, DHA, ARA
Gerber Extensive HA®	cow's milk protein allergy	corn maltodextrin, potato starch	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 protein intolerance, intolerance to hydrolyzed protein, short bowel syndrome, malabsorption	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 oil, DHA, ARA
Puramino®	severe cow's milk protein allergy and/or multiple food protein allergies, or not tolerating protein hydrolysates	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, 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	normal nutrition for term infants, low mineral formula for infants with hypocalcemia or renal disease	corn maltodextrin, lactose, galacto-oligosaccharides	whey protein concentrate (from cow's milk, enzymatically hydrolyzed, reduced in minerals)	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	whey, casein	human milk fat
Term formulas with iron, 20 kcal/oz	normal nutrition for term infants	Lactose and/or corn maltodextrin, galacto-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, coconut, soy, and high oleic sunflower, high oleic safflower oils), DHA, ARA
Soy formulas with iron, 20 kcal/oz**	galactosemia, hereditary lactase deficiency (rare), vegetarian diet, not indicated for use in preterm infants	corn syrup solids or corn maltodextrin, sucrose	soy protein isolate, enzymatically hydrolyzed soy protein isolate	vegetable oil (soy, coconut, 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.

Table 13-10a. 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	47	23	13	0.8	1.2	1.2	0.2	0.06	160	1	8.8	295[2]
EBM + Prolact+4 = 24[3]	24	82	1.9	9	4.6	50	8.2	40	121	64	2.2	2.3	1.8	0.9	0.2	189	27	19.4	NA[4]
EBM + Prolact+6 = 26[3]	26	90	2.4	11	5.2	52	8.4	38	122	64	2.3	2.2	1.8	0.9	0.2	204	40	22.4	NA[4]
EBM + Prolact+8 = 28[3]	28	97	2.9	12	5.7	53	8.4	35	122	64	2.3	2.3	2	0.9	0.2	218	53	25.5	NA[4]
EBM + Prolact+10 = 30[3]	30	105	3.5	13	6.3	54	8.6	33	123	64	2.4	2.3	1.9	0.9	0.3	233	65	28.4	NA[4]
EBM + Prolact+8 (1:1 ratio) = 30[3]	30	104	3.5	13	6.3	54	8.5	33	147	76	2.6	2.6	2.2	1.1	0.3	232	65	29.7	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	0.7	0.3	503	65	16.3	NA[4]
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	455
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	1.6	3	2.5	1.3	0.6	817	124	25	NA[4]
Similac FEBM[5] + EnfaCare = 27	27	90	2.7	12	4.2	41	10.2	45	131	75	1.6	2.9	2.6	1.3	0.6	826	124	24.9	NA[4]
Similac FEBM[5] + NeoSure = 30	30	100	2.9	12	4.7	43	11.1	45	139	78	1.5	3.4	2.8	1.4	0.8	840	129	27.2	NA[4]
Similac FEBM[5] + EnfaCare = 30	30	99	2.9	12	4.6	42	11.1	45	141	79	1.5	3.2	2.8	1.4	0.8	857	130	26.9	NA[4]

1 Adapted from American Academy of Pediatrics Committee on Nutrition: Pediatric Nutrition Handbook, 7th ed. 2014

2 Adapted from Jensen RG, ed. Handbook of Milk Composition, 1995

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

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 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 Program with any questions regarding specific medications.

Suggested Reading

1. Hale TW, Rowe HF.*2014 Medications and mothers' milk.* 16th Edition. Plano, TX: Hale Publishing, 2014.
2. InfantRisk Center – http://www.infantrisk.org
3. Lactmed: Drugs and Lactation Database – http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

TCH Donor Human Milk Protocol

Maternal assent must be obtained and documented in the electronic medical record prior to giving any donor human milk product. All very low birth weight infants (< 1500 g) are eligible for donor HM.

Other potential indications for donor HM (infants >1500 g):

- 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

Table 13-10b. Nutritional components of commercial formulas

	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 Infant 20	20	68	1.4	8	3.6	48	7.6	44	53	29	0.8	1.9	1.2	0.7	1.2	203	41	12.5	300
Good Start Gentle 20	20	68	1.5	9	3.5	46	7.8	46	45	26	0.8	1.9	1.3	0.5	1	203	51	13.3	250
Similac Advance 20	20	68	1.4	8	3.7	49	7.6	45	53	28	0.7	1.8	1.2	0.5	1.2	203	51	12.7	NA[3]
Similac Advance 19	19	64	1.3	8	3.5	49	7.2	43	53	28	0.7	1.8	1.2	0.5	1.2	193	48	12.3	310
Enfamil 24RTF[2]	24	81	1.7	8.5	4.3	48	9.1	43.5	63	35	0.9	2.2	1.4	0.8	1.5	240	61	15.4	370
Similac Advance 24	24	81	1.7	8	4.3	49	9.1	45	63	34	0.8	2.2	1.5	0.6	1.5	243	61	15.2	NA[3]
Enfamil Premature20	20	68	2.2	13	3.4	44	7.3	43	112	61	2.1	1.7	2	1	1.2	910	200	20	260
Gerber Good Start Premature 20	20	68	2	12	3.5	47	7.1	42	111	57	1.6	2.1	1.6	0.9	1.2	676	122	18.7	229
Similac Special Care 20	20	68	2	12	3.7	47	7	41	122	68	1.3	2.2	1.6	1	1.2	845	101	18.8	235
Enfamil Premature24 HP[4]	24	81	2.9	14	4.1	44	8.5	42	134	73	2.5	2.0	2.4	1.2	1.5	1100	240	26	300
Enfamil Premature24	24	81	2.7	13	4.1	44	8.8	43	134	73	2.5	2.0	2.4	1.2	1.5	1100	240	25	320
Gerber Good Start Premature 24 HP[4]	24	81	2.9	14	4.2	47	7.9	39	133	69	2.0	2.5	2.0	1.1	1.5	813	146	25.4	299
Gerber Good Start Premature 24	24	81	2.4	12	4.2	47	8.5	42	133	69	2.0	2.5	2.0	1.1	1.5	813	146	22.5	275
Similac Special Care24 HP[4]	24	81	2.7	13	4.4	47	8.1	40	145	81	1.5	2.7	1.9	1.2	1.5	1008	121	24	280
Similac Special Care 24	24	81	2.4	12	4.4	47	8.3	41	145	81	1.5	2.7	1.9	1.2	1.5	1008	121	22.6	280
Similac Special Care27 HP[4]	27	91	2.9	13	5.5	55	7.9	35	164	91	1.7	3	2.1	1.4	1.6	1135	136	26	305
Enfamil Premature30	30	100	3.3	13	5.1	44	10.9	43	167	91	3.1	2.6	3.1	1.5	1.8	1370	300	30	320
Gerber Good Start Premature 30	30	101	3	12	5.3	47	10.7	42	166	86	2.4	3.1	2.5	1.3	1.8	1015	183	28.1	341
Similac Special Care 30	30	101	3	12	6.7	57	7.8	31	182	101	1.9	3.3	2.3	1.5	1.8	1263	152	28.2	325
Enfamil EnfaCare 22	22	75	2.1	11	3.9	47	7.7	42	89	49	1.2	2	1.7	0.7	1.3	330	56	18.4	230
Similac NeoSure 22	22	75	2.1	11	4.1	49	7.5	40	78	46	1	2.7	1.6	0.9	1.3	261	52	18.7	250
Enfamil EnfaCare 24	24	81	2.3	11	4.2	47	8.4	42	97	54	1.3	2.2	1.8	0.8	1.4	357	60	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	1.4	280	56	20.2	NA[3]
Enfamil EnfaCare 27	27	92	2.6	11	4.8	47	9.5	42	110	61	1.5	2.4	2	0.9	1.6	403	68	22.4	NA[3]
Similac NeoSure 27	27	90	2.5	11	5	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	30	101	2.8	11	5.3	47	10.5	42	121	67	1.6	2.7	2.2	1	1.8	445	75	24.8	NA[3]
Similac NeoSure 30	30	100	2.8	11	5.5	50	10.1	40	105	62	1.4	3.6	2.1	1.2	1.8	350	70	25.2	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	203	34	16.9	260
Pregestimil 20	20	68	1.9	11	3.8	48	6.9	41	64	35	1.4	1.9	1.7	0.7	1.2	236	34	16.9	290
Pregestimil 24	24	81	2.3	11	4.5	48	8.2	40	76	42	1.6	2.3	2	0.8	1.5	282	40	20	340
Similac Expert CareAlimentum 20	20	68	1.9	11	3.7	48	6.9	41	71	51	1.3	2.0	1.6	0.5	1.2	203	30	17.1	370
Elecare 20	20	68	2.1	15	3.3	43	7.3	42	79	57	1.4	2.7	1.2	0.8	1.2	186	41	19	350
Neocate 20	20	68	1.9	11	3.5	46	7.3	43	79	56	1.2	1.9	1.5	0.8	1.0	190	50	16.8	340
PurAmino 20	20	68	1.9	11	3.5	47	7.2	42	64	35	1.4	1.9	1.7	0.7	1.2	203	34	16.9	350
Alfamino 20	20	68	1.9	11	3.4	45	7.4	44	80	53	1.1	1.8	1.6	1.1	1.22	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	1.2	0.5	0.5	204	41	12.4	280
Enfaport 20	20	67	2.4	14	3.7	46	6.8	40	64	35	0.9	2	1.7	0.7	1.2	240	34	19.5	170

[1] All formulas are with iron [2] Ready-to-Feed [3] NA = not available [4] HP = High Protein

- formula" this should be honored unless there is a special medical indication to use an infant formula.

Prolacta® (Donor Human Milk Fortifier) Indications:

- BW ≤ 1250 grams.
- Initial feeding in infants with history of NEC or intestinal perforation/obstruction
- Intolerance to formula or bovine milk-based HMF
- Large PDA
- Prolacta® possible uses (individualized decision, discuss with nutrition team): Impaired blood flow: such as congenital heart disease; Major congenital bowel disorders (e.g., gastroschisis)
- Prolacta® should generally not be used in the presence of cholestasis (conjugated bilirubin > 2mg/dL). Discuss with nutrition team.
- The use of commercial cow milk based HM fortifier is an acceptable option for infants 1250-1500 g BW although usual practice is to use Prolacta® in that setting

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.
- Mother's milk will be analyzed one time when Prolacta® Cream is started and then as needed depending on growth. Sample to be analyzed will be from a 24 hour feeding aliquot.
- Maximize protein intake, and initiate Prolacta® before adding Prolacta® Cream. **(See Table 13-11)**

Donor HM, Donor Human Milk Fortifier, or Donor Human Milk Cream Supplement should be continued until about 34 weeks PMA. In order to facilitate back transfer of VLBW

Table 13-11. 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
140	Prolact +8	4.1	2 kcal/oz
130	Prolact +8	3.8	2 kcal/oz

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®) after review with the TCH Neonatal Nutrition Team. Infants receiving donor HM or donor human milk fortifier should transition to formula at least one week prior to discharge.

Transitioning babies from donor HM 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 3-4, add 4 formula feedings
- Day 5, all formula feedings

Infants Less Than 34 Weeks' Gestation or Less Than 1800–2000 Grams Birth Weight

Initiation of enteral feedings and advancement rates should be individualized based on a patient's weight, age, and clinical status. Infants < 1250 grams should start on trophic feedings as soon as possible. Ill infants may be considered for trophic feeding as soon as clinically stable. Generally, testing with water feedings is discouraged. Trophic feedings are to enhance GI maturation not primarily to provide energy or nutrients. If tolerated and the clinical condition permits, advance by 10-20 mL/kg per day to full enteral feedings. Feedings should be given as bolus feedings every 3 hours. If infant has feeding intolerance consider feeds every 3 hours but given on a pump over 30 minutes. Trophic feedings can enhance feeding advancement, increase gastrin and other enteric hormone levels, and facilitate a maturing intestinal motor pattern.

- Infants who cannot feed orally require oro(naso) gastric feedings.
- Coordination of oral feeding often is developed by 32 to 34 weeks gestation.
- For initiation and advancement rates, **see Tables 13-6a, 6b, 6c, 6d, and 6e.**
- Add Prolact+6 (26 kcal/oz) (liquid donor human milk-based fortifier) when infant is at 60 mL/kg per day unfortified human milk.
- Add Similac® HMF Hydrolyzed Protein Concentrated Liquid fortifier when an infant has tolerated at least 100 mL/kg per day unfortified human milk or if unfortified human milk has been used at greater than 50 mL/kg per day for 5 to 7 days. Add 4 packets of fortifier per 100 mL of milk (24 kcal/oz). One packet of bovine-based fortifier equals 7.5 kcal per packet and is 5 mL.
- For infants < 1250 g BW, if Prolact+® fortifier is not available, infants should receive mother's own milk or donor human milk fortified with Similac® HMF Hydrolyzed Protein Concentrated Liquid.
- Generally, milk volume and concentration are not increased at the same time when using bovine fortifier. Advance the volume of fortified human milk until weight gain is satisfactory.
- Satisfactory weight gain is 15-20 g/kg per 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.
- Healthy premature infants who are consuming all feeds by mouth can receive unfortified human milk.

Vitamin and Mineral Supplementation

- **Table 13–12** provides guidelines.

Table 13–12. Vitamin and Mineral Supplementation

Premature infants receiving:	Adjusted by Weight or Condition	Vitamin/Iron Supplementation per day (suggested)	Iron Goals (mg/kg per day)[8,9]	Vitamin D Goals (IU/day)
Fortified breast milk (Prolacta)	< 2.5kg	2-3 mg/kg Fe 1 mL MV[1]	2-4	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)	2-4	800
Fortified breast milk (Similac HMF Concentrated Liquid)[2]		2-3 mg/kg Fe	2-4	200-400
Preterm formula		None	2-4	200-400
Fortified breast milk (Similac HMF Concentrated Liquid)[2]	If osteopenia or elevated alkaline phosphatase activity > 800	2-3 mg/kg Fe 1 mL D-Visol	2-4	800
Preterm formula	If osteopenia or elevated alkaline phosphatase activity > 800	1 mL D-Visol	2-4	800
Non-fortified human milk	< 2.5kg[3]	2 mg/kg Fe 1 mL MV[1]	2-4	400
Non-fortified human milk	> 2.5kg	1 mL MV with Fe[4]	2-4	400
Transitional formula	< 5 kg	0.5 mL MV with or without Fe[4,5]	2-4	400
Transitional formula	> 5 kg or > 6 months	None	2	400
Term formula	< 3 kg	0.5 mL MV with Fe[4]	2-4	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)[6]	400
Human milk	LOS > 1 week, SGA, < 2.5 kg, or multiple blood draws	1 ml MV with Fe[4]	2	400
Term formula	> 2.5kg	No	1	400[7]

[1] MV = Poly-Vi-Sol

[2] Fortified breast milk (Similac HMF Hydrolyzed Protein Concentrated Liquid)

[3] At discharge and 2 kg or greater can be discharged with 1 MV with Fe as infant will grow into iron intake

[4] Tri-Vi-Sol with iron or Poly-Vi-Sol with iron

[5] Infant will receive 2 mg of iron'/kg at 150 mL/kg of transitional formula. Goal is 2 to 4 mg iron/kg.

[6] Or iron containing complementary foods at 6 months

[7] May take several weeks to achieve

[8] Initiate iron supplementation when full feeds are tolerated and infant is at least 14 days of life

[9] Provide iron supplementation at 2-3 mg/kg for infants < 1500 g birthweight and at 2 mg/kg for infants 1500 to 2500 g birthweight

Infants 34 or More Weeks' Gestation and 1800-2000 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. **(See Table 13–8)**
- 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, **(See Tables 13–6a, and 6e).**
- Infants who are unable to feed orally require oro(naso) gastric feedings.
- Generally, infants 34 or more weeks' gestation and 1800 to 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. The neonatology section recommends that infant formulas < 20 kcal/oz not be used for premature infants, defined as those < 37 weeks gestation at birth. This recommendation is based on the lack of any data demonstrating either safety or health benefits of using lower calorie infant formulas in premature infants. The neonatology section recommends use of term 20 kcal/oz formula for premature infants when term formula is indicated.
- 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.
- 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 of BCM recommends that no infant be provided any commercial thickening agent designed to be added to infant formula or human milk in any our Level 2, 3 or 4 NICU settings. Consideration of the use of such agents should only be done in the context of an IRB-approved research protocol.
- Satisfactory weight gain is 20 to 30 grams per day after the 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 per day.

Vitamin and Mineral Supplementation

- Full-term, breast-fed 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, breast-fed 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 per day.

When to Use Enriched Formula, Fortifier, or Concentrated Formula

Generally, infants born at 34 weeks' gestation or more and 1800-2000 grams or more 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 per day for infants greater than or equal to 2 kg and less than 15 grams/kg per 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 per day), or have diagnoses such as BPD or CHD that require nutrient dense milk or formula.

Statement about use of powdered formulas – Powdered infant formulas are not commercially sterile and *Cronobacter spp* contamination has been reported with its use. 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 nutrient needs.

For infants fed human milk, consider breastfeeding plus a few feedings of formula or adding formula powder 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 and dilute 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

Infants with Chylothorax

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 calories per ounce. Enfaport® can also be used if fortification above 20 calories per ounce is needed (i.e. for 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 **Chapter 5-Gastroenterology.**

Infants with Probiotic Indications

Infants with severe diarrhea or post NEC, may benefit from probiotics supplementation. Consult with nutrition team before introducing probiotics to a NICU infant. A formula containing probiotics or Gerber®Soothe Colic Drops Probiotic Supplement may be used. Pasteurized and frozen human milk fed infants may in some cases also benefit from probiotics. In general, we do not routinely add probiotics to the diet of all infants, but these can be considered in the presence of symptoms including feeding intolerance.

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 also largely is based on infants who

received non-human milk containing enteral nutrition. Therefore, there are few data to base a definitive approach in our nurseries. However, the results of meta-analysis suggests the existence of TANEC especially in premature infants fed diets including infant formula. We recommend the following to enhance consistency in practice amongst our group based on the available literature.

Infants who are born at < 32 weeks PMA who receive a transfusion when < 36 weeks PMA should have feedings held for one feed (1-3 hours) prior to the transfusion, during the transfusion, and for one feed (1-3 hours) after the transfusion. Human milk fed infants may have trophic feedings continued or feedings decreased to trophic feeds during this time period. Infants should have a glucose-containing IV infusion provided when NPO (or trophic feeds), but not necessarily during the infusion if only one IV access site is available for the transfusion itself.

After completion of the transfusion, infants who are receiving human milk should resume full feeds after the single held feeding with close observation of clinical status. Those receiving infant formula should have feeds resumed more slowly with resumption of full volume feeds within 12-24 hours based on close clinical observation.

Older infants do not need feedings held except for infants with a history of NEC, intestinal failure or cardiac disease in whom consideration should be given for holding feeds as per the protocol above.

Tube-feeding Method

A variety of methods are available for tube feeding, and the approach used should be individualized to 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 as a feeding 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 birthweight who do not tolerate feeds although it is best to try to resume feeds over 30 minutes to 1 hour as soon as possible in these cases.
- Transpyloric continuous infusion may be needed in infants with severe gastroesophageal reflux, marked delays in gastric emptying, or both.

Guidelines for Oral Feeding

The majority of hospitalized neonates will have difficulty feeding orally by breast or bottle. This may be due to any or all 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

Figure 13-2. 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

- **See Figure 13-2 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, with an emphasis on safe oral feeding and infant's limited skills.
- 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 **(see Breastfeeding Low Birth Weight Infants section).**
- Initiate nonnutritive oral-motor stimulation (pacifier) as early as possible (e.g., stable, intubated).

Promoting a Positive Oral Feeding Experience

- Facilitate appropriate feeding skills (e.g., coordination of suck-swallow-breath).
- Prevent oral feeding problems (e.g., oxygen desaturation, apnea, bradycardia, aspiration) to achieve safe feeding.
- Prevent oral feeding aversion.

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.
  - » Encourage nursing staff to give detailed feedback on infant's oral feeding performance.
  - » Monitor feeding performance closely and document consistently.
  - » Consider advancing the number of oral feedings per day if infant shows good feeding skills with no oral aversion and demonstrates adequate endurance, even if feedings are partially completed.

Starting Oral Feeding

- At 32 to 34 weeks postmenstrual age (PMA), if clinically stable
- When off positive pressure device. May provide during nasal CPAP if medically stable.
- 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 consultations are in the admitting order sets. Occupational therapists will provide non-nutritive oral stimulation, bottle feeding assessments, bedside swallow assessments, transition to spoon feeding, and co-consult with speech pathologist for craniofacial disorders.
- 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. (**See Figure 13-3 My feeding care map provides visual map)**

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 by:
  - » Consider the presence of the lactation consultant during initial breast feeding to determine efficacy and teach mother how to assess infant's feeding ability.
  - » If indicated, measure milk intake during early breastfeeding by test weighing procedures.
    - o Test weighing measures are performed by weighing the clothed infant under exactly the same conditions before and after breastfeeding on an electronic scale.
    - o 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.

Discharge Planning

- Pre-discharge education and planning is key to breastfeeding success.
- Consider delaying initiation of bottle feedings until the infant achieves two successful breastfeeds a day for mothers who wish to achieve exclusive breastfeeding.
- Breastfeeding progression prior to discharge will depend upon the mother's availability and her infant's feeding ability.
- Consultation with the lactation nurse will provide individualized feeding strategies to assist in progression of breastfeeds.
- Factors to consider for individualized discharge nutrition plan include:
  - » Infant's nutrient and growth needs
  - » Infant's oral feeding ability
  - » Need for test-weighing procedures at home (uncommonly needed)
  - » 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.

Managing Slow Growth in Enterally Nourished Infants

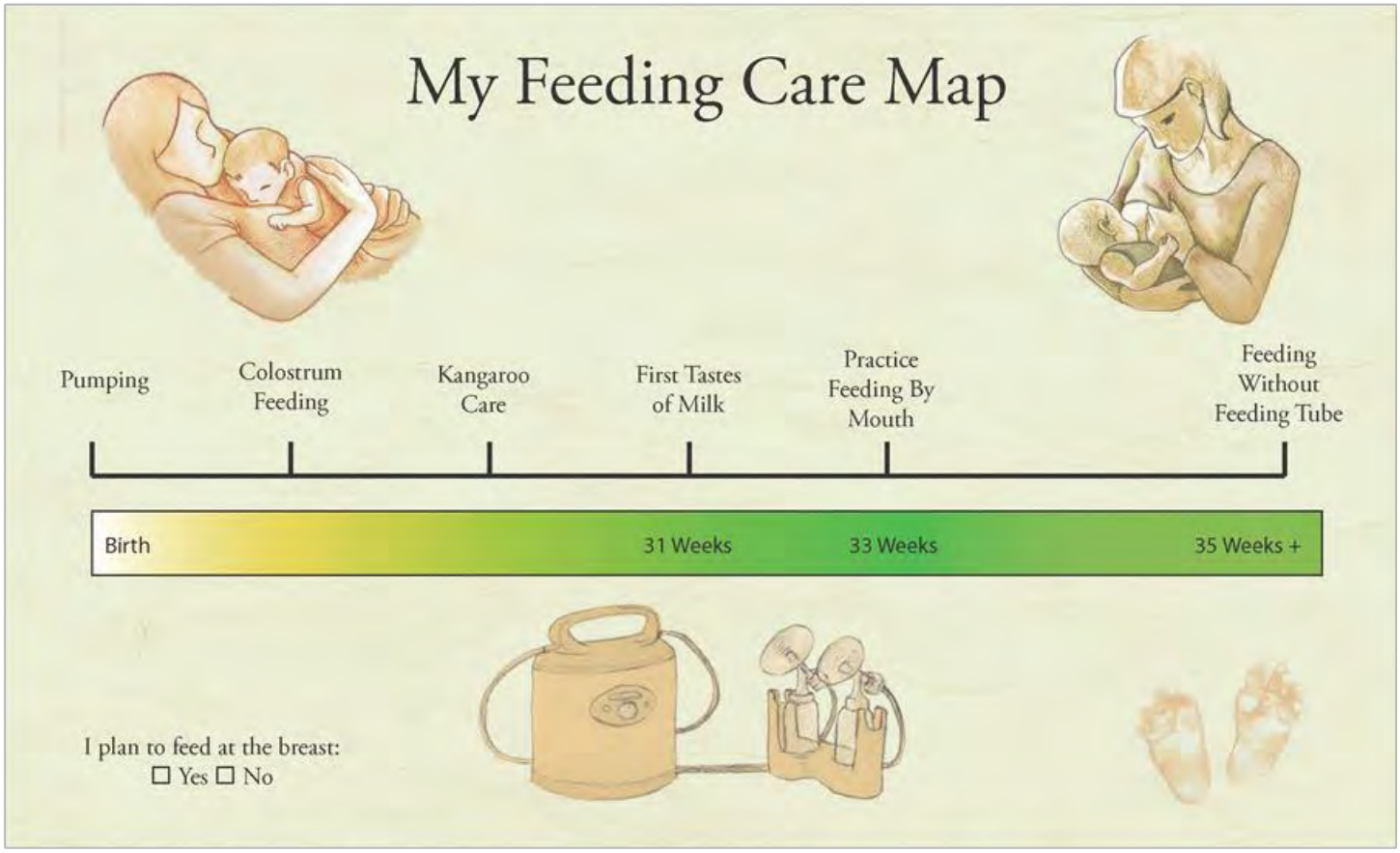
Intervention may be considered for weekly weight gain of less than 15 grams per/kg per day in infants less than 2000 grams or of less than 20 grams per day in infants greater than or equal to 2000 grams. Progress with the following steps sequentially. Allow 3 to 4 days between changes to the nutrition plan to allot sufficient time to evaluate the effects of any nutritional change(s). **(See Nutrition Assessment section on this page.)**

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 packets per 100 mL.
- 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 per day then advance stepwise as tolerated to about 160 mL/kg per day.
- If at goal feeding volume when using Prolacta®, ensure protein intake is meeting estimated needs then add Prolacta Cream at 2 kcal/oz.
- After initiating Prolacta® Cream, request nutrient analysis by milk bank of mother's own milk to determine fat and protein content. If results show milk is lower in caloric density, may increase to Prolacta Cream 4 kcal/oz.
- Advance Prolacta® 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.
- 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.
- Consult with nutrition team to give Abbott Liquid Protein fortifier.
- Alternate feedings between fortified expressed breast milk (FEBM) and 24 to 30 kcal/oz premature formula.
- 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.

Figure 13-3. My feeding care map



(Carmichael-Swanner, Hurst, Hair, July 2016)

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 160 mL/kg per day.
- When fluid volumes are restricted, use ready-to-feed preterm 30 kcal/oz formula and mix with preterm 24 kcal/oz formula to achieve a density greater than 24 kcal/oz.
- If poor growth persists and all other methods are exhausted then consider using single modulars (corn oil, MCT oil, carbohydrate, and protein supplements). Discuss with the registered dietitian for your team.

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. The webpage for the Fenton growth charts is http://www.ucalgary.ca/fenton and tools are available to calculate percentiles and z-scores to compare neonatal growth. **(See Table 13–13, Figure 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.

Table 13-13. Growth Rate Guidelines

Age	Weight	Length (cm/week)	FOC (cm/week)
Newborn Infants (Premature and Term)			
< 2 kg ≥ 2 kg	15 to 20 g/kg/day 20 to 30 g/day	0.8 to 1.1	0.8 to 1.0
Older Infants (> 4 months corrected gestational age)			
4 to 8 months 8 to 12 months	10 to 16 g/day 6 to 11 g/day	0.37 to 0.47 0.28 to 0.37	0.16 to 0.20 0.08 to 0.11

Table 13-14. Suggested Lab Table

	Conjugated bilirubin	• All infants screened during the first 48 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.
TPN	**Glucose**	• Blood glucose concentrations should be monitored in all infants receiving glucose infusions until stable » Monitor BG daily or more often until stable. » For ELBW, stressed, septic, or infants receiving insulin infusions usually monitor BG q 6-12 hrs[1]
	Ionized Calcium, Phosphorus	• Obtain ionized calcium at 24 hrs of age, then daily for first 3 days of life, as Ca and phos are advanced or until levels are stable[1] • If I Cal >1.45 mmol/L check serum phosphorus.
	BUN, Ca, Phos, Alk Phos, Conjugated Bilirubin, Glucose, Electrolytes, ALT	• Monitor after 14 days on TPN as clinically indicated
	Triglycerides	• **BW < 1000g or < 27 wks GA**. Check a TG at 4 & 12 hours after initiation of IL. Stop IL if TG is >250mg/dL. Advance as tolerated if TG is <250 mg/dL. • **BW ≥ 1000g or ≥ 27 at birth, SGA, IUGR,** received postnatal steroids, or believed to be septic. Monitor TG with every advancement. [2,3] • Monitoring TG is generally not needed with every advancement in infants not listed above.[2,3]
	Zinc, Copper	• Every 4 weeks while on TPN with cholestasis as medically feasible
	Ferritin	• Infants on TPN support for >6 weeks, expected to require TPN for an additional 4 weeks.
Enteral	**Alkaline Phosphatase, Phosphorus**	• BW <1500g. (Monitor on 35 days of age) • Monitor weekly until Alk phos <600 and phos >4.5 mg/dL • No need to monitor once Alk phos is <600 units/L and phos is >4.5 mg/dL. • BW >1500g. No need for routine nutritional monitoring. Monitor as clinically indicated.
	Hgb	• BW <1500g. As needed & prior to discharge • BW >1500g. Monitor as clinically indicated.
Prolacta	**Phosphorus**	• Obtain 3-5 days after TPN discontinued, & consider checking again 1 week later if phos is > 8mg/dL. • Serum phosphorus >10mg/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 ≤1000g or ≤27 weeks GA at birth.
[2] Infants with persistent TG values of 200-400 mg/dL should receive IL at 0.5 g/kg/day.
[3] Infants with TG values >400 mg/dL should resume IL at 0.5 g/kg/day when TG is <400mg/dL.

Parenteral Nutrition

Blood glucose concentration should be monitored in all infants receiving intravenous glucose 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.

See intravenous lipid section in this chapter for monitoring guidelines. An ionized calcium and phosphorus should be measured at 24 hours of age and daily during the first 3 days of age until levels have normalized. See sections on hypocalcemia, hypercalcemia and hyperphosphatemia in the metabolic chapter.

Labs to monitor as clinically indicated after 14 days of parenteral nutrition: BUN, Ca, P, alkaline phosphatase activity, electrolytes, glucose, direct bilirubin (conjugated), and ALT. All infants should have an initial conjugated bilirubin measurement made in the first 48 hours of life. (**See Chapter 5-Gastroenterology and Table 13-14. Suggested labs table)**

Suggested labs for 25-26 6/7 week (1st week of life):

- BG in delivery room, then 1 hr. after fluids started.
- BG/lytes and bili panel at 12 hrs.
- Monitor Na and BG every 12 hrs. for first 48 hrs.
- Obtain Chem 10 and ionized calcium daily for 1st 3 days.
- Obtain TG with every advancement

Suggested labs for 23-24 6/7 week (1st week of life):

- BG in delivery room, then check every hour, times 2 until stable. If glucose bolus is given, check BG 30 minutes after bolus.
- Monitor electrolytes and BG every 6 hrs for first 48 hrs.
- BG/lytes and bili panel at 12 hrs.
- Obtain Chem 10 and ionized calcium daily for 1st 3 days
- Obtain TG with every advancement

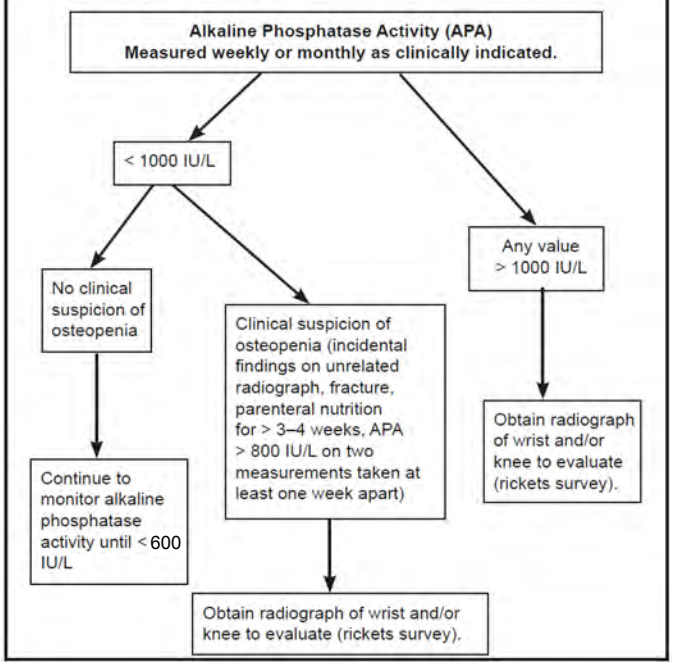
Enteral Nutrition

- **Infants with birth weight less than 1500 g.** Monitor serum phosphorus and alkaline phosphatase activity on day of age 35. Monitor weekly until alkaline phosphates is < 600 IU/L and serum phosphorus is > 4.5 mg/dL. Once alkaline phosphatase activity has declined to < 600 IU/L and serum phosphorous is stable at > 4.5 mg/dL there is no further need for monitoring. Hemoglobin should be monitored as clinically indicated and before discharge. Consider measurement of a serum ferritin before discharge in infants with a hemoglobin < 10 g/dl.
- **Infants > 1500 g birthweight.** There is no indication for any routine nutritional lab monitoring except for a hemoglobin before discharge. Infants who are fluid restricted, or have a prolonged course to full feeds should have phosphorous, alkaline phosphatase activity and hemoglobin monitored as clinically needed.
- **Infants receiving Prolacta®** should have serum phosphorus 3 to 5 days after TPN is discontinued and consider checking additionally 1 week later if initial value is > 8 mg/dL. Serum phosphorus >10 mg/ dL may require holding Prolacta® from all feeds for 1-2 days (or providing it with every other feeding). Obtain an ionized calcium and creatinine when serum phosphorus >10mg/dL. Oral calcium supplementation is generally not recommended in this setting. Discuss with nutrition team.

Osteopenia Risk

Flow Diagram to guide radiographic evaluation for severe osteopenia **see Figure 13-5.**

Figure 13-5. Flow diagram to guide radiographic evaluation for severe osteopenia / rickets.



Post discharge Nutrition

- 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.

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 1500 grams at birth and are discharged exclusively breastfeeding or exclusively fed unfortified human milk may be at risk for nutritional insufficiency including both growth-failure and metabolic bone disease. In addition to providing multivitamins and iron, it is recommended that they be evaluated 2 to 4 weeks after discharge. This evaluation should include weight, length, fronto-occipital circumference (FOC), serum phosphorus, and alkaline phosphatase activity.
- If supplement is needed due to prematurity, poor growth, inadequate volume intake, or fluid restriction:
  - » Suggest up to 3 feedings per day with a 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 not breastfeeding, add 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.
- 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 may benefit from direct dosing with minerals including calcium and phosphorus. Neonatal Nutrition consult is recommended in this case.

Infants on Premature or Premature Transitional Formula

For infants of birth weight less than 1800 grams or infants with a poor growth history, fluid restriction, or abnormal laboratory indices, transition to a premature transitional

formula (Enfamil® EnfaCare® 22 kcals/oz or Similac® NeoSure® 22 kcals/oz).

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. Encourage parents to use ready-to-feed only (until ~ 44 weeks PMA).

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

See Table 13–11.

Introduction of Solid Food to Older Premature Infant

In the NICU, 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.
- Iron-and zinc-fortified infant cereals and meats are excellent first foods.
- For infants with history of intestinal failure consider non-starchy vegetable (i.e. green beans) as a first food.

Figure 13-4a. Fenton growth chart – girls

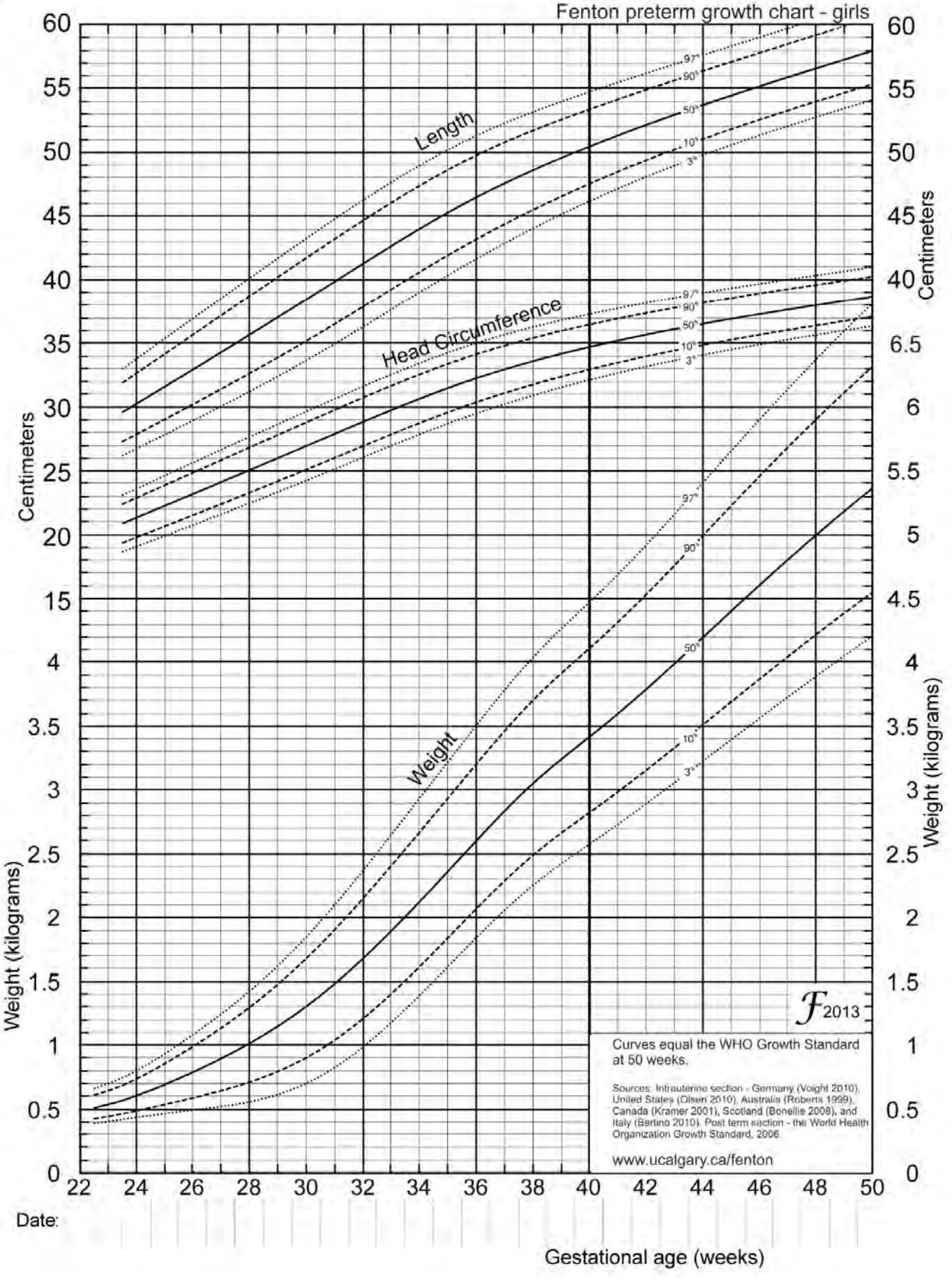
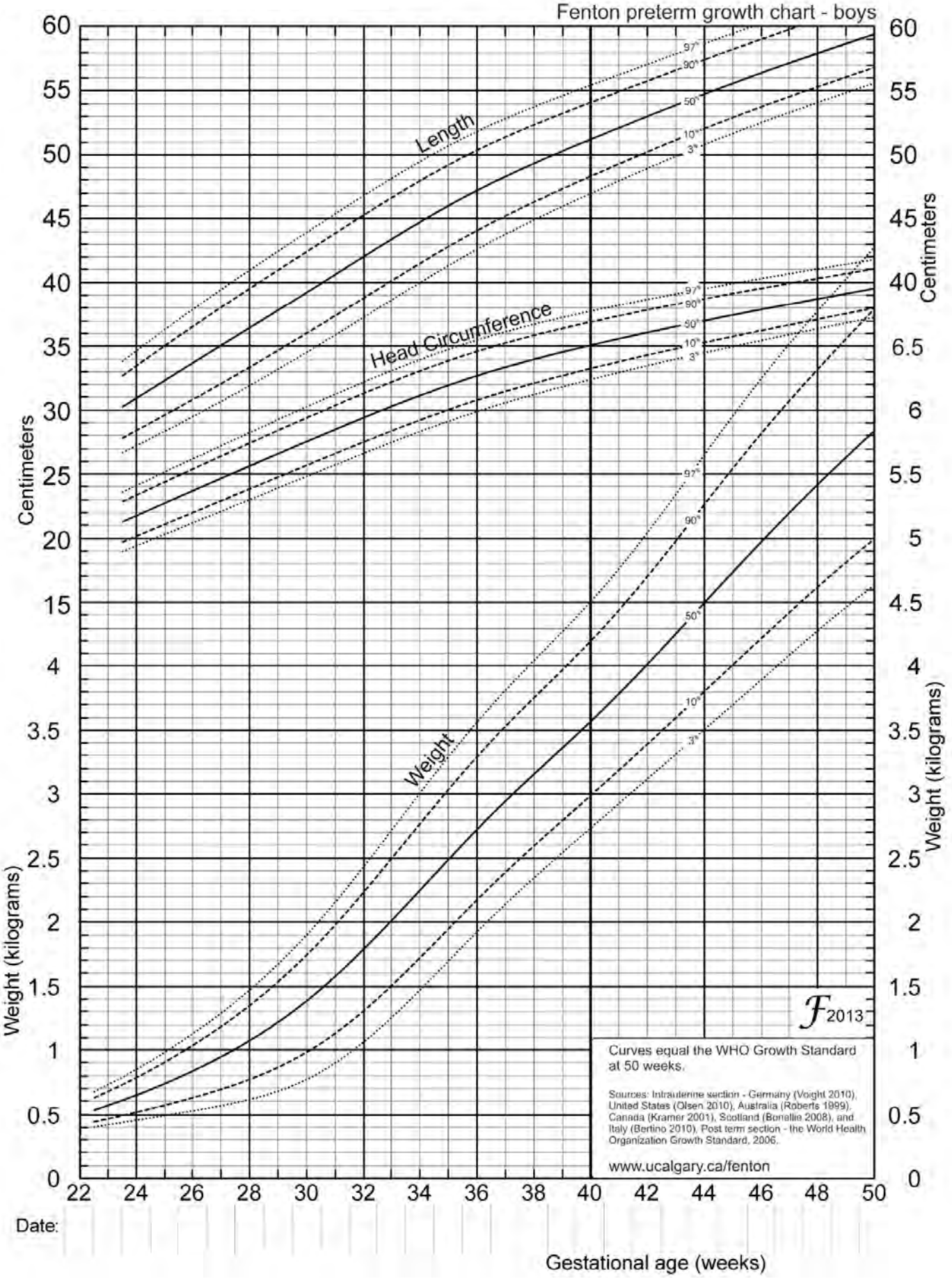


Figure 13-4b- Fenton growth chart - boys



Perioperative Management

General

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. **Most neonates with an emergent surgical condition will lose fluids by:**

- evaporation from exposed bowel,
- by "third spacing" of fluid in obstructed bowel, or
- by direct loss through emesis.

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.

Infants undergoing elective surgery may be given:

- formula up to 6 hours before surgery,
- breast milk up to 4 hours before surgery, and
- clear liquids containing glucose up to 2 hours prior to elective surgery.

While water constitutes approximately 80% of a neonate's total body weight, no infant should remain without fluid intake for longer than 6 hours. If surgery is delayed, IV fluids should be started. Infants with fever, vomiting, diarrhea, or undergoing bowel preparation should have IV infusions started the night prior to surgery.

In general, initial laboratory evaluation includes blood for type and cross-match, CBC, and platelet count. A newborn whose mother has a normal serum BUN and electrolytes also can be expected to have a normal set of electrolytes, BUN, magnesium, and calcium at the time of birth. However, in the child who has had significant fluid losses, serum electrolyte measurements are needed to modify initial empirical fluid and electrolyte replacement therapy. Baseline and follow-up blood gases are indicated in the evaluation of a severely compromised neonate.

If shock is present in a neonate with a surgical problem, it is considered due to hypovolemia until proven otherwise.

Deficits secondary to intravascular volume depletion can, and should, be corrected prior to surgery with proper fluid resuscitation, including the use of blood products. Polycythemia (HCT greater than 60) may be seen in neonates with gastroschisis and, if symptomatic, a partial exchange transfusion may be necessary. With the resuscitation fluid, a solution of 10% dextrose also should be started to assure adequate glucose availability. Hyperglycemia, glucosuria, and subsequent dehydration, particularly prevalent in the smallest infants, should be avoided.

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.

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 entered, the blood bank will hold that unit for up to a week for further patient-specific transfusion. Blood and blood products are usable if stored in properly chilled coolers at the bedside for up to 4 hours. Plate- lets should remain at room temperature. 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 the blood products, and
- respiratory (airway).

Surgery

The most common complications are:

- bleeding,
- infections,
- adhesions,
- fistulae formation,
- wound separation, and
- injuries to adjacent organs.

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 of the hand,
- forearm,
- lower leg, and
- scalp.

The most common method of insertion uses the technique of a catheter, which is guided into the vein over the introducer needle.

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, and
- 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.

Central

Central venous access is indicated when there is need for

prolonged access for medications or TPN, when there is inability to attain peripheral access, and, rarely, for hemodynamic monitoring and access for drawing blood. Percutaneous intravenous central catheters (PICCs) have decreased the need for surgically placed central lines. These catheters are placed via a peripheral vein and threaded to a central position. A PICC may last for several weeks and often is placed by neonatal advanced practice nurses. Non-tunneled catheters can be placed percutaneously into the internal jugular, subclavian, and femoral veins. For long-term access, such as prolonged parenteral nutrition or antibiotic therapy, Silastic™ catheters are preferable because of their pliability and decreased thrombogenicity. They are placed through a subcutaneous tunnel and, in time, the subcutaneous tissue grows into the Dacron cuff to secure the catheter and prevent skin site infections. Dressings should be changed according to unit protocol and in a way to prevent accidental removal of the line while changing the dressing. **Complications of central lines include:**

- malposition,
- pneumothorax, and
- 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 include:**

- breaking or cracking of the line or its constituents
- tunnel or insertion site infections,
- bacteremia from accessing the line, or
- venous thrombosis.

Line thrombosis may be treated by instilling 1.0 mL of tissue plasminogen activator (TPA; 5000 international units per 1 mL vial) using a tuberculin syringe. If aspiration of the clot is not possible in 1 hour, repeat the instillation and attempt aspiration again in 8 hours. If the line is occluded, a volume of 0.1 mL of 0.1 N HCl may be used after consultation with a surgeon. 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.

Stomas, Intestinal

The long-term success of a stoma depends on the type of stoma created, the location selected for placement, careful attention to surgical technique, and the prevention and treatment of common complications. Morbidity from stoma formation remains a significant problem.

Decompressive ostomies are used primarily in emergent situations of imminent bowel rupture or to protect a distal anastomosis. **The most common decompressive ostomies in pediatric surgery are:**

- diverting colostomies (including divided sigmoid loop colostomies) for infants with imperforate anus, and
- leveling colostomies, for children with Hirschsprung disease.

When the bowel is completely divided, as in the case of a bowel resection, the distal end can be over sewn and left in the peritoneal cavity or brought out as a mucous fistula. The mucous fistula is decompressive if there is a known or potential distal obstruction, such as an imperforate anus, or stricture from necrotizing enterocolitis (NEC). In babies with proximal jejunostomies with or without short-gut syndrome, the mucous fistula also can be used to refeed the effluent from the proximal stoma. Diverting stomas in the small bowel differ from colostomies in that the liquid consistency and high volume of stool can be very corrosive to surrounding skin.

To prevent skin breakdown, the stoma must be constructed so that it protrudes significantly from the abdomen. This technique, first described by Brooke for ileostomies, allows 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 may be sufficient. Ischemia of these fragile stomas is very frequent in the immediate postoperative period. 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. The site should 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 avoiding excessive scrubbing.

If dermatitis develops, local wound care can be thought of as analogous to that 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, and
- stricture formation.

These approach 50% to 60% 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.

Specific Surgical Conditions

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 CCAM. **A significant arteriovenous shunt can occur through the sequestration and result in:**

- high output cardiac failure,
- hydrops, or
- pulmonary hemorrhage.

Extralobar sequestration rarely requires resection unless a symptomatic shunt exists. Intralobar sequestrations are electively resected because of the risk of infection.

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, or
- 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 nonoperative therapy before surgical therapy is considered. Resolution of chylothorax is reported in up to 80% of cases treated with MCT, TPN, and chest tube drainage.

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, and
- 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. **The goals of surgical treatment are to achieve:**

- bowel control,
- urinary control, and
- normal sexual and reproductive function.

Significant urologic and anorectal issues may involve:

- sex assignment,
- surgical treatment, and
- 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, and
- performing a colostomy for fecal diversion.

Congenital Cystic Adenomatoid Malformation (CCAM)

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 CCAM 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 CCAMs 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 CCAMs 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 CCAM 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 CCAM 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 CCAM, 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, and
- 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 CCAMs is recommended because of the possibility of later development of rhabdomyosarcoma arising from within the lesion.

Congenital Diaphragmatic Hernia (CDH)

The incidence of CDH is approximately 1 in 4000 live births. Associated anomalies are common, occurring in about 50% of patients. **Anomalies include:**

- congenital heart disease,
- neural tube defects,
- skeletal anomalies,
- intestinal atresias,
- renal anomalies. and
- pulmonary sequestrations

Prenatal sonogram can detect the presence of CDH as early as 12 weeks' gestation. Delivery should occur in a center with neonatal and surgical teams experienced in the care of these infants. Most infants have onset of respiratory distress in the delivery room. **Physical examination may also reveal:**

- a scaphoid abdomen,
- absence of breath sounds on the ipsilateral side, and
- displacement of heart sounds to the contralateral side.

Positive pressure ventilation via bag and mask should be avoided and endotracheal intubation should be accomplished as soon as possible. A large-bore, multiple-hole nasogastric tube should be placed immediately and put to continuous suction to minimize bowel distention. Preductal PaO_2, $TcPO_2$ or oxygen saturation should be monitored. Intubated newborns with CDH should be permitted to breathe spontaneously using a synchronized ventilator mode.

Goals for ventilation should include a strategy of permissive hypercarbia to avoid ventilator-induced lung injury as long as arterial pH is 7.20 or greater. The fraction of inspired oxygen (FiO_2) is adjusted to maintain preductal oxygen saturation by pulse oximeter or blood gas 85% to 95%. Sodium bicarbonate 1 to 2 mEq/kg or tromethamine 1 to 2 mL/kg may be administered as buffers when needed. Peak inspiratory pressures should be maintained at less than 30 cm H_2O, if possible, and mean air- way pressure should be maintained below 15 cm H_2O. High-frequency oscillatory ventilation may be used as a rescue therapy if adequate gas exchange cannot be achieved with conventional ventilation. Indications for extracorporeal life support (ECLS) are discussed separately **(see Extracorporeal Life Support (ECLS) section in this chapter).** For term newborns, the systolic blood pressure should be maintained greater than 50 mm Hg. A small (5 to10 mL/kg) bolus of normal saline may be used to improve cardiac filling. However, the pulmonary function of infants with CDH is exquisitely sensitive to intravascular volume. The use of vasopressors should be considered if the infant remains hypotensive despite a 10 mL/kg bolus of initial fluids. Total parenteral nutrition should be initiated early. Evaluation for accompanying cardiac and renal anomalies should be undertaken, as well as a baseline head ultrasound.

Operative repair should be delayed until the infant has stabilized. Initial postoperative chest radiograph may suggest a large pneumothorax on the side of the defect; this is usually because there is some delay in return of the mediastinal structures to midline. Ability to wean from mechanical ventilation depends on the degree of pulmonary hypoplasia. Survival rates vary among tertiary care centers, although survival rates of 80% to 90% in selected cases have been reported. Good prognostic factors include absence of liver herniation into the thorax and absence of coexisting congenital anomalies. **Long-term sequelae include:**

- chronic lung disease,
- reactive airway disease,
- pulmonary hypertension,
- cor pulmonale,
- gastroesophageal reflux,
- hearing loss,
- developmental delay, and
- motor deficits.

Some inherited disorders (e.g., Pallister-killian Syndrome [tetrasomy 12p mosaicism], trisomy 18, Fryns syndrome) have CDH as part of their presentation. Therefore, consultation with the Genetics Service should be considered.

Congenital Lobar Emphysema (CLE)

CLE, like CCAMs, almost always occur within a single pulmonary lobe, most often the left upper lobe. Identified causes of CLE include:

- intrinsic bronchial abnormalities,
- mucus plugs, and
- 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. Progressive pulmonary insufficiency from compression of adjacent normal lung requires resection of the involved lung.

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.

Duodenal Atresia

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), and
- little meconium in the distal bowel.

Neonates will present with bilious vomiting (the obstruction is distal to the ampulla of Vater in 85% of cases). Physical examination may show a distended stomach. 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.

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 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, and
- aspiration.

Extracorporeal Life Support (ECLS)

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_2delivery 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.

Gastroschisis

Gastroschisis is a congenital defect of the abdominal wall leading to herniation of abdominal contents through a defect 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, or covered with damp Kerlix® gauze and sterile occlusive dressing. A Replogle nasogastric tube should be placed and put to continuous suction. The infant should be positioned (usually on the 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. Preferably, upper extremity IV access should be obtained, 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, or
- placement of a Silastic™ spring-loaded silo in the NICU. Which option is preferred depends on many factors including
- the size of the bowel, rind/position of the bowel,
- size of the abdomen,
- required peak ventilator pressures with reduction, and
- 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.

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. Barium enema shows that the rectum has a smaller diameter than the sigmoid colon. Failure to completely evacuate contrast on a 24-hour follow-up abdominal radiograph also suggests HD. However, contrast enema may be inaccurate in up to 20% of newborns. Definitive diagnosis is made by finding aganglionosis and hypertrophied nerve trunks on a suction rectal biopsy.

The initial goal of therapy is decompression by either rectal irrigations or colostomy. 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,
- diarrhea, and
- explosive, watery, foul-smelling stool on rectal examination.

Enterocolitis can occur either before or after definitive treatment, and 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. If the distance is over 1 cm, a colostomy usually is indicated. IA may comprise part of the VACTERL association. Due to this association, the pre-operative work-up for these patients include a cardiac ECHO, renal ultrasound, and spinal ultrasound (tethered cord). Perineal fistulas may be dilated or repaired by perineal anoplasty. Intermediate and high imperforate anomalies require initial colostomy and delayed posterior sagittal anorectoplasty. Recovery after posterior sagittal anorectoplasty usually is 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. **Sequelae of anorectal malformations can include:**

- constipation,
- fecal incontinence, and,
- rarely, urinary incontinence.

Long-term, well-coordinated bowel management programs are essential to achieve optimal bowel function.

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, and
- 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, and
- 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.

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.

Diagnosis of intestinal atresia usually is made soon after birth. Key features are abdominal distension and vomiting, with the majority failing to pass meconium by 48 hours. Abdominal radiographs typically show dilated air-filled loops of proximal bowel with no air in the rectum. 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, and,
- usually, broad-spectrum antibiotics.

The bowel distal to the atresia is resected and an end-to-end anastamosis is performed. A nasogatric tube is used to decompress the stomach until bowel function returns.

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, or
- 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.

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, or
- the infant appears too ill for non-operative treatment.

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.

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. More than half of infants with omphalocele have associated anomalies and preoperative assessment should be undertaken.

Surgical treatment depends on the size of the infant's abdomen, the size of the defect, and associated anomalies. The goal of surgical treatment 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), and
- ventral and inguinal hernias.

Outcome depends upon associated congenital anomalies with the cardiac anomaly playing the largest determinant of survival.

Sacrococccygeal 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 case 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.

Palliative Care, Pain/Symptom Management, the End of Life And Hospice

15

Introduction

Palliative care is specialized care focused on improving the quality of life for patients and their families facing the problems associated with chronic, life-threatening or terminal illness, through the prevention and relief of suffering. 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.

53-55,000 children die in the US each year. Of those ~29,000 die before their first birthday, many from conditions originating in the newborn period.

In 2000, the American Academy of Pediatrics first described the principles of palliative care for children and called for a palliative care model using an integrated interdisciplinary approach. This statement was reaffirmed in 2007, with a policy statement in 2013 enhancing these concepts.

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. Improved professional and social support for families in need of palliative care, and
5. Continued improvement of pediatric palliative care through research and education.

Palliative care includes pain/symptom control and management of the psychological, emotional, social and spiritual concerns of children and families living with life-threatening or terminal conditions.

Qualifying Patients

Patients who should receive palliative care include:

1. Certain newborns at the threshold of viability (<24 weeks or <500 grams)
2. Newborns with complex or multiple congenital anomalies and
3. Newborns not responding to Neonatal Intensive Care Unit (NICU) 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.

Domains of Palliative Care

In 2004, the National Consensus Project (NCP) published clinical practice guidelines for quality palliative care by outlining 8 domains of care. These guidelines were reaffirmed in 2013. The NCP is a quality improvement project comprised of 9 total, but 4 coalition organizations, including the American Academy of Hospice and Palliative Medicine, the Center to Advance Palliative Care, Hospice and Palliative Nurses Organization, and the National Hospice and Palliative Care Organization.

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

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, and may include a family advocate, clinical pharmacist, dietician, bioethicist, and psychiatrist or psychologist. Because palliative care patients receive interventions from such 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 now available at TCH for Fetal Center and Newborn Center referrals. To obtain a consultation, please call the main Neonatology Service number, 832-826-1380. **(See Figure 15-1-Algorithm for PPACT Consult)**

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 be able 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 first be accurately assessed. Multiple validated neonatal pain assessment tools are available. At Texas Children's Hospital the CRIES and PIPP instruments are used.

Figure 15-1. Algorithm for PPACT consult

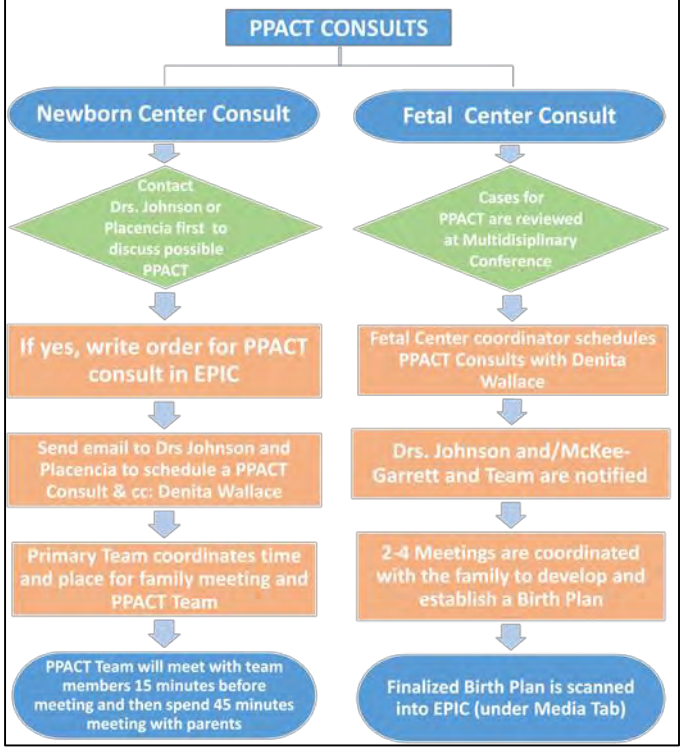


Table 15-1. Cries Scale						
Date/Time						
Crying – Characteristic cry of pain is high pitched 0 – No cry or cry that is not high-pitched 1 – Cry high pitched but baby is easily consolable 2 – Cry high pitched but baby is inconsolable						
Requires O_2 for SaO_2 <95% - Babies experiencing pain manifest decreased oxygenation. Consider other causes of hypoxemia, e.g., oversedation, 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 preceeding this recorded score. 0 – Child has been continuously asleep 1 – Child has awakened at frequent intervals 2 – Child has been awake constantly						
Total Score						

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, and analgesic administration is indicated for a score of 6 or higher. **(See Table 15-1)**

Table 15-2. PIPP Scale				
Gestational age	**≥36 weeks**	**23-35 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 oxygen 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

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.

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. (See Table 15-3)**

Neonatal Abstinence Syndrome (NAS) scoring should never 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. In general, IM or SC injections should only be used as a last resort. 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 15-4** for further dosing information.
****Because of the unique nature of the palliative care setting, medication dosing may differ from the usual recommendations for neonatal analgesia or conscious sedation.**

Table 15.3. 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 15-4. 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	Q2-4 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	Q2-4 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 intransal 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	Q2-4 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	Q1-2 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)	Q4-6 hours Q6 hours Q6 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.**

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. **See Table 15-4**

- 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 to the patient.

- intranasal administration of midazolam has been found to be effective in pediatric palliative care-see formulary.) Habituated Patients

If adequate sedation is difficult to achieve in a narcotic or benzodiazepine resistant patient, consultation with the Anesthesia/Pain Management Service should be considered.

Oral Medications

In the patient who does not have intravenous access, a combination of oral morphine and chloral hydrate may be used.

- Chloral hydrate may be given as a 50 mg/kg dose PO/PR (usual range 25–75 mg/kg per dose). Repeat doses should be used with caution due to accumulation of drug and metabolites.

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.

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 intensive care physician is well-versed in the grief process, and able to address end of life care issues with the family in a receptive and 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.

Understanding and Communicating at the End of Life

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 failure.

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.

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. Health professionals realize the importance of honest communication and empathy with parents around the time of death, as well as the need for continued support of the grieving family after the death has occurred.

Determination of Limitation or Withdrawal of Care

Non-initiation or withdrawal of intensive care for newborns must consider several key areas:

1. Decisions about non-initiation or withdrawal of intensive care 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, or of no benefit, or futile.

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.

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 the withholding or withdrawal 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, also known as the Texas Futile Care Law (1999), states that a qualified patient is one with either an irreversible or a terminal condition. A patient must have only one of the two conditions to qualify for TADA.

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 empowers the attending physician to invoke an institutional review process if parents persist in demanding interventions that the attending physician believes to be inappropriate.

The 1984 "Baby Doe" amendment to the Child Abuse Prevention and Treatment Act (CAPTA) directs Child Protective Services to investigate cases to prevent the withholding of medically indicated treatment from disabled infants with life threatening conditions. The amendment defines treatment as NOT medically indicated if the infant is irreversibly comatose, if it would merely prolong dying, not be effective in ameliorating or correcting all of the life-threatening conditions, if it would be futile in terms of survival, or if it would be virtually futile in terms of survival and be inhumane. Definitions for "life threatening," "prolong dying" and "virtually futile" are in an appendix to 42 U.S.C. § 5106, do not have the force of law, and have never been enforced in Texas or any other state.

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 will usually 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 therapy 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.

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, their 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. Thus, the patient's best interest standard overrides the doctrine of informed consent and right to refusal of care.

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, and the chaplain) may be of help in further discussions. In both instances, the director of nursing and the medical director should be notified.

Bioethics Committee Consultation

If further agreement with the family cannot be reached, a bioethics committee consult should be obtained by contacting the chairperson:

At Texas Children's Hospital:
Dr. James A. Thomas
Professor of Pediatrics-Critical Care
Office: 832-826-6230/832-826-6223
TCH Pager: 97534
jathomas@bcm.edu

At Ben Taub General Hospital:
Dr. Alexie Cintron, M.D.
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.

Imparting Difficult Information

Building a therapeutic relationship and establishing good communication between the medical team and the family is paramount. When talking with the family, the following phrases and ideas can be used as a "communication toolbox," and **the most important aspects of the conversation are highlighted in bold.**

- **Meet in a quiet, private place**
- **Introduce yourself**
- **Refer to the baby by name**
- **Ask what the parents know about their baby's condition**
- **Ask permission to give more information about the baby**
- **Give a warning shot** - for example, tell the family that the news you have to give them is not good, or not what you wanted it to be
- **Pause** - give the family a moment to prepare themselves to hear what you have to say
- **State the bad news clearly and speak directly** - Keep the message concise and use lay language. Expect to repeat the message several times as the shock of the information you are conveying may interfere with the family member hearing what you have to say. Do not use euphemisms for disease or death. Say "he is dying or is dead" rather than "he passed away."
- **Be honest**
- **Review the goals** - Tell the family about two goals of medicine. The first is to add time to life. The second is to add quality to life. If medical interventions do neither, it is no longer appropriate to continue those interventions.
- **Offer choices, if possible** - Inform the parents that there is nothing curative to offer their child. State that the current therapy can continue as it is, but that the outcome will not change. Alternatively, all artificial life support can be discontinued, comfort care provided, and the parents can give their dying infant the love of a mother and father.
- **Give a recommendation** - in cases where there is a choice to make regarding further treatment or redirection of care. A unified approach and clear recommendation from the healthcare team is appropriate and may relieve parents of the some of the burden of decision making in the end-of-life context. The words "withdrawal of treatment", "withdrawal of care", or "there is nothing else we can do" should be avoided. Explain that the infant will continue to be cared for, the family will be supported, and that any symptoms of discomfort will be aggressively managed.
- **Wait quietly** - Periods of silence allow the family to process information more effectively. It also conveys that you are there to support them. Wait for receptive body language from the family before proceeding. The family will not hear the next piece of information until they are ready.
- **Convey empathy** - Parents recognize and appreciate sincerity, compassion, tenderness and emotional availability from the physician and team members conveying bad news. Statements such as "I wish (the test, the surgery, the diagnosis) was different" convey sincerity and help to forge a closer connection with the family.
- **Focus on compassion** - The fundamental question is how best to love this patient. A parent's decision to withdraw life support is an extraordinary act of love and courage. Speaking in terms of loving the baby also focuses the conversation on parenting and gives the family permission to focus on end-of-life issues without feeling as if they are abandoning their role as the patient's mother or father.
- **Ask if the parents have questions** - Ask especially about a family's hopes and fears. Affirming parental concerns and asking about seemingly forbidden topics can help to alleviate fear and anxiety. Use open statements. For example, "Many parents feel as though they are causing their child's death by stopping the ventilator. Are you worried about this?" Guide parents through the process—Families need to be prepared for the dying process. Knowledge about what can be expected, including color changes and reflexive gasping, decreases parental anxiety. Emphasize that support for the baby and the family will always be provided. The unpredictability of the time to death from the time of withdrawal of support should also be addressed.
- **Let the family know that they will not be abandoned** - For example, a conversation might include the statement: "We will continue to provide the best medical care for your infant that will include frequent assessments by trained staff. We will be adjusting medications so that your infant is comfortable." Expect to have multiple conversations with the family
- **Tell them exactly when you plan to meet with them again** - parents who experience a normal grief reaction will not hear all of what you have to say immediately after receiving distressing news.
- **Ask parents what their thoughts are and how they are coping with the information presented** - Asking parents these questions allows the practitioner to view the baby's death from the parents' perspective and to better meet the parents' needs.

Documentation

The attending physician of record should document in the chart the reasons why the patient qualifies for withdrawal or redirection of care, as well as the discussion of these qualifying factors with the surrogate decision maker (see who may execute a directive on behalf of a patient under the age of 18 below; however, in the NICU the surrogate decision maker will almost always be the parents). If the patient is actively dying, there is no need for this documentation to be witnessed. However, if the patient is being electively transitioned to comfort care or withdrawal/limitation of support and adequate time exists, a Directive to Physicians should be utilized. The

Directive to Physicians may be verbal or writ- ten. If verbal, the conversation between the physician and the surrogate decision maker should be observed by two witnesses unrelated to the family and patient and who have no role in the patient's medical care (see witness requirements below; these witnesses may be other medical personnel in the NICU who are not directly caring for the infant). The note should document that the surrogate decision maker agrees with the modification of the plan of care and should include the names of the witnesses. A Directive to Physicians may also be signed by the surrogate decision maker and two unrelated witnesses.

After the care team discusses the terminal and/or irreversible diagnosis and care plan with the family, a "Do Not Attempt Resuscitation" (DNAR) should be entered in the patient's chart. The attending physician should honor the family's wishes as previously documented when completing this form. If there is any uncertainty as to whether a specific intervention should be withheld, that decision should be discussed further with the family. In the case of the active withdrawal of life sustaining therapy, a DNAR form is not necessary.

Sec. 166.035. **EXECUTION OF DIRECTIVE ON BEHALF OF PATIENT YOUNGER THAN 18 YEARS OF AGE**. The following persons may execute a directive on behalf of a qualified patient who is younger than 18 years of age:

1. patient's spouse, if the spouse is an adult;
2. patient's parents, or
3. patient's legal guardian.

Acts 1989, 71st Leg., ch. 678, Sec. 1, eff. Sept. 1, 1989. Renumbered from Sec. 672.006 by Acts 1999, 76th Leg., ch. 450, Sec. 1.03, eff. Sept. 1, 1999.

Sec. 166.003. **WITNESSES**. In any circumstance in which this chapter requires the execution of an advance directive or the issuance of a non- written advance directive to be witnessed:

1. each witness must be a competent adult; and
2. at least one of the witnesses must be a person who is not:

- a person designated by the declarant to make a treatment decision,
- a person related to the declarant by blood or marriage,
- a person entitled to any part of the declarant's estate after the declarant's death under a will or codicil executed by the declarant or by operation of law,
- the attending physician,
- an employee of the attending physician,
- an employee of a health care facility in which the declarant is a patient if the employee is providing direct patient care to the declarant or is an officer, director, partner, or business office employee of the health care facility or of any parent organization of the health care facility, or
- a person who, at the time the written advance directive is executed or, if the directive is a non-written directive issued under this chapter, at the time the non-written directive is issued, has a claim against any part of the declarant's estate after the declarant's death.

Added by Acts 1999, 76th Leg., ch. 450, Sec. 1.02, eff. Sept. 1, 1999.

The Transition to Comfort Care

Supporting the Family

The time around 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, however brief, 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. For NICU 3-4 patients in WT and if possible, the baby should be placed in the Rooming-In room or private room. At the Pavilion for Women-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. Low lighting is preferable.
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 and pagers of those in attendance should be silenced or turned off.
7. If no family is available, a Texas Children's Hospital staff member should hold the baby as he or she dies.
8. A memory box should be created and given to the family before leaving the hospital, which includes:
   - 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.
   - The Now I Lay Me Down to Sleep Foundation (NILMDTS) (www.nowilaymedowntosleep.org) is an organization administering a network of volunteer photographers who are available upon request to come to the hospital and take pictures of the baby and family before or after death. These photographs are donation based and offered at no charge.

- Multiples should be photographed together, whether living or dead.

9. The family should be encouraged to hold, bathe, dress and diaper their infant. There is no time limit for these activities. Parents or other family members may want to hold the baby after the body has been chilled in the morgue. The body may be gently re-warmed prior to their arrival under an open warmer or isolette.
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.

Care of the Dying Infant

Care should focus on keeping the infant comfortable. The baby should be swaddled in warm blankets while being held, or kept warm by open warmer or isolette. All painful interventions including blood draws should be discontinued. 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, feeding may cause pulmonary edema, aspiration pneumonia, worsen cardiac failure, or cause abdominal distention. All unnecessary intravenous catheters and equipment should be removed and wound sites covered with sterile gauze. Blow-by oxygen and 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. 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, the majority of neonatal patients die from a painful ailment. 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. It is important to anticipate the acute symptoms expected when a patient is extubated. First doses of medication should be given prior to extubation, and an adequate level of sedation should be achieved to avoid patient air hunger. Responding to air hunger after extubation is frequently inadequate.

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.

Death of the Infant

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. 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. However, ultimately the baby's best interest comes first. If further treatment of the infant is determined to be futile and the parents remain unable to accept this, the primary team should discuss the patient's case with the medical director and consider a bioethics consult.

Organ Donation

Infants are not organ donation candidates if they are less than 40 weeks of gestation, medically unsuitable as determined by LifeGift, or the parents object or cannot be reached within 24 hours following the death. However, the LifeGift Organ Donation Center should still be notified of the death even in these circumstances, and the coordinator's name and the date and time of the conversation should be documented. LifeGift is available 24 hours a day, 7 days a week including all holidays. Organ donation can be a gratifying way for families to make a gift that allows their own child's tragedy to benefit other children. Heart valves may be donated postmortem in babies 36 weeks of gestation or greater.

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

Autopsies are performed on weekdays between 9 am and 2 pm, and on Saturday between 8 am and 12 pm. However, a pathologist is on-call 24 hours a day 7 days a week, and an autopsy may be performed at any time if clinically indicated. 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 physician of record 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.

When requesting an autopsy, a copy should be sent to Denita Wallace, as well as the neonatologist(s) of record.

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

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 a interdisciplinary group of physicians, nurses, and other personnel, such as chaplains, health aides, volunteers and bereavement counselors. Hospice care provides a sup- port 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 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 Woman's Place at the PFW offers psychiatric care to mothers followed in the Fetal Center.

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. When the infant is actively dying, contact the chaplain immediately. 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 type issues exemplify the importance of providing culturally competent care in this setting Telling parents that many caretakers might prefer palliative care for their own infants in the same situation may allow parents to see that their infant is not a subject of discrimination.

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 own experienced 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 our own feelings, coping styles, and behavior while communicating with parents at the end of their infant's life.

To help support NICU staff, the Newborn Center hosts several Remember and Reflect events throughout the year.

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Appendix: Overview of Nursery Routines

Charting

Charting at TCH and Ben Taub is now done electronically using the Electronic Medical Record (EMR). This software contains templates for most neonatal physician charting including H&P, progress notes, procedure notes and discharge summaries.

Lab Flow Sheets

The EMR contains a variety of selectable flow sheets for vital signs and laboratory values.

Problem Lists

Problem lists can be extremely helpful, especially with complex patients. In the EMR these can be entered in the form of appropriate diagnostic codes and should be kept current on all patients in all units.

Procedure Notes

A note that includes clinical indications, appropriate procedural descriptions, parental consent, and outcome should accompany all procedures, including transfusions. A template is available in the EMR for this purpose but additional information can be added.

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 practioners are expected to

- Speak to the mother/father **on admission** of the infant to any nursery,
- Try to speak to the mother daily while she is in the hospital,
- Document in the chart the content of conversations (or the failed attempts if no phone or other response), and
- Write in the Progress Notes the regularity of parent visits when known.

Consultations

All requests for consultations should first be cleared through the Neonatology Faculty or Fellow.

Child Life

Child Life services is a field 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.

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

Discharge or Transfer Documentation

Discharge planning begins upon admission. Insuring or establishment of a medical home for our patients should begin with a query to the family for who will be the follow-up physician. If the family does not have one then every effort should be made to find a medical home for this patient long before discharge.

At discharge or transfer to room-in on the floor,

Record

- date of birth, gestational age, and birth weight,
- discharge or transfer weight,
- recent FOC,
- latest hematocrit, reticulocyte count (if relevant), newborn screen results and dates, and
- any other pertinent labs.

Note

- the arrangements for normal newborn care, clinic and/or consultants for follow-up, and dates of the appointments,
- discharge diet, and
- all medications (including iron and vitamins).

Order

- • discharge medications (1- to 2-month supply) with transfer orders for floor.

At Ben Taub

For complex discharges that require Level 2 or Special Needs Clinic or 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, a list of medications, and the plan of care at the time of discharge.

Infection Control

Hand Hygiene

All personnel who handle newborn infants in the unit should perform an initial scrub from fingertips to elbows using soap and water. Alternatively, alcohol-based hand cleansers may be used. Jewelry (except wedding bands) and watches should be removed before hand washing and should remain off until contact with the newborn is finished. Sleeves of clothing should remain above the elbows during hand hygiene and while caring for patients (including sleeves of white coats).

After the initial washing and before and after handling patients or their equipment, hands should be washed for 15 seconds with soap and water, or a golf ball-sized spray of alcohol-based foam, or an appropriate amount of alcohol-based gel. If hands are visibly soiled, they should be washed with soap and water.

Gloves

Use of gloves is determined by individual hospital infection control policies. Hand hygiene should be performed before gloving and after glove removal.

Gowns

Cloth gowns are not required when entering the nursery. However, gowns are to be worn by anyone who will be holding an infant against their clothing or by anyone who requests a gown while in the nursery.

Liquid impermeable gowns should be worn when entering an isolation area only. These gowns are not to be worn outside of the 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.

Stethoscopes

Each patient should have a dedicated stethoscope. Stethoscopes should be cleaned with alcohol before and after each patient use.

Isolation Area

In the isolation area, infection controls are to be strictly enforced. **Hand hygiene is mandatory on leaving these areas even if there has been no patient contact.** Cover gowns must be worn over scrub suits and removed when leaving this area.

Charts

Consider patient charts "dirty." Hands must be washed after handling a chart and before handling a patient.

Nutrition Support after Discharge

(See *Nutrition Support* chapter.)

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.

ROP Screening

(See *General Care (babies < 1500 grams)* and *Follow-up* sections in *Care of Very Low Birth Weight Babies* chapter)

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.

Table A-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
Sepsis risk factors	Maternal fever or PROM > 24 hours without chorioamnionitis and asymptomatic baby	Maternal fever ≥ 101 and chorioamnionitis Or Pedi Evaluation – baby with mild symptoms	Pedi Evaluation Baby with significant symptoms
Diabetic mother	All classifications	Symptomatic	
Congenital anomalies	Minor that are non-life threatening e.g club foot, renal pyelectasis, DDH, ear tags		Major anomalies
In-utero exposure	Marijuana or cocaine HIV positive HSV without active lesions PPD positive without active TB	Illicit drugs except marijuana or cocaine Active maternal HSV lesions at delivery, maternal active TB, maternal varicella	

(Blair-Deal, Garcia-Prats July, 2014)

General Guidelines—Ben Taub General Hospital

Triage of Admissions

Newborn Nursery Transition Area

The Normal Newborn Transition Area is incorporated into the Newborn Nursery. More complex infants are transitioned in the Level 2 nursery or NICU. **(See Table A–1.)**

Daily Activities

Rounds

Rounds are made daily during morning hours.

Code Warmer Activities

Neo Rapid Response Team

(Neonatology Fellow, Upper level resident, Neo Charge Nurse, Neo Respiratory Therapist, Pedi intern) Labor and delivery has 12 LDRP's (labor, delivery, recover, post-partum) for low risk patients and 2 operative suites for caesarian 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 as 3a (311 *1) 3b (311 *2), 3c (311 *3) Level 2 (311 *4). 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/package).

Since there has been a great emphasis on reduction of wound infections on OB patients, all of the physicians are required to use BTGH laundered scrubs. Access to the pyxis that contains these scrubs should be done on your first day of the rotation.

Please practice exemplary professionalism when called into these rooms. 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 12 noon in the 3rd-floor conference room. All residents and students on the nursery rotation should plan to attend. Rounds will be interrupted to assure participation by residents.

Pediatric Grand Rounds are each Friday from 8:30 to 9:30 am at Texas Children's Hospital in the lower level auditorium, and it can be seen by videoconference in the 3-D classroom.

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. iStat will be available for blood gas analysis as well as a metabolic panel in both level 3 and level 2 nurseries.

Ordering TPN and Other Fluids

At Ben Taub, TPN must be reordered daily. The order must be placed by 1 pm to be processed by the pharmacy that same day. 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 $D_{10}W$ formulation is available in the pyxis in the NICU.

Cardiology Consultations

Pediatric Cardiology

Currently, TCH pediatric cardiology provides limited services (ECG, Holter Scans, cardiac ECHO) to our patients here at BTGH. Cardiac ECHO's are available on a weekday 9 am-4 pm by calling the TCH ECHO lab. Assistance for arranging follow-up can also be arranged through consultative services as soon as the appropriate paper work is completed. **See Pediatric Resident Website** for necessary forms or call the TCH Cardiology Clinic to have the forms faxed.

ECG's are performed on the nursery service and sent digitally to the TCH electrophysiology lab. Turn-around time for the reports which are faxed to us is usually 24 hours. Holter scans are also done here and will be scheduled through our ECG lab here at BTGH. These scans are also sent to TCH electrophysiology with turn-around time or 48-72 hours.

Ophthalmology

For ROP screening guidelines, **see Follow-up section in Care of Very Low Birth Weight Babies chapter**.

Notify Pediatric Ophthalmology upon the patient's initial admission to the NICU by faxing a copy of the patient's face sheet and a data form provided by ordering the consult in EPIC.

Babies with ROP who require eye surgery generally are transferred to Texas Children's.

Ben Taub's Ophthalmology Service, which can be reached through the page operator, performs non-ROP ophthalmology consults.

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.

Discharge Planning

Texas Health Steps 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 be scheduled at their nearest location to set their medical home.
- All newborns with an elevated initial direct bilirubin (0.4 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 bili to assist in data collection. If the initial direct bili is less than 0.4, the baby does not need a repeat direct bili at Health Steps clinic at the two week visit despite the value of any repeat direct bili values (per Dr. Harpavat, GI).
- Normal newborns in CPS care or in the process of foster care
- Intermediate Care Nursery (ICN) Patients-Level II– Infants from the ICN 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 child care 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 gestation or greater 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 in Level II

*** 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
- 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 of 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.

It is extremely difficult for the Newborn follow-up clinic to schedule an outpatient ECHO or referral, as it can take up to 1 hour of our nurses' time, which makes managing patient load very difficult So please do not send patients to clinic with a written plan of "ECHO (or other service or referrals) to be scheduled by THS for outpatient follow up."

If infant needs referral to another service for follow up after discharge, the referral and appointment must be made prior to discharge.

General Guidelines— Texas Children's Hospital

NICU rounds are made during morning hours. Residents who want to perform procedures or attend deliveries under the supervision of a member of the Neonatology Section are encouraged to do so during the afternoon and evening hours.

Schedule lab work, X rays, ultrasound exams, etc. for routinely scheduled times, unless a true emergency exists.

All procedures, including transfusions, should be accompanied by a note that includes indications and outcome.

At the time of discharge, all patients should have a final note that includes weight, FOC, hematocrit, newborn screen result, physician follow-up, discharge diet, and medications. Pertinent follow-up appointments also should be listed.

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.

Texas Children's Night Call Activities

Night time patient care is provided by

- Neonatology faculty and fellow
- Residents
- NNPs
- Transport Team

Night call activities involve transport and stabilization of new admissions, delivery room calls, ongoing management of patients, and response to patient emergencies in the nurseries. Preferentially, routine care, elective care, and patient transfers are done during daytime hours.

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.

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