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I. INTRODUCTION
Welcome to the NICU at Children’s Hospitals and Clinics of Minnesota, St. Paul Campus. We are a regional perinatal center serving primarily the greater St. Paul area, as well as western Wisconsin. Although most of our babies are delivered at United/Children’s Perinatal Center, about 15% of our babies are transported in from other hospitals. We provide level II and level III neonatal diagnostic and supportive care including mechanical ventilation, high frequency ventilation, nitric oxide therapy and pediatric surgery. This does not include ECMO; for this therapy, patients are referred to the NICU at the Minneapolis campus. In addition, we offer a regional Infant Apnea Program and staff the NICU Developmental Follow-Up Clinic.

II. GOALS OF RESIDENT ROTATION
1. Understand pathophysiology and treatment of common newborn diseases;
2. Develop procedural skills in newborn resuscitation and emergency intervention;
3. Recognize clinical and laboratory signs of a sick newborn and develop appropriate treatment plans;
4. Recognize common congenital malformations and syndromes;
5. Identify high-risk obstetrical factors;
6. Understand normal newborn physiology and examination findings.

III. ROLES
A. Fellow and Attending
In general, both the fellow and attending will make daily rounds on every patient. On occasion, rounds will be under the direction of the fellow. No significant change in plans made during rounds should be made without consultation with the fellow or attending. The on-call fellow or attending should be notified of all admissions (day or night). The fellow is available for supervision of all procedures during the daytime. There is an in-house attending or 3rd year fellow 24/7 that can provide supervision of all patient care and procedures.

B. Neonatal Nurse Practitioners
Neonatal nurse practitioners are nurses with advanced education/training and certification in neonatal resuscitation and stabilization. They function as care providers in collaboration with staff physicians. They are skilled at NICU invasive procedures. They are present 24 hours per day in-house and will assist you in attending all deliveries, providing daily patient care and performing procedures as needed. In addition, they are responsible for all outside transports.
C. Pediatric Interns
Pediatric interns are MDs in their first year of pediatric specialty training. They will provide care to patients in the NICU in collaboration with the fellow and staff physicians. They will attend deliveries as well as perform common neonatal procedures during their rotation in the NICU. Pediatric interns will work a 6-day/week rotation throughout their NICU month, with no overnight call responsibilities. Each intern will always have one day per week off, with the day off being scheduled on either Friday, Saturday, or Sunday. They will sign-out their patient population at 5:30pm each day to the overnight on-call coverage team.

D. Charge Nurses
The charge nurse decides where the infants will be placed in the NICU and makes the assignments for RN staffing of the unit. The charge nurses are the “go-between” for staff RNs and the providers. Charge nurses are extremely valuable in making sure the day-to-day operations run smoothly.

E. Social Workers
Social workers provide support to families while their babies are hospitalized in the NICU. In general, this includes emotional support as families adjust to having an ill or premature baby, assisting with finding resources in the hospital or community, and helping the families understand communications with the medical team. NICU social workers are also committed to supporting staff members, realizing that families’ experience is directly affected by the resiliency of those caring for their baby.

F. Care Managers
Care managers coordinate the pre-discharge, discharge and follow-up experience for the NICU patients. They deal with various insurance issues, and also are involved with pre-discharge education of families. They also coordinate transfers back to referral hospitals when medically appropriate.

IV. ROUNDS
Residents should arrive at the NICU each morning in time to be updated on their patients by the previous on-call team, typically no later than 7:30am. It is expected that you will have examined all patients who are critically ill prior to rounds, with any non-critical patients to be examined during rounds. Rounds commence at 8:15 am in the Radiology Department where x-rays are reviewed prior to formal rounds in the NICU.

On weekends, rounds begin in the NICU at 7:30 am and X-ray rounds will take place once the on-call radiologist arrives.
V. RESIDENT WEEKEND/ WORKLOAD EXPECTATIONS
- Each intern will be assigned to work one day of the weekend, with the other day being off. The weekend workday will function the same as the weekday, however, one intern will cover ALL of the resident patient population since the other resident will have the day off.
- Each intern will have a maximum of 5 patients. If there is an “open” spot in your patient census, then you will be expected to take a new patient, with hopes of you participating in the delivery room and admission process of each new patient if admitted during your work hours.

VI. DAILY NOTES
- “SOAP” format progress notes should be written in the EMR each day your patients.
- A procedure note must be completed in the EMR for all procedures.
- A “Change in status” note must be written in the EMR any time a major change in patient status occurs.
- A Post-Op note must be completed in the EMR when a patient returns from surgery.

VII. CONSULTATIONS
Only the attending neonatologist or fellow can decide to obtain a subspecialty consult, and choose the designated consultant. Typically, the attending or fellow will contact the consultant, however, this should be clarified during rounds regarding who will be responsible for making the call to the consultant.

VIII. CONSENT/ PARENT NOTIFICATION
- A general consent to treatment is signed by the parents upon admission to the NICU for all admission and subsequent NICU treatments and procedures. However, out of courtesy, all parents should be informed of any procedures that are happening to their baby.
- Parents should be notified of any consults, major test results, or significant changes in their infant’s condition.
- Parents should be informed prior to any blood transfusion (PRBC, FFP, Platelets, etc). The transfusion order will ask if consent has been obtained; once informed consent is obtained you do not need to obtain informed consent for each transfusion (unless that is an issue with that family), but out of courtesy, the family should still be informed that a transfusion will take place.
IX. CONFERENCES/DIDACTIC TEACHING SESSIONS

- The third Thursday of each month there is a Mortality Conference where all NICU and delivery room deaths or adverse events will be discussed as well as review of all autopsies with Pathology.
- The NICU Fellows will give didactic lectures in the afternoons, after rounds, on specific topics.
- You are expected to attend the general pediatric residency noon lectures held at Children’s – St. Paul held daily from noon-1pm.

X. SUPPLEMENTAL EDUCATIONAL CURRICULUM

- A 4-week educational reading series is posted on our website, www.newbornmed.com, and it is the expectation that you read each week’s assigned readings during your 4 week rotation and complete the post-test after each reading to demonstrate completion. Completion of the reading series is mandatory and will be a part of your evaluation. The reading lists can be found under the resident/fellow tab on the website and the password is “meconium”.
- It is recommended that you register for CLIPP Cases (computer assisted learning in pediatrics project). To register, go to www.clippcases.org, and click on “CLIPP Pediatric” cases. Click on “go to cases”. “You are new user?” → click “register”. Fill in your information using your university x500 email address. Your user name and password will be emailed to you.
  
  The following Pediatric CLIPP cases should be reviewed during your month in the NICU:
  
  #1 (Eval of newborn infant)  #15 (vomiting)
  #2 (prenatal and newborn visits)  #18 (poor feeding)
  #7 (newborn resp distress)  #25 (apnea)
  #8 (jaundice)  #26 (not gaining weight)
  #9 (lethargy)  #29 (hypotonia)

  The following Family Medicine CLIPP cases are pertinent: #24 (fussiness).

XI. INFECTIOUS CONTROL

1. Follow posted isolation procedures on the doors of patient rooms
2. Wash hands thoroughly upon entering the NICU each day. Foam-in and Foam-out of all patient rooms.
3. Wear gloves for all patient contact (no exceptions!)
4. No rings, watches, bracelets are allowed in the NICU.
5. No painted or artificial fingernails are allowed in the NICU
6. There is no specific dress code in the NICU. However, parents and staff appreciate a neat appearance if you wear street clothes. Feel free to wear scrubs daily, if you want. If you are attending deliveries you should wear scrubs or place appropriate gowns over your street clothes.
XI1. MISCELLANEOUS NICU INFORMATION

- TPN orders need to be completed by 2:00 pm daily because the TPN is formulated in the Minneapolis campus central pharmacy and has to be couriered over to our campus in the late afternoon.
- We do not infuse Calcium through peripheral IVs/peripheral PICC lines.
- Routine “AM” labs are drawn between 0600-0700. Standing lab order times should be 1500, 2200, and 0300. Please try to place lab orders at the scheduled times, unless clinical status requires deviation.
- When ordering labs, specify date and time of lab as well as if the nurse will obtain the specimen (e.g. Patient has central access) or if laboratory will draw specimen (capillary stick or venipuncture).
- When infant has a Broviac catheter labs should be ordered for 2000 as this is when the line will be “broken/opened” when new TPN is hung.
- Weekly nutrition labs, when indicated, are ordered for Monday mornings. These typically include prealbumin, alkaline phosphatase, hemoglobin, and reticulocyte count. Occasionally, if the infant has severe osteopenia or malnutrition, assessment of Ca, Mg, Phos will be included. If the infant is on diuretics or TPN, a basic metabolic panel should be ordered.
- So terminology is standard, we consider the birth date = day of life 1
- Drug dosing should be reported as mg/kg/day
- Intake should be reported as “XX” ml/kg/day and “XX” calories/kg/day
- Urine output should be reported as “XX” ml/kg/hr
RESPIRATORY MANAGEMENT

I. Differential Diagnosis and Initial Management of Respiratory Distress
II. Respiratory Distress Syndrome
III. Non-Invasive Ventilation
IV. Conventional Ventilation
V. High Frequency Ventilation
VI. Persistent Pulmonary Hypertension of the Newborn
VII. Nitric Oxide
VIII. Apnea and Bradycardia
IX. Oxygen Saturations
X. Chronic Lung Disease
I. DIFFERENTIAL DIAGNOSIS AND INITIAL MANAGEMENT OF NEONATAL RESPIRATORY DISTRESS

Neonatal respiratory distress is the number one reason for admission to the NICU. Differential diagnosis includes:
1. Transient tachypnea of the newborn (TTN)
2. Respiratory distress syndrome of prematurity (RDS)
3. Meconium aspiration syndrome (MAS)
4. Congenital pneumonia
5. Sepsis
6. Congenital cyanotic heart disease
7. Persistent pulmonary hypertension of the newborn (PPHN)
8. Anatomical abnormalities of airway or lungs (choanal atresia, bronchomalacia, etc.)
9. Pneumothorax
10. Developmental abnormalities of the lungs (Congenital diaphragmatic hernia, tracheoesophageal fistula, Congenital cystic adenomatoid malformation, etc.)
11. Mechanical abnormalities of the lungs (rib cage anomalies, pleural effusion, spinal muscular atrophy, etc.)

The initial evaluation of an infant with respiratory distress includes a thorough history and physical exam.

History points to consider:
• Maternal GBS status positive? Treated? Labor?
• Chorioamnionitis?
• Meconium?

Physical exam points to consider:
• Vitals – hypotension? Fever?
• In distress or simply tachypneic?
• Capillary refill/skin color?
• Breath sounds equal?
• Murmur?
• Femoral pulses palpated?

The top 4 causes of respiratory distress include TTN, RDS, congenital pneumonia, and meconium aspiration syndrome. These assessments of these top diagnoses will be discussed below.

Transient tachypnea of the newborn:
• Symptoms usually present within the first 6 hours of life and last for 12-24 hours
• Respiratory distress is usually mild
• CBC normal
• CXR: bilateral perihilar streaking, fluid in fissure, normal to hyperinflated lung volumes (>8ribs)
• Treatment: Supportive, O₂, may include r/o sepsis

Respiratory distress syndrome:
• All preterm infants are susceptible and late preterm infants (35-37 weeks) most common Level II NICU admission diagnosis
• Mild respiratory distress that worsens over time
• CBC normal
• CXR: bilateral “reticulogranular” hazy opacities, LOW lung volumes
• Treatment: positive pressure (HFNC/CPAP), if intubated give surfactant, r/o sepsis, supportive

Congenital pneumonia:
• Mild to moderate respiratory distress
• CBC with normal or elevated WBC
• CXR: focal opacity that does not clear on serial CXRs, normal lung volumes
• Treatment: IV antibiotics, supportive, O₂

Meconium aspiration syndrome:
• Occurs in 1-4% of deliveries complicated by meconium stained amniotic fluid
• Respiratory symptoms mild → severe
• May have PPHN (preductal sats higher than postductal sats)
• CBC normal
• CXR: bilateral patchy opacities, hyperinflated lungs
• Treatment: r/o persistent pulmonary hypertension (pre/post-ductal sats), r/o sepsis, supportive, O₂

Commonly, an infant admitted for respiratory distress has a concurrent sepsis evaluation undertaken, as sepsis cannot be excluded as a contributing factor to their symptomatology. A complete blood count with differential, blood culture, arterial blood gas and chest x-ray are standard procedures to evaluate the infant with respiratory distress. Ampicillin (100mg/kg/dose q12 hours) and gentamicin (4mg/kg/dose q24-48 hours) are routinely started after the blood culture is obtained, and duration of antibiotic therapy is determined once the etiology of the respiratory distress is identified. Serial chest x-rays can be helpful in elucidating the final etiology of the infant’s respiratory problems.

General rules of thumb:
• If supplemental oxygen need not escalating and not in a lot of distress, can obtain CBC with differential, blood culture, blood gas, and chest x-ray while observing on cardiorespiratory monitors. Empiric antibiotic coverage (ampicillin, gentamicin) is typically started on all infants admitted and requiring supplemental oxygen.
• Occasionally, if the infant has no supplemental oxygen need but grunting respirations and the clinical history is not suspicious for infectious etiology, the lab work and chest x-ray can be obtained and the infant can simply be observed on cardiorespiratory monitors without starting empiric antibiotics.
• If symptoms “severe” or oxygen needs escalating, would suggest Arterial blood gas to be obtained to evaluate PaO₂, pre- and post-ductal saturation monitoring to evaluate for shunting/evidence of persistent pulmonary hypertension of newborn (PPHN), and potentially an echocardiogram to evaluate intracardiac anatomy and pulmonary pressures.
II. RESPIRATORY DISTRESS SYNDROME OF PREMATURITY

Respiratory distress syndrome (RDS) is the most common respiratory disorder in preterm infants. RDS is primarily caused by inadequate pulmonary surfactant. Surfactant deficiency places the premature infant at high risk to develop acute onset of respiratory distress. Weak chest and inter-costal musculature, decreased alveolar radius, and immature neurologic control of the respiratory centers all compound the infants’ respiratory difficulties. These factors all combine to promote atelectasis, V/Q mismatch, hypoventilation and hypoxemia.

Clinically, RDS is characterized by acute onset of respiratory distress including tachypnea, inter-costal retractions, nasal flaring, or “grunting” expiratory respirations. Radiographically, RDS is characterized by diffuse reticulo-granular infiltrates and low lung volumes. In the past few decades, the introduction of antenatal steroids and exogenous surfactant has greatly improved outcomes in RDS. Low gestational age is the greatest risk factor for RDS. See Table 1. Other risk factors for RDS are male gender, c-section without labor, perinatal asphyxia, Caucasian race, infant of diabetic mother, and chorioamnionitis. RDS occurs in approximately 50% of infants born at less than 30 weeks gestational age.

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>Incidence of RDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>501-750 gm</td>
<td>86%</td>
</tr>
<tr>
<td>751-1000gm</td>
<td>79%</td>
</tr>
<tr>
<td>1001-1250gm</td>
<td>48%</td>
</tr>
<tr>
<td>1251-1500gm</td>
<td>27%</td>
</tr>
</tbody>
</table>

RDS often requires the use of positive airway pressure, non-invasive or invasive, to minimize the atelectasis and V/Q mismatch. Short-term complications associated with RDS and its treatment are air leak syndromes (pneumothorax, pulmonary interstitial emphysema) and intracranial hemorrhage. Long-term complications associated with RDS and its treatment are the development of chronic lung disease, retinopathy of prematurity, and neurologic impairment.

The three most important advances in preventing and treating RDS have been: 1) antenatal glucocorticoids, 2) continuous positive airway pressure and positive end-expiratory pressure, and 3) surfactant replacement therapy. Antenatal steroids accelerate fetal lung maturity by increasing formation and release of surfactant as well as maturing the lung structure. Antenatal steroids also reduce the incidence of intraventricular hemorrhage, an effect that is independent of the pulmonary benefits.

Surfactant is naturally produced phospholipid-based molecule made by type II alveolar cells starting at approximately 24 weeks gestation when fetal lung development reaches
the “saccular stage”. Surfactant functions to reduce alveolar surface tension and prevent atelectasis/lung collapse. Due to the high incidence of surfactant deficiency in extremely premature babies, routine use of supplemental exogenous surfactant given via endotracheal tube became a mainstay of NICU respiratory therapy since the early 1990’s. It has clearly been shown to increase survival in the premature population. Exogenous surfactant improves oxygenation, decreases air leaks, reduces mortality due to RDS and overall mortality.

We routinely intubate infants <26 weeks gestational age in the delivery room and give exogenous surfactant. The respiratory status of infants >26 weeks is assessed in the delivery room and either CPAP is applied if the respiratory status is adequate or the infant is intubated if the respiratory status is ineffective. Our unit typically administers Survanta, an exogenous surfactant, at 4ml/kg the endotracheal tube. At this time, an infant must be intubated in order to receive surfactant, although clinical trials are looking at other delivery methods including nebulization and administration through a laryngeal mask airway.
III. NON-INVASIVE VENTILATION TECHNIQUES IN THE NICU

This section will cover the most common non-invasive respiratory therapies employed in the NICU. These include continuous positive airway pressure (CPAP), biphasic continuous positive airway pressure (SiPAP), noninvasive intermittent positive pressure (NIPPV), high-flow nasal cannula (HFNC), and low-flow nasal cannula (LFNC). A brief description of each mode, its use in the NICU, and any clinical guidelines we use on our NICU will be included.

A. Non-invasive Positive Airway Pressure: CPAP, SiPAP, and NIPPV

I. Continuous Positive Airway Pressure (CPAP)
   - Mechanisms of effect: Splinting open airways, increasing residual lung volume, prevent alveolar collapse, preserve endogenous surfactant, decrease V/Q mismatch, decrease airway resistance, decrease work of breathing, stabilize respiratory pattern
   - BENEFITS
     Decreases apnea of prematurity (Miller, J Pediatr 1995)
     Decreasing extubation failure (Davis, Cochrane Database 2003; Davis, Arch Dis Child Fetal Neonatal Ed 2007)
   - RISKS
     Trauma to nasal septum
     Potential association with late onset Gram-negative sepsis (Graham, Pediatr Infect Dis J 2006)
     Increased air leak syndromes
   - The “unknowns” of CPAP
     Very few established guidelines (Roehr, 2007)
     How much PEEP? 4-10 cm H2O have been described
     Is it better to use Binasal vs. single prongs? Studies suggest binasal prongs superior
     In the delivery room what mode of CPAP delivery is best, a flow-inflating bag, self-inflating bag, or T-piece resuscitator? Still unknown
     In the NICU should CPAP be delivered by Bubble CPAP, ventilator CPAP, Infant Flow CPAP or HFNC?
     How/when to stop CPAP -- Abruptly? Wean PEEP? Cycled trials off?
     **Randomized controlled trials are needed to establish “best practice” for delivering CPAP**

II. Biphasic CPAP = “SiPAP”
   - Mechanism of effect: similar to described in CPAP, however, positive end expiratory pressure cycles between a “higher” pressure and a “lower” pressure and the patient can breathe multiple times at each level of pressure.
   - BENEFITS/RISKS are similar to CPAP, however, there is a theoretical increased risk of air leak syndromes due to the intermittent higher PEEP exposure that is
not synchronized with inhalation
- Many “unknowns” of SiPAP as it is relatively new to the respiratory care of neonates

III. Nasal Intermittent Positive Pressure Ventilation (NIPPV)
- NIPPV is the use of small inspiratory bursts of positive pressure delivered by CPAP apparatus to facilitate movement of a tidal volume. Most studies evaluating NIPPV have used synchronized NIPPV, assisting the infant with the pressure burst on inhalation. However, at this time, there are no FDA approved devices in the USA that allow for synchronization of NIPPV.
- NIPPV was first described in premies in 1980s for apnea of prematurity but fell out of favor after reports of GI perforation (Garland, Pediatr 1985)
- BENEFITS of NIPPV:
  NIPPV superior to CPAP for preventing extubation failure (Davis, Cochrane 2001)
  NIPPV superior to CPAP for reducing apnea of prematurity (Lemyre, Cochrane 2002)
  ** the question is whether synchronization of NIPPV is necessary to get superiority over CPAP for preventing extubation failure and AOP**
- NIPPV as a primary therapy for RDS?
  Small studies encouraging
  Ali (Pediatr Pulm 2007) – NIPPV decreases WOB and chest wall dysynchrony
  Kugelman (J Pediatr 2007) – NIPPV compared to NCPAP decreases need for intubation/mechanical ventilation and decreases rate of BPD
  Bisceglia (Minerva Pediatr 2007) – NIPPV compared to NCPAP decreases duration of respiratory support
- The UNKNOWNS of NIPPV
  Variability of application (Owen, Arch Dis Child Fetal Neonatal Ed 2007)
  Synchronized vs. non-synchronized?
  What rate to cycle the inspiratory bursts? 10-60bpm reported
  What PIP should be used on inspiratory burst? 7-20cm H₂O reported
  Should NIPPV be used as a first-line therapy vs. “rescue” if failing CPAP?
  **Randomized controlled trials needed for defining optimal use of NIPPV in NICU setting**

B. High Flow Nasal Cannula (HFNC)

High flow nasal cannulas (HFNC) are one of the newer respiratory therapy agents introduced into the NICU setting within the last decade. Commercially marketed HFNC delivery systems are available for use on premature and term infants. The goal of HFNC is to provide positive end-expiratory pressure (PEEP) in a less invasive way than conventional nasal continuous positive airway pressure (CPAP). The current data in premature infants is limited, at best, and difficult to compare all studies as multiple
HFNC devices were investigated. We currently use the Fisher & Paykel HFNC system. Most trials have shown acceptable tolerance of HFNC compared to CPAP no significant changes in work of breathing. The only randomized controlled trial published to date (4/10) by Campbell and colleagues showed increased extubation failure if infants were extubated to HFNC versus extubated to CPAP. This information, combined with other published observational and crossover studies, would suggest that the amount of PEEP delivered by HFNC IS NOT as much as delivered by CPAP.

- **Proposed benefits of HFNC**
  - Heated and humidified air (HFNC)
  - Decreased nasal septum breakdown
  - Higher flow rates with potential for delivering PEEP
  - Increased patient comfort

- **Potential concerns of HFNC**
  - Hand-made systems are connected directly to gas flow source – need a pop-off to avoid potential for high pressure delivery to patient
  - Nostrils/mouth occluded, Hypotonia, Hand-made systems without pop-off – could lead to increased air leaks
    - Pneumocephalus/pneumo-orbitis described (Jasin, J Perinatol 2008)
  - Only RCT shows more extubation failure if extubated to HFNC vs. CPAP
  - Limited amount of data in neonates

- See Table 1 for review of current literature

### Table 1. Review of High Flow Nasal Cannula Studies in Premature Infants

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>HFNC System</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sreenan</td>
<td>2001</td>
<td>Crossover</td>
<td>Hand made</td>
<td>EEEP &amp; apnea on HFNC vs. CPAP</td>
</tr>
<tr>
<td>Saslow</td>
<td>2006</td>
<td>Observational</td>
<td>Vapotherm</td>
<td>WOB on Vapo HFNC vs. CPAP</td>
</tr>
<tr>
<td>Woodhead</td>
<td>2006</td>
<td>Crossover</td>
<td>Vapotherm and standard NC</td>
<td>Nasal mucosa, WOB, reintubation on Vapo HFNC vs. standard NC run at high flow rates</td>
</tr>
<tr>
<td>Campbell</td>
<td>2006</td>
<td>RCT</td>
<td>Hand made</td>
<td>Reintubation w/in 7 days when extubated to HFNC vs. CPAP</td>
</tr>
<tr>
<td>Shoemaker</td>
<td>2007</td>
<td>Retrospective</td>
<td>Vapotherm</td>
<td>Death, BPD, vent days pre/post introduction of HFNC</td>
</tr>
<tr>
<td>Spence</td>
<td>2007</td>
<td>Observational</td>
<td>Fisher &amp; Paykel</td>
<td>IPP on various flows vs. CPAP</td>
</tr>
<tr>
<td>Holleman-Duray</td>
<td>2007</td>
<td>Retrospective</td>
<td>Vapotherm</td>
<td>Morbidities and death pre/post introduction of HFNC</td>
</tr>
<tr>
<td>Kubicka</td>
<td>2008</td>
<td>Observational</td>
<td>Vapotherm and Fisher &amp; Paykel</td>
<td>Oral cavity pressure at various flows</td>
</tr>
<tr>
<td>Wilkinson</td>
<td>2008</td>
<td>Observational</td>
<td>Fisher &amp; Paykel without pressure limiting valve</td>
<td>IPP on various flows</td>
</tr>
<tr>
<td>Lampland</td>
<td>2009</td>
<td>Crossover</td>
<td>Fisher &amp; Paykel</td>
<td>EEEP on HFNC vs. CPAP</td>
</tr>
</tbody>
</table>
C. High Flow Nasal Cannula Guidelines in NICU at Children’s – St. Paul

** All babies with mild RDS should start on NCPAP initially until stabilized and requiring <30% FiO2 with acceptable RDS scores.
- Usually this means a baby will be on NCPAP for at least 24-48 hours before considering transition to HFNC.
- HFNC delivers less CPAP than NCPAP and should be considered a “wean” in therapy. Therefore, one must carefully consider its use in the small preterm infant as they have very compliant chest walls and are prone to atelectasis that may not tolerate less positive pressure.
- Potential reasons to transition to HFNC: long term need for CPAP, nasal septal breakdown, patient intolerance of NCPAP/patient comfort, mechanical difficulties with NCPAP.

** In general, infants should NOT be placed on HFNC as a first line treatment for respiratory distress
** In general, infants should NOT be placed on HFNC immediately after extubation. If positive pressure is required, the infant should be extubated to CPAP/SiPAP/NIPPV.

** Recommended HFNC Clinical Guidelines:**

** Transition to HFNC starting at 2 lpm of flow as a starting point.
- If FiO2 does not increase more than 10-20% from pre-HFNC level, stay.
- If FiO2 increases >20% or other signs of distress/worsening, increase HFNC by 1 lpm to a maximum of 4 lpm or place infant back on CPAP.

** Weaning HFNC
- If FiO2 is <30%, wean flow by 1 lpm to a minimum of 1 lpm. However, often times can just discontinue HFNC at 2 lpm when FiO2 <30% and wean to low flow cannula.
- HFNC system is obstructive at flows less than 1 lpm and baby should be put on low-flow NC when ready to wean from HFNC 1 lpm.

Please remember, these are guidelines, and may be changed at the discretion of the care provider.

D. Low Flow Nasal Cannula
Low flow cannulas are employed to deliver oxygen at liter flows of 1L/min or less. Typically the low flow cannulas are used in patients that do not need positive pressure assistance, but rather, need supplemental oxygen to keep their oxygen saturations in the appropriate range for gestational age. The order to place a patient on LFNC must be written by the care team, however, the titration of oxygen and gas flow is typically carried out by the bedside nurse. Please see guidelines below.
E. Guidelines for use of Blenders to deliver LFNC oxygen

INITIAL LOW FLOW CANNULA ORDERS (what will be written in patient chart):
“Start 0.5L/min low flow cannula at 50% supplemental oxygen by blender”
“Adjust oxygen to keep saturations 80-92% in infants <28 weeks CGA and 85-94% in infants ≥28 weeks CGA”
“Call H/O if at any point the calculated effective FiO₂ need is ≥40% for >1 hour”

GUIDELINES FOR CHANGING GAS FLOW:

INITIAL SET-UP OF LOW-FLOW CANNULA:
1. Patients requiring low-flow nasal cannula oxygen will be started on 0.5 L/min in 50% oxygen delivery by blender with titration of the oxygen up or down as needed to keep saturations 80-92% in infants <28 weeks and 85-94% in infants ≥28 weeks corrected gestational age.
2. Calculate effective FiO₂ once goal saturations are met (See tables at patient bedside for calculation of effective FiO₂). RN should chart effective FiO₂ in patient’s chart.

TITRATION UPWARD IN FiO₂ (has to be ordered by MD/NNP):
3. If EFFECTIVE FiO₂ need is ≥40% (See Tables at patient bedside for calculation of effective FiO₂) for >1 hour, nasal cannula flow should be increased by 0.25-0.5L/min as needed every 1-2 hours to a maximum of 1L/min.
4. If patient unable to have effective FiO₂ of <40% on 1L/min, the patient should be transitioned to HFNC or CPAP at the neonatologist/fellow’s discretion.

WEANING OF LOW-FLOW CANNULA (should be done per protocol by bedside RN without specific order):
5. When patient has an EFFECTIVE FiO₂ need of <30% (See Tables for calculation of effective FiO₂) for more than two consecutive hours, nasal cannula flow should be decreased in the following manner from 0.5L/min to:
   a. 0.25L/min
6. If patient has an effective FiO₂ of 21% (room air) on 0.25 L/min, then a trial off of low flow cannula to room air will be performed.
7. If the patient is unable to maintain adequate saturations in room air trial, the infant will be placed back on low flow nasal cannula directly off the wall oxygen source (100% O₂) using a micro-flowmeter without a blender.
   a. Patient will be started on 0.1-0.15 L/min and wean to minimum amount of flow necessary to achieve adequate oxygen saturations for gestational age
8. Stop weaning process when effective FiO₂ need ranges from 30-40%, and re-initiate weaning once patient meets criteria stated above.
NOTE: Patients requiring nasal cannula flow of >1 L/min will be on the Fisher-Paykel heated, humidified high-flow nasal cannula system. Infants who remain on 1 L/min LFNC for greater than 4 hours should have humidification added to the circuit coming off the wall.

Please remember, these are just guidelines, and can be changed at the discretion of the care provider.
IV. CONVENTIONAL MECHANICAL VENTILATION TECHNIQUES IN THE NICU

Please read the review of Conventional Mechanical Ventilation by Dr. Martin Keszler (J Perinatol 2009; 29:262-275) attached at the end of this section for a good overview of mechanical ventilation in the NICU. What follows is a general overview of conventional mechanical ventilation (CMV) concepts and techniques. The general goal of CMV is to achieve targeted blood gas values for both oxygenation and ventilation by optimizing pulmonary mechanics and gas exchange and minimizing lung injury. Neonates are at high risk of impaired gas exchange due to their high metabolic rate, decreased functional residual capacity, and decreased lung compliance.

Hypercapnia (↑CO₂) is usually caused by hypoventilation or severe ventilation-perfusion mismatch (V/Q mismatch). Elimination of CO₂ is directly proportional to alveolar minute ventilation. Alveolar minute ventilation is the product of tidal volume (minus dead space) and frequency. Tidal volume is the volume of gas inhaled/exhaled with each breath. Frequency is the number of breaths per minute. Dead space is usually relatively constant. Therefore, increasing an infant’s tidal volume or frequency increases minute ventilation and decreases PaCO₂. In particular, changes in tidal volume have a more pronounced effect on changing PaCO₂ values compared to changes in frequency. Hypoxemia (↓O₂) is usually due to V/Q mismatch, right→left shunting, diffusion abnormalities or hypoventilation. V/Q mismatch is the most predominant cause of hypoxemia in infants who have RDS. Oxygenation is determined by the fraction of inspired oxygen (FiO₂) and the mean airway pressure (MAP). Mean airway pressure is the average pressure to which the lungs are exposed during the respiratory cycle. Hypoxemia can be treated by optimizing MAP (increasing PIP and PEEP), increasing FiO₂, and assuring that blood oxygen content/delivery is optimal (adequate hemoglobin + optimal blood flow/cardiac output).

<table>
<thead>
<tr>
<th>Ventilator Variable</th>
<th>Effect on PaO₂</th>
<th>Effect on PaCO₂</th>
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<tr>
<td>↑ PIP</td>
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<td>↓ PIP</td>
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<tr>
<td>↓ Frequency (rate)</td>
<td>N/A</td>
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<td>↑ I:E ratio</td>
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In our NICU we most commonly use a fully assisted synchronized mode (assist control) of volume-targeted ventilation. When ordering this in Cerner, it is called PC/AC with volume targeting added. The orders will include the following:

- **Mode:** PC/AC
- **Rate:** typically 60 breaths/min for infants <1000kg; 40 breaths/min for infants >1000kg
- **Tidal volume:** 5-8ml/kg
- **PIP:** **do not need to order this because volume targeting**
- **PEEP:** 5-6 cm H₂O
- **I Time:** 0.3 seconds

With the hopes of minimizing ventilator induced lung injury (VILI), we aim to optimize lung recruitment with adequate PEEP and MAP while minimizing overdistention/volutrauma/barotrauma of the lung. With this in mind, permissive hypercapnia is fairly standard practice in the NICU with tolerance of PaCO₂ levels of 45-65 mmHg and arterial pH of 7.25 – 7.32. Ventilator support is weaned aggressively as tolerated.
V. HIGH FREQUENCY VENTILATION TECHNIQUES IN THE NICU

First described in the 1970’s, high-frequency ventilation (HFV) is a form of mechanical ventilation that uses small tidal volumes, sometimes less than anatomical dead space, and very rapid ventilator rates (2-20 Hz or 120-1200 breaths/min). Potential advantages of this technique over conventional mechanical ventilation (CMV) include the use of lower proximal airway pressures, the ability to adequately and independently manage oxygenation and ventilation while using extremely small tidal volumes, and the preservation of normal lung architecture even when using high mean airway pressures \(^1\)\(^-\)\(^6\). HFV’s ability to sufficiently oxygenate and ventilate the fragile preterm lung with airway pressures that are lower than that used with CMV as well as its use for alveolar recruitment and distribution of medicines such as inhaled nitric oxide (iNO) makes it a crucial constituent of neonatal respiratory therapy.

Currently, there are three general types of HFV: high-frequency positive-pressure ventilation (HFPPV), which is produced by conventional or modified CMVs operating at rapid rates; high-frequency jet ventilation (HFJV), which is produced by ventilators that deliver a high-velocity jet of gas directly into the airway; and high-frequency oscillatory ventilation (HFO), which is produced by a device that moves air back and forth at the airway opening and produces minimal bulk gas flow. Ventilators that deliver HFPPV, because of small internal compressible volumes and high gas flow rates, may simply be more efficient at moving small tidal volumes of gas into and out of the lung. HFJV and HFO appear to enhance both the distribution and diffusion of respiratory gases. Both shift the transition point between convective and diffusive gas transport progressively cephalad from the acinus into the large airways. The net effect of this shift is efficient CO\(_2\) elimination relatively independent of mean lung volume .\(^7\)

High-frequency Positive Pressure Ventilators. High-frequency positive-pressure ventilators (HFPPV) usually are CMVs adapted to operate at rapid rates. This includes a group of ventilators often referred to as high-frequency flow interrupters. The term flow interrupter originally was used to describe a group of ventilators that were neither true oscillators nor true jets. Some had jet-type injectors but delivered their bursts of gas not directly into the airway but into the ventilator circuit some distance back from the trachea and endotracheal tube. For this reason, these machines also were called setback jets. For the purposes of our discussion we consider all of these hybrid machines as HFPPVs.

Because all conventional pressure-preset neonatal ventilators will cycle at rates up to 150 breaths/min, all of them can be used to produce HFPPV. The only neonatal HFPPV device available in the United States that is designed to cycle at more rapid rates is the Infant Star HFV (Nellcor Puritan Bennett, Pleasanton, CA, USA). Although no longer in production, the Infant Star HFV is still widely used. This device has been referred to as both a jet and an oscillator. Because it has neither an injector in the airway like a jet ventilator or the active exhalation of an oscillator, it is neither. This
ventilator has a set of microprocessor-controlled pneumatic valves that alter inspiratory flow to achieve preset peak inspiratory pressures (PIPs). Although there is a Venturi system on the exhalation valve to facilitate expiration and prevent inadvertent positive end-expiratory pressure (PEEP), exhalation is still passive. This ventilator has been used in clinical trials to treat severe pulmonary air leaks and lung diseases unresponsive to CMV. It was approved by the FDA for these purposes.

**High-Frequency Jet Ventilators.** High-frequency jet ventilators (HFJV) deliver short pulses of pressurized gas directly into the upper airway through a narrow-bore cannula or jet injector. HFJVs are capable of maintaining ventilation over wide ranges of patient sizes and lung compliances. These systems have negligible compressible volumes and operate effectively at rates from 150 to 600 breaths/min (2.5 –10 Hz), with the most common rates, 240-420 breaths/min, being less than those typically used in HFOV. Exhalation during HFJV is a result of passive lung recoil. An open ventilator-patient circuit is essential and the HFJV is used in combination with a CMV to provide optimal oxygenation. Tidal volumes are difficult to measure but appear to be equal to or slightly greater than anatomic dead space. Jet ventilators have been tested extensively in laboratory animals and have been used clinically in adults and neonates. The Bunnell Life Pulse jet ventilator (Bunnell Inc., Salt Lake City, UT, USA) was designed specifically for infants (Figure 11.4). Using the triple-lumen endotracheal tube adapter, this device delivers its jet pulse into the endotracheal tube through the adapter's injector port, then servo controls the background pressure, or driving pressure, of the jet pulse to maintain a constant predetermined pressure within the endotracheal tube. This device is approved for clinical use in neonates and infants. With HFJV, CO₂ removal is achieved at lower peak and mean airway pressures than with either HFPPV or HFO. Although effective in homogeneous lung disorders, such as respiratory distress syndrome (RDS), only one randomized multicenter trial has demonstrated a beneficial pulmonary effect (lower rates of chronic lung disease) with the use of early HFJV over CMV in RDS. HFJV appears to be most effective in non-homogeneous lung disorders where CO₂ elimination is the major problem, such as air leak syndromes [i.e. pulmonary interstitial emphysema (PIE)] . It has also appears to be safe and effective when used in neonatal transport and can be used with simultaneous delivery of inhaled nitric oxide (iNO).

**High-Frequency Oscillators.** High-frequency oscillators (HFO) are a type of HFV that use piston pumps or vibrating diaphragms, operating at frequencies ranging from 180 to 2400 breaths/min (3–40 Hz), to vibrate air in and out of the lungs. During HFO, inspiration and expiration are both active (proximal airway pressures are negative during expiration). Oscillators produce little bulk gas delivery. A continuous flow of fresh gas rushes past the source, generating or powering the oscillations. This bias gas flow is the system’s only source of fresh gas. A controlled leak or low-pass filter allows gas to exit the system. The amplitude of the pressure oscillations within the airway determine the tiny tidal volumes that are delivered to the lungs around a constant mean airway pressure. This allows avoidance of high peak airway pressures for ventilation as well as maintenance of lung recruitment by avoidance of low end-
expiratory pressures. HFOs have been tested extensively in animals and humans. Today the most commonly used neonatal HFO is the SensorMedics 3100A oscillator (Cardinal Health, Yorba Linda, CA, USA), which is approved for use in both the United States and Canada. This ventilator has been approved for clinical use in neonates and provides ventilation and oxygenation, with no need for combination with CMV like the HFJV. This device produces its oscillations via an electronically controlled piston and diaphragm. Frequency (3 to 15 Hz or 180-900 breaths/min), percent inspiratory time, and volume displacement can be adjusted, as well as resistance at the end of the bias flow circuit. Variations in bias flow rate and the patient circuit outflow resistor control mean airway pressures. Ventilation is proportional to the product of frequency and the square of the tidal volume \((f \times V_t^2)\), thus a decrease in frequency or increase in tidal volume by way of an increase in set amplitude should cause increased carbon dioxide removal.

**GENERAL CONCLUSIONS:** To date there have been 16 randomized controlled clinical trials of elective use of HFV versus CMV for the treatment of neonates with respiratory insufficiency, primarily in babies with respiratory distress syndrome of prematurity. The studies include HFV in the form of HFPPV, HFJV, and HFO. The majority of the studies (11 of 16) were unable to demonstrate any significant difference in pulmonary outcomes between babies treated with HFV versus CMV. The remainder of the studies demonstrated a small, yet significant reduction in chronic lung disease (CLD) in the HFV treated groups. In 2007, the Cochrane Database provided a review and meta-analysis of clinical trials of elective HFO versus CMV in preterm infants with acute pulmonary dysfunction. The review demonstrated no evidence of effect on mortality and no clear advantage to the preferential use of elective HFO over CMV as the initial ventilation strategy in premature babies with respiratory distress. High volume strategy of HFO, piston-oscillators, lack of lung protective strategies in the CMV groups, early use of HFO (< 6 hours), and inspiratory: expiratory ratio of 1:2 was associated with the trials that demonstrated a reduction in chronic lung disease in the HFO groups. The Cochrane database also reviewed the elective use of HFJV versus CMV, and in the three studies reviewed concluded that there may be a decreased risk of CLD in the elective HFJV groups. However, the authors cautioned these apparent positive findings with the fact that one study had increased adverse neurologic outcomes in the HFJV group. Overall, grouped analysis of all randomized, controlled studies to date would not support the selective use of early or elective HFV over CMV in premature babies with respiratory insufficiency.

**References for HFV:**


VI. PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

PPHN is persistence after birth of high pulmonary arterial pressure that is characteristic of fetal circulation. In fetal life, pulmonary blood flow is low (5-10% of cardiac output) due to high pulmonary vascular resistance and shunts. At birth, pulmonary vascular resistance normally falls dramatically when the lungs inflate and oxygenation increases. If this normal transition fails, pulmonary vascular resistance remains elevated and right to left shunting occurs through the PFO and ductus arteriosus. Subsequent acidosis and hypoxia are potent pulmonary vasoconstrictors.

Clinically this presents most often in term babies with quick onset of respiratory distress at birth or within the first few hours of life. Cyanosis and increased work of breathing are commonly noted. Pre-ductal (right upper extremity) oxygen saturations are greater than post-ductal (either lower extremity) oxygen saturations, with a difference in ≥10% suggesting significant pulmonary hypertension.

Clinical scenarios associated with PPHN include:
1. Abnormal pulmonary vascular development: chronic fetal hypoxia, infant of diabetic mother, alveolar capillary dysplasia
2. Pulmonary hypoplasia: congenital diaphragmatic hernia, prolonged oligohydramnios, Potter’s syndrome
3. Postnatal pulmonary vasoconstrictors: sepsis, pneumonia, meconium/blood/amniotic fluid aspiration, perinatal asphyxia
4. Congenital heart disease: total anomalous pulmonary venous return

Evaluation of an infant with suspected PPHN includes pre-/post-ductal saturation monitoring with oxygen supplementation to keep pre-ductal saturation >90%, sepsis evaluation/treatment, echocardiogram, and evaluation/treatment of acidosis, poor perfusion, electrolyte abnormalities, agitation, and polycythemia. Most infants with significant PPHN will require intubation and mechanical ventilation to correct hypoxemia and respiratory acidosis. If the infant is intubated for significant PPHN, then iNO will be started at 20ppm to promote pulmonary vasodilation and improve oxygenation. These infants are often critically ill and unstable. If mechanical ventilation combined with iNO does not provide effective oxygenation, normal acid-base status, or hemodynamic stability, then ECMO is needed. The center for neonatal ECMO for Children’s Hospitals and Clinics of MN is located on the Minneapolis campus, and thus an infant in our unit who requires ECMO will be transferred.
VII. INHALED NITRIC OXIDE

Nitric oxide (NO) is a free radical, produced by the endothelium, that causes vascular smooth muscle relaxation and vasodilation via its active second messenger cGMP. NO production is critical to the transition from fetal (high pulmonary pressures and pulmonary vasoconstriction) circulation to postnatal (low pulmonary pressures and pulmonary vasodilation) circulation. Infants who fail to make this transition in circulatory status appropriately have persistent pulmonary hypertension of the newborn (PPHN). Infants with PPHN have decreased serum levels of NO metabolites as well as decreased serum levels of cGMP, again suggesting adequate NO and subsequent cGMP levels are a key component to decreasing pulmonary vascular resistance after birth.

Inhaled nitric oxide (iNO) is an exogenous gas given through the endotracheal tube that produces selective pulmonary vasodilatation. iNO has been shown in multiple clinical trials investigating the treatment of PPHN to be safe, an effective pulmonary vasodilator, to improve oxygenation, and decrease the need for ECMO. iNO has only recently been studied in other neonatal diagnosis, primarily in the prevention and treatment of chronic lung disease of prematurity (CLD). A promising large randomized controlled trial by Ballard et al. demonstrated that a prolonged use of tapering doses of iNO started on extremely premature infants who still required mechanical ventilation at 7 days of age decreased their rates of CLD as compared to the group that did not receive iNO. Ongoing studies are investigating the use of iNO in premature infants.

iNO causes the oxidation of hemoglobin and produces methemoglobin, which has decreased oxygen-carrying capacity. Typically methemoglobin is restored to its usual oxygen-carrying state by enzymatic reduction. Methemoglobinemia (metHgb >5%) occurs in approximately 10% of newborns treated with iNO and typically resolves with decreasing the iNO dose. Infants on iNO should have daily metHgb levels to assess for toxicity.

iNO is typically started at 20 part per million (20 ppm) to produce maximal pulmonary vasodilation. As oxygenation improves, supplemental FiO2 decreases (typically <40%), and mean airway pressures normalize, iNO can be weaned. iNO is usually weaned from 20ppm to 5ppm in decreasing steps by 5ppm every 1-2 hours. If a patient is particularly sensitive to the weaning steps, then longer time periods between the decreasing doses is often utilized. Once a patient is at 5ppm, weaning typically is done by 1ppm every few hours until off. Weaning from 5ppm is taken more gradually with close attention to signs of intolerance as “rebound” pulmonary hypertension may occur. Sudden discontinuation of iNO will almost always cause “rebound” pulmonary hypertension, and thus, weaning is always done very cautiously with close attention to the patient’s respiratory status throughout the process.
Suggested References for NO:

Finer N, Barrington K. Nitric oxide for respiratory failure in infants born at term or near term. Cochrane Database of Systematic Reviews 2006.

VIII. APNEA AND BRADYCARDIA

Pathologic apnea is defined as a respiratory pause of ≥20 seconds or apnea associated with bradycardia or color change. Apnea may be central, obstructive, or mixed. Central apnea is cessation of respiratory effort. Obstructive apnea is the inability to breathe despite respiratory effort, usually due to upper airway obstruction. Mixed apnea is a combination of both central and obstructive apnea. Premature infants most commonly have central or mixed apnea. Typically, most premature infants outgrow pathologic apnea by 34-35 weeks gestational age. Apnea and bradycardia events are noted on continuous bedside cardiorespiratory monitoring and will be noted in the infant’s chart by nursing with comments as to the circumstances around the event and what intervention, if any, was needed to get the infant to resume a normal breathing pattern. New onset of apnea or a change in the frequency or severity of apnea/bradycardia spells can be an important signal of change in patient status, in particular, infection.

Differential diagnosis for the etiology of apnea includes:
1. Apnea of prematurity
2. Infection (sepsis, meningitis, UTI, pneumonia)
3. Necrotizing enterocolitis
4. Intracranial hemorrhage
5. Seizures
6. Hydrocephalus/CNS malformations
7. Anemia
8. Polycythemia
9. Atelectasis/Hypoxemia
10. Gastroesophageal reflux
11. Vagal stimulation (common with feeding related apnea, suctioning)
12. Following anesthesia
13. Maternal drug withdrawal
14. Upper airway obstruction
15. Side-effect of Prostaglandin E1 infusion
16. Congenital hypoventilation syndrome

All “treatable” causes of apnea should be evaluated and treated as indicated in any infant. Apnea of prematurity if often a diagnosis of exclusion based on premature gestational age and no evidence of other “treatable” causes of pathologic apnea. Treatment of mild apnea of prematurity may only include occasional mild cutaneous stimulation. Apnea may also be treated with increased respiratory support including nasal cannula, CPAP, or occasionally mechanical ventilation if apnea is severe and persistent. If apnea/bradycardia events are frequent (≥5 per day) or require significant intervention (vigorous stimulation or CPR), then methylxanthine therapy (caffeine, aminophylline) is initiated. Methylxanthine therapy will typically be continued until >32 weeks gestational age, at which time if the patient is not having significant apnea/bradycardia spells, a trial of discontinuing the medication will be undertaken.
Due to caffeine’s long half-life (3-7 days), this therapy needs to be discontinued well before discharge to ensure that significant apnea does not return once the medication is fully out of the infant’s body.

Treatment of Apnea with Methylxanthines (Aminophylline, Caffeine) Indications:
1. To treat infants who are having frequent (5 or more episodes per day) or severe (requiring vigorous stimulation or CPR) apnea or bradycardia. Prior to prescribing aminophylline or caffeine, treatable causes of apnea should be excluded, i.e., anemia, seizures, sepsis, hypoxemia, metabolic abnormalities, or gastroesophageal reflux.
2. To normalize an abnormal pneumogram or MMU prior to discharge.
3. To facilitate weaning from ventilatory support.

Our NICU uses the following criteria as evidence that a premature infant has “outgrown” their premature breathing patterns and apnea of prematurity:
1. The infant is fully off of all methylxanthine support (typically >5-7 days since last dose of Caffeine, and 2-3 days since last dose of Aminophylline)
2. No documented evidence of significant events on bedside nursing notes/charting for minimum of 24-48 hours
3. Acceptable pneumogram

What are pneumograms?
Pneumograms (CR-scan, MMU)
All infants less than 34 weeks gestational age and any infant (regardless of gestational age) who has experienced significant clinical apnea should have a pneumogram (12-hour recording of heart rate, respiration, and O2 saturation) performed prior to discharge.

CR-Scan - A Cardio-respiratory Scan is a continuous recording of heart rate, breathing pattern, nasal airflow, and oxygen saturation (by pulse-ox); this type of scan is particularly useful if there is concern oxygenation, as in infant with BPD and/or on supplemental oxygen or if one is trying to differentiate between central and obstructive apnea.

MMU - A Memory Monitor Unit recording only records when monitor limits are violated (therefore only giving a brief “snapshot” of the monitored variables). The MMU is the routine type of scan done on infants who you are assessing if they have “outgrown” their apnea of prematurity and baseline oxygen saturations are not in question.

A pneumogram or MMU is not a test for SIDS. It does document the presence or absence of significant apnea or bradycardia, or isolated prolonged desaturation. Clinically significant events may occur before or after a pneumogram. Therefore, a normal or acceptable pneumogram does not necessarily mean a monitor can be discontinued.
When ordering a pneumogram, you need to specify which type (MMU or CR Scan), and, in the case of an MMU, you need to specify the duration (usually a minimum of 12 hours, although if a patient is admitted at night, it may end up being less than 12 hours until morning). You should also specify how the patient should be placed during the pneumogram (e.g. head of bed flat vs. upright). A neonatologist will interpret the pneumogram results upon completion of the study.
IX. OXYGEN SATURATIONS

WHY
Reduce rate of Chronic Lung disease by reducing the cellular damage and its resultant morbidity and mortality associated with excessive oxygen administration.
Decrease ROP rates.
Allow for slower adaptation period from intrauterine to extra uterine oxygen saturations.
   Provide an approach to oxygen administration that takes into consideration the range of developmental changes that occurs between extremely premature and term infants.

WHAT
The focus will be upon specific target oxygen saturations, rather than a range.
The earlier the gestation, the lower the initial oxygen saturation targets.

HOW
Four target oxygen saturation cards will hang from the side of the monitor. Nurse will choose appropriate target for gestational age and Velcro to the top edge of the monitor. Nurse will update as baby ages.
Less than 28 weeks choose the red card with the target number of 85%. Alarm limits should then be set at low of 80% and high of 90% for the babies that are in supplemental O₂.
   28-34 weeks choose the yellow card with the target number of 88%. Alarm limits should then be set at low of 85% and high of 93% for the babies that are in supplemental O₂.
35 and above weeks choose the green card with the target number of 92%. Alarm limits should then be set at low of 85% and high of 96% for the babies that are in supplemental O₂.
Use the blue card that says see orders for all other babies that have a specified saturation level due to Cardiac or high risk of PPHN. The provider will then need to place the order of the parameters that are needed.
The high saturation limit can be set at 100% if the baby is in room air.
The low saturation limit will stay according to the gestational age above when in room air.
When an order has been placed for oxygen to be used on a baby, use the conditional order sets to choose the appropriate saturation limits for the gestational age. The card posted on the monitor should be the same as the order chosen in Cerner.
As the gestation of the baby changes the bedside nurse will update to the appropriate card on the monitor and change the conditional order in Cerner to match the new target alarm limits.
X. CHRONIC LUNG DISEASE OF PREMATURITY

Chronic lung disease (CLD) of prematurity defines the population of premature babies who have long-term lung damage and still require oxygen supplementation at 36 weeks post-menstrual age. The etiology of CLD is multi-factorial and likely includes such factors as alveolar developmental arrest, inflammatory cascade activation, oxygen toxicity, pulmonary edema, ventilator-induced lung injury, and the increased survival of younger preterm infants. Unfortunately, despite improvements in maternal and neonatal care including the use of antenatal steroids, exogenous surfactant, and improved mechanical ventilator strategies, CLD rates have remained stagnant over the past few decades.

Multiple strategies are employed in the NICU to minimize CLD in premature infants. Mechanical ventilation strategies aim to be “lung-protective” which entails the delicate balance of optimization of lung recruitment and avoidance of lung over-distention. Lung protective strategies include optimization of mean airway pressure and PEEP for recruitment and utilization of permissive hypercapnia to allow for use of low tidal volumes and low peak pressures to minimize over distention. Strategies are also in place to minimize oxygen exposure and toxicity, as this is known to increase risk of CLD as well as retinopathy of prematurity.

Some medical strategies to reduce CLD include the use of vitamin A supplementation to promote alveolarization and lung growth, the use of early caffeine therapy, as well as the use of diuretics and steroids. Vitamin A supplementation is given per our unit protocol (please see pharmacist for protocol details) and briefly provides vitamin A supplementation for the first month of life or until the infant is on full enteral feedings as therefore has a source of vitamin A, whichever comes sooner. Caffeine therapy is started in all very low birth weight infants within the first week of life, regardless of their respiratory needs, as this has been shown to treat apnea and bradycardia events, decrease extubation failure, and decrease CLD rates. Although short-term benefit may be achieved, the long-term efficacy of steroids and diuretics to prevent chronic lung disease is controversial, and therefore, our neonatology group has devised guidelines for their use in infants who are between 34-36 weeks gestation. Please see guidelines below.

Chronic lung disease is one of the common morbidities of extreme prematurity and mortality is approximately 25% in infants with severe CLD, in particular those infants who require tracheostomy and mechanical ventilation at the time of discharge to home. The main cause of death in these infants is cor pulmonale, lower respiratory tract infections, and sudden death.
Recommendations for the Use of Steroids and Diuretics in Chronic Lung Disease at ≥ 34 Weeks CGA.

AIMS:
1. Reduce Incidence of Chronic Lung Disease (as defined by supplemental O₂ need at 36 wks CGA.)
2. Provide consistency in diuretic and steroid use among neonatology providers in infants with CLD and relatively low oxygen requirements.

RECOMMENDATIONS:
Infants at 34 weeks CGA with persistent oxygen need of an effective FiO₂ ≤ 0.3 on low flow blended nasal cannula will have consideration of the following interventions in attempt to wean off oxygen. Prior to initiation, a discussion with parents regarding the speculative benefits of these treatments should occur.

1. At ≥34 weeks postmenstrual age: institute a trial of furosemide (Lasix) at 2 mg/kg/day po daily x 7 days.
   If trial results in reduction of oxygen need, consideration should be given to initiation of long-term chlorothiazide (Diuril) at 40 mg/kg/day (+/- sodium and potassium supplements).

   AND/OR:

2. At ≥34 weeks postmenstrual age for persistent supplemental oxygen need +/- diuretic trial: institute prednisolone or methylprednisolone at 1 mg/kg/dose Q 8 hours x 72 hours.
   Infants should be observed for rebound oxygen need for 5-7 days post steroid use.

RELATIVE CONTRAINDICATIONS:
1. Lasix: Hypokalemia or nephrocalcinosis
2. Prednisolone/methylprednisolone: Hypertension

These clinical practice recommendations should be considered as suggested clinical practice and the choice to pursue these treatment options will remain at the discretion of rounding neonatologist or fellow.

Suggested Reading:


STATE-OF-THE-ART

State of the art in conventional mechanical ventilation

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Despite a shift to noninvasive respiratory support, mechanical ventilation remains an essential tool in the care of critically ill neonates. The availability of a variety of technologically advanced devices with a host of available modes and confusing terminology presents a daunting challenge to the practicing neonatologist. Many of the available modes have not been adequately evaluated in newborn infants and there is paucity of information on the relative merits of those modes that have been studied. This review examines the special challenges of ventilating the extremely low birth weight infants that now constitute an increasing proportion of ventilated infants, attempts to provide a simple functional classification of ventilator modes and addresses the key aspects of synchronized ventilation modes. The rationale for volume-targeted ventilation is presented, the available modes are described and the importance of the open-lung strategy is emphasized. The available literature on volume-targeted modalities is reviewed in detail and general recommendations for their clinical application are provided. Volume guarantee has been studied most extensively and shown to reduce excessively large tidal volumes, decrease incidence of inadvertent hyperventilation, reduce duration of mechanical ventilation and reduce pro-inflammatory cytokines. It remains to be seen whether the demonstrated short-term benefits translate into significant reduction in chronic lung disease. Avoidance of mechanical ventilation by means of early continuous positive airway pressure with or without surfactant administration may still be the most effective way to reduce the risk of lung injury. For babies who do require mechanical ventilation, the combination of volume-targeted ventilation, combined with the open-lung strategy appears to offer the best chance of reducing the risk of bronchopulmonary dysplasia.


Keywords: mechanical ventilation; newborn; tidal volume; lung injury

Introduction

Technological advances in the design of mechanical ventilators and improved understanding of factors responsible for ventilator-induced lung injury (VILI) have occurred over the past two decades, resulting in improving outcomes in extremely low birth weight (ELBW) infants. Today, few infants die of acute respiratory failure; early mortality is now predominantly from other complications of extreme prematurity, such as infection, necrotizing enterocolitis or intracranial hemorrhage. Although further reduction in mortality remains an important goal, focus has shifted from reducing mortality to reducing the still unacceptably high incidence of chronic lung disease. Though high-frequency ventilation has shown promise in this regard, inconsistent results and continued concerns about the hazards of inadvertent hyperventilation have limited its acceptance as first-line therapy in infants with uncomplicated respiratory distress syndrome (RDS).1

At the present time, respiratory support in newborn intensive care continues to evolve rapidly. Utilization of noninvasive respiratory support has become widely accepted as the most effective means of reducing the risk of VILI. Although the concept is very attractive and supported by a number of uncontrolled and cohort studies, it must be pointed out that we currently lack the definitive randomized clinical trial data to validate the presumed benefits of nasal continuous positive airway pressure (N-CPAP) as the primary mode of respiratory support.2 Surfactant, if used at all, is now increasingly administered without prolonged mechanical ventilation, thus potentially preserving the well-documented benefits of surfactant replacement therapy, while avoiding the dangers of prolonged mechanical ventilation. Whether and under what circumstances brief intubation for surfactant administration is indicated remains unclear. Administration of nebulized surfactant during N-CPAP is a potentially attractive approach that is currently under investigation. Nasal intermittent mandatory ventilation (IMV) may be able to augment an ELBW infant’s inadequate respiratory effort without the complications associated with endotracheal intubation. This approach may be of substantial benefit in reducing the incidence of ventilator-associated pneumonia and thus avoiding the contribution of postnatal inflammatory response to the development of bronchopulmonary dysplasia (BPD). Detailed discussion of noninvasive respiratory support is beyond the scope of this paper; the reader is referred to other reviews on this important topic.3–5

Notwithstanding the lack of unequivocal data, substantial shifts in clinical practice have become evident, resulting in a reduction
in the number of infants receiving mechanical ventilation. Most of the infants who now receive mechanical ventilation are much smaller and more immature than those ventilated only 10 years ago. They often require ventilation for extended periods for reasons not directly related to lung disease. Data from clinical trials of respiratory support conducted many years ago may thus not be directly applicable to the extremely immature infants that now constitute the majority of ventilated infants.

For the more severely ill infants who require mechanical ventilation, a new generation of microprocessor-based ventilators with technologically advanced features enabling effective synchronized (also known as patient-triggered) ventilation has become widely available. Even more promising is the advent of volume-targeted modalities of conventional ventilation that, for the first time, allow effective control of delivered tidal volume ($V_T$) for neonatal ventilation. In this review, I will briefly cover the unique challenges of ventilating ELBW infants, discuss the basic modes of synchronized ventilation, describe the concept of volume-targeted ventilation, examine relevant literature and briefly discuss the clinical application of the techniques.

**Basic ventilator terminology/general classification of ventilation modes**

The rapid evolution of ventilator technology with increasing availability of a variety of basic and complex modes of respiratory support has led to a great deal of confusion in terminology and general concepts of mechanical ventilation. Because different manufacturers employ different nomenclature to describe often closely related modes of ventilation, communication between users of different devices has become increasingly difficult. Most of the ventilators used in newborn infants today are designed to span the entire age range from preterm newborn to adults and may have a variety of modes that have never been evaluated in newborn infants. Detailed discussion of the terminology is beyond the scope of this paper. The interested reader is referred to in-depth reviews of the subject. For the purpose of this review, only the basic terminology for modes that are primarily used in newborn infants will be defined briefly.

Basic modes of mechanical ventilation are best classified on the basis of three factors:

- How is each breath initiated?
- How is gas flow controlled during breath delivery?
- How is the breath ended?

Breaths can be initiated by a timing mechanism without regard to patient inspiratory effort. These modes are known as controlled ventilation. Alternately, breaths may be triggered by the patient’s inspiratory effort, in which case we refer to assisted, also known as synchronized or patient-triggered ventilation.

The primary control variable for gas flow during the breath may be pressure (pressure-controlled/pressure-limited ventilation) or delivered $V_T$ (volume-controlled ventilation, VCV).

Breath termination may occur based on elapsed time (time cycled), or based on cessation of inspiratory flow (flow or volume cycled).

In addition to these basic modes, a variety of hybrid modes have been developed that combine features of several of the basic types. A complete discussion of all available modes is beyond the scope of this paper, but the basic neonatal modes will be discussed in subsequent paragraphs.

**Unique challenges in mechanical ventilation of newborn infants**

*Lung mechanics*

Small infants with noncompliant lungs have very short time constants and normally have rapid respiratory rates (RRs) with very short inspiratory times ($T_i$’s) and have limited muscle strength. This situation imposes great technological challenges on device design, especially in terms of breath triggering, breath termination and $V_T$ measurement. These are the reasons why the introduction of synchronized ventilation into clinical practice in newborn infants lagged substantially behind its use in adults.

*Uncuffed endotracheal tubes*

Uncuffed endotracheal tubes (ETTs) have traditionally been used in newborn infants, because of concern about pressure necrosis of the neonatal tracheal mucosa and the small size of the tubes that makes inflatable cuffs more difficult to incorporate. As a consequence, majority of infants have some degree of leak around the ETT, especially later on in their course as the larynx and trachea progressively dilate as a result of exposure of these immature structures to cyclic stretch at a rate of as much as 3600 times per hour or more than 86 000 times per day. The leak is always greater during inspiration than in expiration, because the pressure gradient driving the leak is greater during inspiration and because the airways, including the trachea, distend with the higher inspiratory pressure. Therefore, it is important to measure both inspiratory and expiratory $V_T$, with the latter more closely approximating the volume of gas that had entered the patient’s lungs. It is critical to appreciate that the magnitude of the leak (or indeed its presence) varies from moment to moment. This is because the ETT is inserted only short distance beyond the larynx; therefore, the leak will change with any change in the infant’s head position, slight tension on the ETT and so on. Leak around ETT also imposes additional challenges in breath triggering and termination, as discussed below.

*Measurement of tidal volume*

The importance of very accurate $V_T$ measurement in any sort of volume-controlled/volume-targeted ventilation of ELBW infants...
should be self-evident, given that infants weighing 400 to 1000 g require $V_T$'s in the range of 2 to 5 ml.

Flow and volume measurement has traditionally been performed at the junction of the breathing circuit and the ventilator. This placement is convenient and avoids extra wires and the added instrumental dead space (IDS). However, in neonates this remote placement results in major inaccuracy of the $V_T$ measurement. When the $V_T$ is measured at the ventilator end of the circuit, the value does not account for compression of gas in the circuit and humidifier, distention of the circuit or leak around the ETT. The loss of volume to gas compression is a function of the compliance of the ventilator circuit relative to the patient’s lungs and to the volume of the circuit/humidifier, relative to the patient’s lungs. In large patients with cuffed ETT, the volume injected into the circuit correlates reasonably well with the actual $V_T$ entering the lungs and the volume loss to compression of gas in the circuit can be readily corrected by available algorithms. In small infants whose lungs are tiny and stiff, compared to the volume and compliance of the circuit/humidifier, the loss of volume to the circuit is not readily corrected, especially in the presence of significant ETT leak.

Traditional volume-controlled ventilation

Volume-controlled/volume-cycled ventilators deliver a constant, preset $V_T$ with each ventilator breath. In theory, these volume ventilators allow the operator to select $V_T$ and frequency and therefore directly control minute ventilation. The ventilator delivers the preset $V_T$ into the circuit generating whatever pressure is necessary, up to a set safety pop off, generally set at a pressure $>40$ cm H$_2$O. A maximum $T_I$ is also set as an additional safety measure. Inspiration ends when the preset $V_T$ has been delivered or when the maximum $T_I$ has elapsed. The latter ensures that with very poor lung compliance, the ventilator does not maintain inspiration for a prolonged period trying to deliver the set $V_T$.

The major limitation of volume-controlled ventilators is that what they actually control is the volume injected into the ventilator circuit, not the $V_T$ that enters the patient’s lungs. This limitation is based on the fact that, as discussed previously, the $V_T$ measurement does not account for compression of gas in the circuit and humidifier and distention of the compliant circuit. Most importantly, the variable leak around uncuffed ETTs used in newborn infants makes accurate control of delivered $V_T$ very difficult with traditional volume-controlled modes. A recent paper by Singh et al.,$^7$ did demonstrate the feasibility of VCV when special measures are taken to compensate for these problems. In that study, the set $V_T$ was manually adjusted at frequent intervals to achieve a target exhaled $V_T$ measured by a proximal flow sensor at the airway opening.

Pressure-controlled ventilation

Currently, the standard in neonatal mechanical ventilation is intermittent positive pressure ventilation using time-cycled, pressure-limited (TCPL), continuous flow ventilators. This practice evolved largely because of the difficulties with traditional VCV described above. The basic design of these ventilators can be thought of as a T-piece circuit with continuous flow of gas and a valve that directs gas flow into the patient or allows it to continue around the circuit. A pressure-limiting valve controls the maximum pressure in the circuit during inspiration (peak inspiratory pressure, PIP) and a second valve maintains a certain level of positive pressure during the expiratory phase (positive end-expiratory pressure, PEEP).

In their basic form these ventilators require the clinician to set inspiratory and expiratory time ($T_I$, $T_E$, which together determine the RR), PIP, PEEP, inspiratory flow rate and FiO$_2$. During inspiration, the expiratory valve closes, the circuit is pressurized and gas flows into the patient. Once the pressure within the patient circuit reaches the PIP, additional gas escapes through the pressure-limiting valve. When the $T_I$ has elapsed, the expiratory valve opens, allowing circuit pressure to fall rapidly to the level of PEEP. The valve remains open with circuit pressure at the PEEP level with fresh gas flowing in the circuit available for spontaneous breathing, until the end of $T_E$, at which point the valve closes again and the cycle repeats.

Pressure-limited ventilators overcome the difficulties associated with VCV and are simple to use. However, their chief disadvantage is that $V_T$ delivery is not directly controlled, but rather is the dependent variable that fluctuates as a function of inspiratory pressure and lung compliance.

Synchronized ventilation

Rationale, types of triggering devices and potential pitfalls

The standard mode of ventilation used in newborn infants before the introduction of synchronized ventilation was known as IMV. This TCPL mode of ventilation provides a set number of ‘mandatory’ mechanical breaths. The patient continues to breathe spontaneously, using the fresh gas flow available in the ventilator circuit. Unfortunately, the irregular respiratory pattern of the baby frequently leads to asynchrony between the infant and the ventilator. High airway pressure, poor oxygenation and large fluctuations in intracranial pressures result when the ventilator breath occurs just as the infant exhales. Heavy sedation and muscle paralysis were often employed to prevent the baby from ‘fighting the ventilator’. These interventions resulted in greater dependence on respiratory support, lack of respiratory muscle training, generalized edema and inability to assess the neurological status. The advantages of synchronizing the infant’s spontaneous effort with the ventilator cycle, rather than using muscle relaxants, are
intuitively obvious, though large clinical trials clearly documenting their superiority are lacking.

The introduction of synchronized ventilation into neonatal care lagged far behind its use in adults due to technological challenges imposed by the small size of preterm infants. The ideal triggering device must be sensitive enough to be activated by a small preemie, must be relatively immune from auto-triggering and must have a sufficiently rapid response time to match the short T₁'s and rapid RRs seen in small premature infants. Variable leak of gas around uncuffed ETTs further complicates the situation. The types of triggering devices used in clinical care and their relative advantages are listed in Table 1. Clinical and laboratory experience has shown that flow triggering using a flow sensor at the airway opening (at the ETT adaptor) is ultimately the best compromise currently available. At this time, all infant ventilators in common use utilize this triggering mode. An emerging technology, which recently became available, uses the electrical activity of the diaphragm (EAdi), as assessed by trans-esophageal electromyography to trigger inspiration. This approach, though not yet adequately evaluated in newborn infants, is attractive because it has the shortest trigger delay, does not require a flow sensor and is not affected by ETT leakage.

Although flow triggering is the best currently available method, it is important to be aware of the potential problems of this mode of triggering. The interposition of the flow sensor adds approximately 1 ml of dead space to the breathing circuit, which becomes a larger proportion of the V₁ in the tiniest infants. The second problem is susceptibility to auto-triggering in the presence of a leak around the ETT. Any substantial leak flow during the expiratory phase will be (mis)interpreted by the device as inspiratory effort and would trigger the ventilator at an excessively rapid rate. When recognized, the problem can be corrected by decreasing trigger sensitivity. However, the magnitude of the leak often changes quite rapidly, requiring frequent adjustment.

**Table 1** Comparison of triggering methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Impedance</td>
<td>No added dead space, noninvasive</td>
<td>Poor sensitivity, many artifacts</td>
</tr>
<tr>
<td>Pneumatic capsule</td>
<td>Rapid response, no extra dead space, leak tolerant</td>
<td>Positioning is critical, no longer commercially available</td>
</tr>
<tr>
<td>Pressure</td>
<td>No added dead space, leak tolerant</td>
<td>Poor sensitivity, long trigger delay, high WOB</td>
</tr>
<tr>
<td>Airflow</td>
<td>Very sensitive, rapid response</td>
<td>Added dead space, leak sensitive</td>
</tr>
<tr>
<td>Diaphragm EMG</td>
<td>Sensitive, most rapid response, leak tolerant</td>
<td>Requires careful positioning of probe</td>
</tr>
</tbody>
</table>

Abbreviations: EMG, electromyography; WOB, work of breathing.

Furthermore, when the trigger is made less sensitive, increased effort is needed to trigger the device and there is a longer trigger delay; both highly undesirable. One device, the Draeger Babylog (Draeger Medical Inc., Telford, PA, USA), offers an effective solution to this problem, utilizing a proprietary leak compensation technology that derives the instantaneous leak flow throughout the ventilator cycle and mathematically subtracts this flow from the measured value. This effectively eliminates the leak-related problem of auto-triggering and allows the trigger sensitivity to remain at the most sensitive value, preserving rapid response time and minimal work to trigger the device.

**Basic modes of synchronized ventilation**

**Synchronized intermittent mandatory ventilation**

Synchronized intermittent mandatory ventilation (SIMV) provides a preset number of mechanical breaths as in standard IMV, but these are synchronized with the infant's spontaneous respiratory effort, if present. Spontaneous breaths in excess of the set rate are not supported. This results in uneven V₁'s and high work of breathing (WOB) during weaning, an important issue particularly in extremely small and immature infants with correspondingly narrow ET. The high airway resistance of narrow ET, limited muscle strength and mechanical disadvantage conferred by the infant's excessively compliant chest wall typically result in small, ineffective V₁. Because instrumental dead space (IDS) is fixed, very small breaths that largely rebreathe the dead space gas will contribute little to effective alveolar ventilation (alveolar ventilation = minute ventilation—dead space ventilation). To maintain adequate alveolar minute ventilation, relatively large V₁ is thus required with the limited number of mechanical breaths provided by the ventilator.

**Assist control**

Assist control (AC) is a TCPP mode that supports every spontaneous breath, providing more uniform V₁ delivery and lower WOB. The clinician still sets a ventilator rate for mandatory ‘backup’ breaths, which provides a minimum rate in case of apnea. This rate should normally be below the infant’s spontaneous rate to allow the infant to trigger the breaths. The goal here is to have the infant and the ventilator work together, resulting in lower ventilator pressure. Because the infant controls the effective ventilator rate, weaning is accomplished by lowering the PIP rather than ventilator rate. In this fashion, the amount of support provided to each breath is decreased, allowing the infant to gradually take over the WOB. This slightly less intuitive weaning strategy appears to be one reason for the apparent reluctance to adopt this mode.

**Pressure support ventilation**

Pressure support ventilation (PSV) is a flow, rather than TCPP mode that supports every spontaneous breath just like AC but also terminates each breath when inspiratory flow declines to a preset...
threshold, usually 10 to 20% of peak flow. This feature eliminates
the inspiratory hold (prolonged $T_i$ that keeps the lungs at peak
inflation) and thus presumably provides more optimal synchrony.
In turn, this should limit fluctuations in intrathoracic and
intracranial pressure that occur when an infant exhales against
the high positive pressure during inspiratory hold. In some devices,
PSV can be used to support spontaneous breathing between low-
rate SIMV, to overcome the problems associated with inadequate
spontaneous respiratory effort and high ETT resistance. Here, the
PSV support is set as $X$ cm H$_2$O above PEEP. In other ventilators,
PSV is used as a stand-alone technique, much like AC. In either
case, it can be thought of as a pressure boost given for each
spontaneous breath and lasting only as long as there is inspiratory
flow. Unlike in adult-type ventilators, when used as a stand-alone
technique, there is a backup mandatory rate, so a reliable
spontaneous respiratory effort is not an absolute requirement. The
pressure is set the same way as with AC, in other words PIP/PEEP.
It must be recognized that changing to PSV results in shorter
$T_i$ and may lead to atelectasis, unless adequate PEEP is used to
maintain $P_{aw}$.

**Novel techniques of assisted ventilation**

**Proportional assist ventilation**

Proportional assist ventilation (PAV) is a technique not currently
available in North America. It is based on elastic and resistive
unloading of the respiratory system, aiming to overcome the added
workload imposed by poor lung compliance and high airway and
ETT/ventilator circuit resistance.$^{11}$ The ventilator develops
inspiratory pressure in proportion to patient effort—in essence a
positive feedback system. The concept assumes a mature respiratory
control mechanism and a closed system. Unfortunately, neither of
these assumptions is valid in the preterm infant with an uncuffed
ETT. For example, the common problem of periodic breathing
would be accentuated by the ventilator, with less support being
generated with hypopnea and excessively high level of assist
provided when the infant becomes agitated. Also, because the
system responds to inspiratory flow and volume, a large leak
around the ETT would be interpreted as a large inspiration
around the ETT would be interpreted as a large inspiration
potential leading to dangerously large $V_t$. Limited clinical data
are available in preterm infants and the technique remains
experimental.

**Neurally adjusted ventilator assist**

Neurally adjusted ventilator assist (NAVA) is a promising approach
that uses the patient’s own respiratory control to drive the
ventilator.$^{12}$ The system monitors the EAdi to trigger and modulate
inspiration by means of bipolar electrodes mounted on a
nasogastric feeding tube and positioned in the esophagus at the
level of the diaphragm. In this way, the ventilator automatically
adjusts the level of support in proportion to the inspiratory effort.
NAVA is still experimental in newborn infants, but the concept is
quite attractive because the system is not affected by leak around
endotracheal tubes. However, like PAV, it utilizes a positive feedback
algorithm and assumes that the respiratory control center is
mature, which is not a valid assumption in the preterm infant. It
may be possible to overcome this limitation by incorporating
minimal and maximal support levels, but this approach is yet to be
fully validated.

**Choice of synchronized modes**

Despite years of routine use, there is no consensus regarding the
relative merits of AC and SIMV, the two most widely used modalities
of synchronized ventilation. There are no large prospective trials
with important clinical outcomes, such as incidence of air leak,
chronic lung disease or length of ventilation to prove the
superiority of one mode over the other. Short-term clinical trials
have demonstrated smaller and less variable $V_{T}^{*}$, less tachypnea,
more rapid weaning from mechanical ventilation and smaller
fluctuations in blood pressure with AC, when compared to
SIMV.$^{13–16}$ There are important physiological considerations
suggesting that SIMV may not provide optimal support in very
premature infants. However, many clinicians still prefer SIMV,
especially for weaning from mechanical ventilation. This is based
on the assumption, unsupported by data, that fewer mechanical
breaths are _a priori_ less damaging and on the belief that the
ventilator rate must be lowered before extubation. It has now been
unequivocally demonstrated that lung injury is most directly
caused by excessive $V_{T}$, irrespective of the pressure required to
generate that $V_{T}$. Rate of 60 breaths per min compared to 20
to 40 was shown to result in less air leak with unsynchronized
IMV,$^{20}$ lending further support to the putative advantage of AC with
its smaller $V_{T}$ and higher mechanical breath rate over SIMV. Many
clinicians also believe that assisting every breath prevents
respiratory muscle training. This concern is also unfounded and
highlights the limited understanding of the patient—ventilator
interaction during synchronized ventilation. As illustrated in
Figure 1, the $V_{T}$ with synchronized ventilation is the result of the
combined inspiratory effort of the patient (negative intrapleural
pressure on inspiration) and the positive pressure generated by the
ventilator. This combined effort (the baby ‘pulling’ and the
ventilator ‘pushing’) results in the transpulmonary pressure,
which, together with the compliance of the respiratory system,
determines the $V_{T}$. Thus, as ventilator inspiratory pressure is
decreased during weaning, the infant gradually assumes a
greater proportion of the WOB and in the process achieves training
of the respiratory muscles. Ultimately, the ventilator pressure is
decreased to the point when it only overcomes the added resistance
of the ETT and circuit, at which point the infant should be
extubated.
Figure 1 Interaction of patient and ventilator pressures to generate delivered tidal volume (VT) with different modes of synchronized ventilation. The VT is the result of the combined inspiratory effort of the patient (negative intrapleural pressure on inspiration) and the positive pressure generated by the ventilator. This combined effort (the baby ‘pulling’ and the ventilator ‘pushing’ VT) results in the transpulmonary pressure, which, together with the compliance of the respiratory system, determines the VT.

Clinical trials of synchronized ventilation
Despite nearly universal acceptance of synchronized mechanical ventilation in newborn intensive care, there is a surprising paucity of information on the impact of this modality on major outcomes, such as mortality, chronic lung disease or length of hospitalization. A number of small studies have shown improvement in short-term physiological outcomes (Table 2), but demonstrating the ‘bottom line’ long-term outcome improvement with synchronized ventilation has been elusive. The only available randomized trials suffer from important design and device limitations, leaving clinicians with the unsatisfactory situation of using an ‘unproven therapy’ on a daily basis.

Principles of VILI and rationale for controlling VT during mechanical ventilation
Pressure-limited ventilation became the standard mode in newborn intensive care, because early attempts to use traditional VCV soon proved to be impractical in small preterm infants. Pressure-limited ventilation continues to be the primary mode of ventilation in newborns because of its relative simplicity, ability to ventilate effectively despite large ETT leak, improved intrapulmonary gas distribution due to the decelerating gas flow pattern and the presumed benefit of directly controlling PIP. The major disadvantage of pressure-limited ventilation is that the VT varies with changes in lung compliance. Such changes may occur quite rapidly in the immediate postnatal period as a result of clearing of lung fluid, recruitment of lung volume and surfactant replacement therapy. The consequences of such rapid improvements in compliance are inadvertent hyperventilation and lung injury from excessively large VT’s (volutrauma). As few as six excessively large breaths can cause sustained adverse effects on lung function, suggesting that it may be impossible to respond rapidly enough with manual adjustment of inspiratory pressure to prevent lung injury. Inadvertent hyperpventilation to PaCO2 <25 mm Hg occurred in 30% of ventilated newborn infants during the first day of life in a recent study, indicating that hypocapnia continues to be a common problem despite increasing awareness of its dangers.

Direct control of PIP is believed by many to be an important benefit of pressure-limited ventilation. Despite extensive evidence that excessive volume, rather than pressure, is the key determinant of VILI, the misconception that pressure is the main factor in VILI and air leak remains widespread. Dreyfuss and Saumon demonstrated 20 years ago that severe acute lung injury occurred in small animals ventilated with large VT, regardless of whether that volume was generated by positive or negative inspiratory pressure. In contrast, animals exposed to the same high inspiratory pressure but in whom the movement of the chest wall and diaphragm were limited by external binding experienced much less acute lung damage. This landmark paper and other similar experiments clearly show that excessive VT, not pressure by itself, is primarily responsible for lung injury. However, it has been only recently that full appreciation of the importance of volutrauma and the dangers of inadvertent hyperventilation have brought about renewed interest in directly controlling VT during neonatal ventilation.

Insufficient VT also causes significant problems. At any level of inspiratory pressure, insufficient VT may develop because of decreasing lung compliance, increasing airway resistance, airway obstruction, air-trapping or decreased spontaneous respiratory effort. Inadequate VT leads to hypercapnia, increased WOB, increased oxygen consumption, agitation, fatigue, atelectasis and possibly increased risk of intraventricular hemorrhage (IVH). Low VT also leads to inefficient gas exchange due to increased dead space to VT ratio. It should thus be obvious that relatively tight control of VT delivery during mechanical ventilation is highly desirable. Indeed, this is the reason why VCV remains the standard of care in adult and pediatric respiratory support.

Table 2 Demonstrated short-term benefits of synchronized ventilation

<table>
<thead>
<tr>
<th>Author</th>
<th>Population/mode</th>
<th>Benefit</th>
</tr>
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<tbody>
<tr>
<td>Berenstein et al., Am J Respir Crit Care Med 1994</td>
<td>30 NB/IMV</td>
<td>Higher and more consistent VT</td>
</tr>
<tr>
<td>Cleary et al., J Pediatr 1995</td>
<td>10 NB &lt;32 weeks &lt;12 h/IMV</td>
<td>Improved ventilation and oxygenation</td>
</tr>
<tr>
<td>Jarreau et al., Am J Respir Crit Care Med 1996</td>
<td>6 NB with RDS/AC</td>
<td>Decreased work of breathing</td>
</tr>
<tr>
<td>Smith et al., Int Care Med 1997</td>
<td>17 NB with RDS/IMV</td>
<td>Less tachypnea</td>
</tr>
<tr>
<td>Quinn et al., J Pediatr 1998</td>
<td>59 NB &lt;32 week/AC</td>
<td>Decreased catecholamine levels</td>
</tr>
</tbody>
</table>

Abbreviations: AC, assist control; NB, newborns; RDS, respiratory distress syndrome; SIMV, synchronized intermittent mandatory ventilation; VT, tidal volume.
Importance of the open-lung strategy

The clear evidence that excessive $V_T$, rather than high pressure, is the primary determinant of lung injury have caused most clinicians to either use one of the forms of volume-targeted ventilation or at least monitor the delivered $V_T$. The critical importance of distributing this $V_T$ evenly into an optimally aerated lung has not been as widely appreciated and requires special emphasis. Caruso et al. demonstrated that when using PEEP of 0, lung injury in rats was not reduced by the use of low, compared to high $V_T$. Tsuchida et al. showed that in the presence of atelectasis, the nondependent (that is, aerated) lung was the most injured area. This is because, as can be seen in Figure 2, if excessive atelectasis is allowed to persist, the normal, physiological $V_T$ entering only the open alveoli will inevitably lead to overexpansion of this relatively healthy portion of the lung with subsequent volutrauma/biotrauma. Atelectasis leads to exudation of protein-rich fluid with increased surfactant inactivation and release of inflammatory mediators, a process known as ‘atelectotrauma’. Shear forces and uneven stress in areas where atelectasis and overinflation coexist add to the damage. The ‘open-lung concept’ (OLC) is central to optimizing the impact of volume-targeted ventilation: its benefits cannot be realized without ensuring that this $V_T$ is distributed evenly throughout the lungs!

In practical terms, the open lung is achieved by applying adequate PEEP. For a variety of reasons, including poorly conceived animal studies where moderate to high levels of PEEP were applied to animals with normal (that is, very compliant) lungs, resulting in significant hemodynamic impairment, many clinicians fear using adequate levels of end-expiratory pressure. This ‘PEEP-o-phobia’ is only slowly being overcome and remains one of the most important obstacles to optimizing the way conventional mechanical ventilation is practiced. By contrast, the importance of optimizing lung inflation has long been recognized by users of high-frequency ventilation, where the optimal lung volume strategy has become standard practice and is widely understood to be the key to its success. However, although there are a number of animal studies indicating that conventional ventilation with the OLC can achieve similar degrees of lung protection as high-frequency oscillatory ventilation (HFOV), suggesting that optimizing lung volume rather than frequency is the key factor, the clinical application of the OLC with conventional ventilation has not been extensively evaluated in clinical trials.

Finally, it is important to understand that there is no single ‘safe’ PEEP level. Optimal PEEP must be tailored to the degree of lung injury (that is, lung compliance). For infants with healthy lungs and thus normal lung compliance, PEEP of 5 cm H$_2$O is adequate and PEEP of 6 cm H$_2$O may result in overexpansion of the lungs with circulatory impairment and elevated cerebral venous pressure. On the other hand, atelectatic, poorly compliant lungs may require PEEP levels of 8 to 10 cm H$_2$O or more to achieve adequate alveolar recruitment and improve ventilation/perfusion ratio. Because we seldom ventilate infants with healthy lungs, PEEP of $<5$ cm H$_2$O should be the exception, rather than the rule.

Volume-targeted ventilation modes

Confusion in terminology exists in the realm of volume-oriented ventilation as well. Although the focus on targeting an appropriate $V_T$ is the key element, it is important to recognize that there are differences in how different ventilation modes exert control over $V_T$. Devices designed to span the full range of patients from newborns to adults all have the traditional volume-controlled modes we described earlier. Although the terminology of ‘volume-targeted ventilation’ has been recently used to describe this entity, standard VCV is distinct from the neonatal modes of volume-targeted ventilation. For the purpose of this article, the term volume-targeted ventilation refers to modifications of pressure-limited ventilation that adjusts inspiratory pressure and/or time to target a set $V_T$. These modes are also distinct from other pressure-limited ventilators that also claim to offer volume-targeted ventilation but actually employ a simple volume-limit function that merely terminates inspiration when the maximum allowed $V_T$ is exceeded, without actively modulating the inspiratory pressure.

Pressure-regulated volume control

Pressure-regulated volume control (PRVC) is a pressure-limited, time-cycled mode that when initially activated adjusts inspiratory pressure to target a set $V_T$, based on the pressure required to achieve the target $V_T$ of four test breaths. Subsequent adjustments are based on the $V_T$ of the previous breath. Breath to breath increment is limited to 3 cm H$_2$O, up to 5 cm H$_2$O below the set upper pressure limit. The main problem with the PRVC mode of the Maquet Servo 300 and to a lesser extent the Servo-i (Maquet Inc., Bridgewater, NJ, USA; formerly Siemens, Solna, Sweden) is the inaccuracy of $V_T$ measurement performed at the ventilator end of the circuit, rather than at the airway opening. The new Servo-i has a circuit compliance compensation feature that effectively adjusts the displayed $V_T$ to correct for loss of volume to the circuit, a major improvement over the previous version. Unfortunately, this compensation is ineffective in the presence of even small to moderate ETT leak. Any appreciable leak causes constant alarms, which typically lead the user to disable the feature with the result being inability to accurately determine the $V_T$.

Recently, a second flow sensor that permits monitoring of actual $V_T$ has been made available, though the $V_T$ regulation is still based on the volume measured at the ventilator outlet.

Volume-assured pressure support

The volume-assured pressure support (VAPS) mode on the Bird VIP Gold (Viasys Medical Systems, Conshohocken, PA, USA) is a hybrid...
mode designed to ensure that the targeted $V_T$ is reached. Each breath starts as a pressure-limited breath, but if the set $V_T$ is not reached, the device converts to flow-cycled mode by prolonging the $T_i$ with a passive increase in peak pressure. This may result in a rather prolonged $T_i$ leading to expiratory asynchrony. Targeting $V_T$ based on inspiratory $V_T$ is susceptible to error in the presence of significant endotracheal tube leak. Furthermore, there is no provision for automatically lowering inspiratory pressure as lung compliance improves. The focus is on ensuring an adequate $V_T$; no provision is made to avoid inadvertent hyperventilation and allow for automatic weaning. The newer Avea ventilator by Viasys shares the basic concept of VAPS, but the algorithm has been refined to respond earlier in the respiratory cycle and avoid excessively long $T_i$’s. The Avea also adds a volume-limit function that will terminate inspiration if the upper limit of $V_T$ is exceeded. This added function should reduce the risk of volutrauma and hyperventilation. The regulation of delivered volume based on inspiratory $V_T$ has both advantages and disadvantages. It allows the device to respond within the given breath, but it is more susceptible to leak around ETT, which is larger during inspiration.

**Volume guarantee**

The Draeger Babylog 8000 plus (Draeger Medical Inc., Telford, PA) has a volume guarantee (VG) option that may be combined with any of the basic ventilator modes (AC, SIMV, PSV). Like PRVC, the VG mode is a volume-targeted, TCPL form of ventilation. The operator chooses a target $V_T$ and selects a pressure limit up to which the ventilator operating pressure (the working pressure) may be adjusted. The microprocessor compares the $V_T$ of the previous breath, using exhaled $V_T$ to minimize possible artifact due to air leak, and adjusts the working pressure up or down to achieve the set $V_T$. The algorithm limits the amount of pressure increase from one breath to the next, to avoid overcorrection leading to excessive $V_T$. This, and the fact that the exhaled $V_T$ of the prior breath, is used means that with very rapid changes in compliance or patient inspiratory effort, several breaths are needed to reach target $V_T$. Contrary to a widespread misconception, the microprocessor does not average the $V_T$ of several breaths to determine working pressure. Additionally, to overcome the potential disadvantage of using the exhaled $V_T$ of the previous breath and minimize the risk of excessively large $V_T$, the microprocessor opens the expiratory valve, terminating any additional pressure delivery if the inspiratory $V_T$ exceeds 130% of the target—in essence a volume-limit function. By design the algorithm is geared toward slower adjustment for low $V_T$ and more rapid adjustment for excessive, potentially dangerous $V_T$. There is a separate algorithm for spontaneous (assisted) and untriggered machine breaths to ensure that the target $V_T$ is more stable when the infant’s respiratory drive is inconsistent. The autoregulation of inspiratory pressure makes VG a self-weaning mode. Because weaning occurs in real time, rather than intermittently in response to blood gases, VG has the potential to achieve faster weaning from mechanical ventilation.

**Volume limit**

Volume limit is a function of the Bear Cub 750 PSV and its equivalent in Europe, the Leoni Plus (Viasys Medical Systems). This is not true volume-targeted ventilation, as the only enhancement over simple pressure-limited ventilation is a volume-limit setting; when the limit $V_T$ is exceeded, the device terminates inspiration thus avoiding excessive $V_T$ delivery. This premature breath termination may lead to very short $T_i$’s. There is no automatic adjustment of inspiratory pressure and no provision to ensure that adequate $V_T$ is delivered when compliance or patient effort decreases. The reliance on inspiratory $V_T$ measurement means that significant leak around the ETT may lead to inadequate $V_T$ delivery.

**Targeted tidal volume**

This is in essence a simple volume-limit function available on the SLE 5000 (Specialised Laboratory Equipment Ltd, South Croydon, UK). The device increases the rise time of the pressure waveform to improve the chance of effectively limiting $V_T$ to the desired target. When the volume-limit function is turned off, the PIP automatically drops to 5 mbar above the PEEP to avoid potentially excessive $V_T$ due to inappropriately high PIP setting; the user must then actively adjust the PIP. The same limitations of volume-limit apply: there is no automatic adjustment of inspiratory pressure and no provision to ensure that adequate $V_T$ is delivered when compliance or patient effort decreases. Reliance on inspiratory $V_T$ measurement may lead to inadequate $V_T$ delivery with significant leak around the ETT.

**Clinical studies of volume-oriented ventilation**

**Volume-controlled ventilation**

Two published studies evaluated the effectiveness of VCV in newborn infants in the modern era using the Bird VIP ventilator. Both used the time to achieve either alveolar/arterial oxygen difference ($\text{AaDO}_2$) $<100 \text{ torr}$ or mean airway pressure $<8 \text{ cm H}_2\text{O}$ as the primary end point. The first study included 50 infants with mean birth weight (BW) close to 1800 g. Tidal volume of 5 to 8 ml kg$^{-1}$ was targeted in both groups. Infants randomized to VCV reached success criteria faster and had shorter duration of ventilation ($122 \pm 65 \text{ h}$ for VCV vs $162 \pm 134 \text{ h}$). There was a trend toward less BPD and IVH in the VCV group. These encouraging results demonstrated feasibility of this mode of ventilation in larger preterm infants, but left the question unanswered as to whether this modality is useful in the much smaller infants who today constitute the large majority of ventilated infants.

The newer model of the Bird VIP Gold that allows lower $V_T$ settings and accurate monitoring of exhaled $V_T$ at the airway...
opening made it possible to address this question. Singh et al., 7 randomly assigned 109 preterm infants 24 to 31 weeks and 600 to 1500 g to VCV or to TCPL ventilation using the same primary outcome. Exhaled $V_T$ of 4 to 6 ml was targeted in both groups. There was no difference in the primary outcome in the overall group, but a post hoc analysis showed faster weaning from VCV in infants <1000 g. There was no difference in the duration of ventilation, $O_2$ requirement or other secondary outcomes. Though the results did not clearly show superiority of VCV, the study demonstrated the feasibility of the mode even in ELBW infants, at least under the rigorous conditions of the study. It is important to appreciate that the set $V_T$ was manually adjusted at least hourly to maintain the target exhaled $V_T$ monitored at the airway opening. It remains to be seen whether this approach is feasible under routine neonatal intensive care unit (NICU) conditions. Additionally, because there is normally an inverse relationship between airway pressure and oxygenation, a more meaningful end point would have been $A_{\text{a}}DO_2 <100$ torr and mean airway pressure <8 cm H$_2$O.

**Pressure-regulated volume control**

Piotrowski et al., 42 studied 57 preterm infants <2500 g who were randomly assigned to PRVC or unsynchronized TCPL ventilation. The $V_T$ was initially set at 5 to 6 ml kg$^{-1}$ with additional 4 to 5 ml added to compensate for volume loss in the circuit. Subsequently, the $V_T$ was adjusted based on clinical assessment of chest rise and on blood gas values. There was a lower incidence of severe IVH in the PRVC group and a trend to fewer pneumothoraces. Twenty-one percent of the infants died during the study, but survival and other complications were not different. Duration of mechanical ventilation was similar for the groups overall, but significantly shorter for the PRVC group in infants <1000 g. It is unclear if the survival statistics were affected by the relatively high mortality or whether the apparent difference in pneumothorax and IVH were related to the use of unsynchronized IMV in the control group.

A more recent study using the Servo 300 ventilator evaluated 212 preterm infants randomly assigned to PRVC or to pressure-limited SIMV. 43 Infants were to remain on the assigned mode of ventilation until extubation or death, unless predetermined crossover criteria were met. Mean BW was similar in the SIMV (888 ± 199 g) and PRVC (884 ± 203 g) groups with mean gestational age of about 27 weeks. No differences were detected between SIMV and PRVC groups in the primary outcome, the proportion of infants alive and extubated at 14 days (41 vs 37%, respectively), length of mechanical ventilation in survivors or the proportion of infants alive without supplemental oxygen at 36 weeks postmenstrual age. More infants crossed over from PRVC than from SIMV. The authors concluded that PRVC offered no demonstrable advantage over SIMV.

**Volume-assured pressure support**

No published studies exist on the performance or clinical impact of VAPS in newborn infants.

**Volume guarantee**

Cheema and Ahluwalia 44 examined the feasibility of VG in 40 premature newborn infants with RDS. In a 4-h crossover trial they compared AC with and without VG in infants with acute RDS, and SIMV with and without VG during weaning. Lower PIP was seen in
both VG groups and there were fewer excessively large \( V_T \) during the VG periods. The authors concluded the VG mode was feasible and may offer the benefit of lower airway pressures.

We showed in a short-term crossover study that VG combined with AC, SIMV or PSV led to significantly lower variability of \( V_T \), compared to AC or SIMV alone.\(^{45}\) In contrast to the earlier study, we noted similar PIP, probably because, unlike Cheema et al., we allowed the working pressure to be adjusted both up and down by raising the pressure limit from the baseline period. The use of VG does not alter the relationship between PIP, compliance and \( V_T \), therefore, there is no reason to expect the PIP to be lower for the same \( V_T \).

In a group of very low birth weight infants recovering from acute respiratory failure Herrera et al.\(^{46}\) showed that, compared to SIMV alone, short-term use of SIMV + VG decreased mechanical support and enhanced spontaneous respiratory effort while maintaining gas exchange relatively unchanged. The shift of the WOB to the infant is because 4.5 ml kg\(^{-1}\) is a relatively low target \( V_T \) for SIMV, where the usual \( V_T \) of machine breaths is 6 ml kg\(^{-1}\).\(^{1,16,47}\) Almost complete shifting of the WOB to the infant was seen when the target \( V_T \) was reduced to 3 ml kg\(^{-1}\), indicating that this value is too low. There was a reduction in excessively large \( V_T \) during both VG periods.

Olsen et al.\(^{48}\) compared 4-h periods of PSV + VG with SIMV alone in a crossover trial of 14 large preterm infants with mean gestational age of 34 weeks. The AaDO\(_2\), PaCO\(_2\) and dynamic compliance were similar during both periods. Minute ventilation and mean airway pressure were higher and end-expiratory volume was lower during PSV + VG compared to SIMV. The authors concluded that use of PSV + VG could not be recommended but this conclusion should be viewed with caution because of significant concerns about the study design, data acquisition and interpretation.\(^{49}\)

In the first randomized controlled trial of VG, we demonstrated that VG combined with AC maintained PaCO\(_2\) and \( V_T \) within a target range more consistently than assist/control alone during the first 72 h of life in preterm infants with uncomplicated RDS.\(^{50}\) There was a 41% reduction in \( V_T >6 \) ml kg\(^{-1}\) and a 45% reduction in PaCO\(_2\) <35 mm Hg. This paper demonstrated that excessively large \( V_T \) and hypocarbia could be reduced, though not eliminated with the use of VG, suggesting the potential of VG to reduce many of the adverse effects of mechanical ventilation.

Lista et al.\(^{53}\) provided the most convincing evidence to date about the potential benefits of volume-targeted ventilation. They randomly assigned 53 preterm infants with RDS to PSV alone or PSV + VG, using set \( V_T \) of 5 ml kg\(^{-1}\). Pro-inflammatory cytokine levels were lower in the tracheal aspirate of infants in the VG group. Duration of mechanical ventilation was 8.8 ± 3 days in the VG group compared to 12.3 ± 3 days with PSV alone (mean weighted difference −3.5, CI: −5.13 to −1.87). These data strongly support the hypothesis that VG may reduce VILI.

Nafday et al.\(^{52}\) compared SIMV to PSV + VG in a randomized study involving 34 preterm infants with RDS. They did not find a difference in the primary outcome, the time to extubation or other important clinical outcomes, but this ‘pilot’ study lacked adequate statistical power. More importantly, the original group assignment was only maintained for the first 24 h, likely negating any possible differences. Significantly fewer blood gases were needed in the VG group.

Abd El-Moneim et al.\(^{55}\) studied 25 premature infants in a double crossover study with SIMV alternating with PSV + VG. The latter achieved a similar oxygenation level as SIMV but with significantly lower PIP. PO\(_2\) values were similar, but infants with strong respiratory drive had episodes of hyperventilation during PSV + VG. Infants had a more rhythmic respiratory pattern during PSV-VG, suggesting better infant–ventilator synchrony. The lower PO\(_2\) values with PSV + VG were predictable, because the \( V_T \) used during baseline low rate SIMV was by design matched during the PSV period. The mean \( V_T \) of 5.9 ml kg\(^{-1}\) is consistent with the usual \( V_T \) observed during SIMV, but 30 to 45% larger than what is normally used in PSV when each breath is supported. The authors concluded that PSV+VG is safe and feasible and felt that their results should encourage wider use of PSV-VG in premature infants.

To determine whether VG is more effective when combined with AC or SIMV, we studied 12 ELBW infants (BW 679 ± 138 g) in a short-term crossover trial.\(^{54}\) As anticipated, \( V_T \) was more stable with AC + VG, because the interval between supported breaths is longer during SIMV, leading to slower adjustment of working pressure. An unexpected finding was that during SIMV, the infants had significantly lower and more variable SpO\(_2\), more tachycardia and tachypnea. By design, the 5 ml kg\(^{-1}\) \( V_T \) was identical, but significantly higher PIP was required during SIMV to achieve the same \( V_T \). The tachypnea, tachycardia and lower, more variable oxygen saturation suggest that the reason for the higher PIP was that these ELBW infants were tiring during the SIMV period and contributing less effort by the end of the 2-h period when the measurements were obtained. This conclusion is based on the realization that during synchronized ventilation, the delivered \( V_T \) is the result of the combined inspiratory effort of the baby and the positive ventilator pressure; as the baby tires and contributes less, the ventilator needs to generate higher PIP to deliver the same \( V_T \).

Dawson and Davies\(^{55}\) examined the relationship between \( V_T \), minute ventilation and PaCO\(_2\) in patients ventilated with SIMV + VG. They reported that 96.5% of the blood gases during the first 48 h were within their acceptable range of 25 to 65 torr, when the \( V_T \) was set at a mean value of 4 ml kg\(^{-1}\). More importantly, only 1/288 (0.3%) PaCO\(_2\) values were less than 25 torr.

To determine if a lower \( V_T \) may be advantageous, Lista et al.\(^{56}\) randomly assigned 30 preterm infants <32 weeks gestation to receive AC + VG ventilation with either 3 or 5 ml kg\(^{-1}\) target \( V_T \). Bronchoalveolar lavage on days 1, 3 and 7 revealed an increase in...
pro-inflammatory cytokines in the low VT group, most likely because of atelectasis resulting from the combination of low VT and low end-expiratory pressure of 3 to 4 cm H2O that was used. An accompanying editorial points out the critical importance of using the open-lung approach to ensure that the VT is evenly distributed throughout the entire lung, not just a small proportion of open alveoli.\(^5\)

A similar effect may explain the findings of a small randomized study by Dani et al.\(^6\), which compared pro-inflammatory cytokines in a group of 25 preterm infants approximately 1100 g and 28 weeks gestation randomly assigned to receive PSV + VG or HFOV delivered by the SensorMedics 3100 oscillator using a high lung volume strategy. There was no difference in survival, length of ventilation or oxygen requirement. IL-8 and IL-10 levels were lower in infants receiving HFOV at the end of 4 days. The combination of PSV (short T\(_i\)) and PEEP of 3 cm H2O used by the authors would result in a low lung volume strategy on PSV + VG, compared with high lung volume strategy with HFOV. Mounting evidence shows that optimization of lung volume is key to lung protection, regardless of what ventilation mode is used. VG applied to a poorly inflated lung is unlikely to be optimally lung protective.

Polimeni et al.\(^5\) compared SIMV and SIMV + VG in ELBW infants with frequent episodes of hypoxemia (forced exhalation episodes) during alternating 2-h periods of ventilation. When using target VT of 4.5 ml kg\(^{-1}\), no benefit was seen. In a second phase, 20 infants were studied with and without VG using a target VT of 6.0 ml kg\(^{-1}\). The frequency of hypoxic episodes did not change, but the mean episode duration was shorter and the proportion of mechanical breaths with VT \(\leq\) 3 ml kg\(^{-1}\) was reduced during SIMV + VG vs SIMV alone. Because with SIMV the VT of mechanical breaths is normally about 6 ml kg\(^{-1}\), SIMV + VG with a target of only 4.5 ml kg\(^{-1}\) is therefore unlikely to overcome the effects of forced exhalation, given the low SIMV rate of 16 per min. In work only presented as abstract, we have documented more rapid recovery from episodes of forced exhalation with AC + VG and a target of 4.5 ml kg\(^{-1}\), compared to AC alone.

Scopesi et al.\(^6\) compared SIMV alone to SIMV + VG, AC + VG and PSV + VG in a small crossover trial of 10 preterm infants in the recovery phase of RDS. All VG modes delivered VT very close to the target volume. The mean variability of VT from preset VT was significantly lower in AC and PSV modes than in SIMV. The PIP was much lower with all VG periods than with baseline SIMV, because a VT of only 3.5 ml kg\(^{-1}\) was selected. These larger infants were able to generate adequate VT\(_i\) on their own, but the low target VT\(_i\) led to greater than usual variability in all the VG modes studied.

Cheema et al.\(^6\) examined the effect of VG with VT\(_i\) of 4 ml kg\(^{-1}\) on the incidence of hypocapnia on the first arterial blood gas after initiation of mechanical ventilation. The incidence of hypocapnia was 32% with AC + VG, compared to 57% with AC alone, but this difference fell short of statistical significance in this small

prospective trial, possibly due to a type II error. They noted a significant negative correlation between gestational age and PaCO\(_2\). The fact that the smallest infants had higher PaCO\(_2\) values reflects the impact of fixed IDS that we recently documented. When infants \(<25\) weeks gestation were excluded, the decrease in hypocapnia became significant. The authors’ conclusion that VG was not found to be effective is not warranted, as the study lacked statistical power and failed to select appropriate VT targets.

In his most recent publication, Lista et al.\(^6\) studied 40 infants with RDS randomly assigned to AC + VG (VT\(_i\) = 5 ml kg\(^{-1}\)) or HFOV (both with a Draeger Babylog 8000 plus). Levels of IL-6, IL-8 and tumor necrosis factor were measured in tracheal aspirate on days 1, 3 and 7. The duration of oxygen dependency was significantly shorter and the IL-6 levels were lower on day 3 and 7 with AC + VG. The possible reasons for the different outcome of this study compared to that of Dani et al.\(^6\) are many. Lista used a more appropriate PEEP of 5 cm H\(_2\)O and the T\(_i\) was likely longer with the AC than PSV used by Dani. Though the authors state that the high volume strategy was used with HFOV, no data are provided to substantiate how effectively this was done. It is likely that there was not the same dramatic difference in lung volumes favoring HFOV as in the study by Dani, allowing for a fairer evaluation of the effect of VG.

To address the concern regarding possible untoward effects of the additional IDS of the flow sensor and to establish normative data for target VT in ELBW infants, we reviewed 344 paired observations of VT\(_i\) and arterial blood gas measurements in 38 infants \(<800\) g at birth (mean 627 g, range 400 to 790 g) during the first 24 h of life.\(^5\) The VT\(_i\) per kg required for normocapnia was inversely related to BW (r = -0.70, P < 0.01), indicating some effect of the fixed IDS. Mean VT\(_i\) of infants \(\leq\) 500 g was 5.9 ± 0.4 vs 4.7 ± 0.4 ml kg\(^{-1}\) for those \(\geq\) 700 g (P < 0.001). The absolute mean set and measured VT\(_i\) was 3.11 ± 0.64 and 3.17 ± 0.64 ml, respectively, barely above the estimated instrumental plus anatomical dead space of 3.01 ml. While maintaining normocapnia, 47% of all VT\(_i\)’s were less than or equal to the estimated dead space. We concluded that there is an impact of IDS in the tiniest infants but there is no need to forgo synchronized and volume-targeted ventilation due to concerns about the IDS. Effective alveolar ventilation occurs with VT\(_i\) at or below dead space, suggesting that a spike of fresh gas penetrates through the dead space gas, similar to what occurs with high-frequency ventilation. In a companion study, we showed that with advancing postnatal age, the VT\(_i\) needed to maintain adequate ventilation rose from a mean of just over 5 ml kg\(^{-1}\) on day 1 to over 6 ml kg\(^{-1}\) by the end of the third week despite mild permissive hypercapnia (PaCO\(_2\) of 55) in infants \(<800\) g.\(^4\)

**Volume limit**

There are no published studies on the performance or clinical impact of volume-limit function.
Summary of clinical trials

The body of literature on volume-targeted ventilation continues to expand rapidly, but none of the studies are sufficiently large to unequivocally demonstrate ultimate benefit of this approach. VG has been studied most extensively, but it remains to be seen whether the demonstrated short-term benefits translate into significant reduction in air leak, chronic lung disease, neuroimaging abnormalities or length of hospitalization. The Cochrane review last updated in 2005 included four randomized trials in the meta-analysis, totaling 178 preterm infants entered during the first 72 h of life. Two studies used VCV (Piotrowski et al. and Sinha et al.) and two used VG (Lista et al. and Keszler and Abubakar). No significant difference was found for death at hospital discharge. Volume-controlled/targeted ventilation resulted in significant reductions in duration of ventilation (weighted mean difference (WMD) −2.93 days (−4.28, −1.57)) and rates of pneumothorax (typical RR 0.23 (0.07, 0.76), risk difference (RD) −0.11 (−0.20, −0.03), number needed to treat (NNT) 9). There was a significant reduction in severe (Grade 3 or 4) IVH in the volume-controlled/targeted group (typical RR 0.32 (0.11, 0.90), RD −0.16 (−0.29, −0.03), NNT 6) and a reduction in the incidence of BPD (supplemental oxygen at 36 weeks) among surviving infants of borderline statistical significance (typical RR 0.34 (0.11, 1.05), RD −0.14 (−0.27, 0.00), NNT 7). Although it is debatable whether VC and VG studies should be combined and it is unknown whether when updated with the more recent studies these conclusions will be strengthened, it is clear that evidence is mounting in support of strategies that attempt to control delivered Vf.

Clinical application

Despite the lack of definitive evidence of superiority to standard IMV, the benefits of synchronized ventilation are generally accepted with very few, if any, NICUs that have not adopted these techniques. As discussed above, the choice of SIMV or AC is, to some extent, a matter of personal preference and practice style. In reality, there is little difference between the two in the acute phase of respiratory failure, especially in the extremely premature or gravely ill infant who has little or no respiratory effort of their own, or the patient who is heavily sedated or even paralyzed. Under these circumstances, we are really providing simple IMV, regardless of the ventilator mode selection. However, the differences between SIMV and AC/PSV become more pronounced during weaning and are especially important in the smallest infants with narrow endotracheal tubes. Prolonged ventilation with low SIMV rates should be avoided in these infants, as it imposes an undesirably high WOB. To a significant degree, this problem may be overcome by adding PSV to the spontaneous breaths during SIMV. Although this approach is effective, it adds complexity and does not appear to have any advantage over PSV used alone, as long as atelectasis is avoided by using adequate level of PEEP.

The use of volume-targeted ventilation is best implemented soon after birth, because it is the time of most rapid changes in lung compliance. The choice of optimal Vf is critical to success of any volume-targeted mode. Exhaled Vf of 4 to 5 ml kg−1 is appropriate in the typical preterm infant with RDS. Extremely small infants require Vf close to 6 ml kg−1 to compensate for the IDS of the flow sensor. With advancing postnatal age, some increase in anatomical and physiological dead space occurs, necessitating slightly higher Vf. If low-rate SIMV is used, the target Vf needs to be higher than with AC or PSV. Even distribution of the Vf into an adequately recruited lung is key to lung injury prevention. With devices that measure and regulate Vf at the ventilator end of the circuit, the set Vf must be substantially higher than exhaled target Vf to compensate for the compression of gas in the ventilator circuit. The compliance compensation feature of the Servo-i is helpful in overcoming this problem, but does not function effectively in the presence of ETT leakage.

Each ventilator functions differently and it is critical that the user becomes familiar with the specific features of their device. The reader is referred to user manuals of their respective devices for further guidance. Detailed clinical guidelines for the Draeger Babylog are available in a recent publication. A ventilator is only a tool in the hands of the clinician; a tool that can be used well, or not. Yet, we talk of ‘VILI’, as though the machines were to blame for the undesirable outcome. Perhaps the term ‘physician-induced lung injury’ is more appropriate, for we are the ones that select the ventilator settings!

Conclusion

A host of new modalities and techniques has been made available for the treatment of respiratory failure. Our understanding of how to optimally use these devices, while improving constantly, remains somewhat behind the pace of technological innovation.

Improvements in outcomes such as BPD are increasingly difficult to demonstrate, as each incremental improvement leaves ‘the bar’ that much higher. Avoidance of mechanical ventilation by means of early CPAP with or without surfactant administration may still be the most effective way to reduce the risk of chronic lung disease. For babies who do require mechanical ventilation, the combination of volume-targeted ventilation, combined with the open-lung strategy appears to offer the best chance of reducing the risk of chronic lung disease.

References

State of the art in mechanical ventilation

M Kesler


35 Vanacquez de Arda OF, Gommers D, De Jaegere A, Lachmann B. Mechanical ventilation with high positive end-expiratory pressure and small driving pressure amplitude is as effective as high-frequency oscillatory ventilation to preserve the function of exogenous surfactant in lung-laved rats. Crit Care Med 2000, 28: 2921—2925.


Clinical Trials of Inhaled Nitric Oxide Therapy in the Newborn
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Clinical Trials of Inhaled Nitric Oxide Therapy in the Newborn
John P. Kinsella, MD*

OBJECTIVES
After completing this article, readers should be able to:

1. Describe the benefits of inhaled nitric oxide in the treatment of persistent pulmonary hypertension of the newborn.
2. Determine the range of appropriate initial doses of inhaled nitric oxide therapy for term neonates.
3. Delineate the potential role of inhaled nitric oxide in conjunction with extracorporeal membrane oxygenation.
4. Describe the lung-specific effects of low-dose inhaled nitric oxide therapy in preterm newborns who have severe hypoxemic respiratory failure.

Introduction
Early reports of the use of inhaled nitric oxide (iNO) in term newborns who had persistent pulmonary hypertension showed both acute and sustained improvement in oxygenation. Subsequently, randomized controlled trials of iNO in term newborns confirmed that this selective pulmonary vasodilator improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO). Results of a more recent randomized controlled trial of iNO in term newborns corroborate the findings of previous studies. These studies should provide sufficient evidence of the safety and efficacy of iNO to support regulatory approval of this therapy for persistent pulmonary hypertension of the newborn (PPHN). However, less is known about the potential role of iNO in preterm newborns. In this review, we summarize the key findings of clinical trials in the term newborn and the current status of iNO in the preterm newborn.

iNO in Term Newborns
After the publication of pilot trials with iNO, which documented marked improvement in oxygenation in term newborns who had PPHN, several randomized, controlled trials were conducted and demonstrated further the efficacy of iNO in PPHN. For example, these studies reported acute improvement in oxygenation after 30 minutes of iNO treatment. iNO reduced the need for ECMO, and lung recruitment strategies augmented the response to iNO when PPHN complicated the course of patients who had parenchymal lung disease. However, none of the studies was designed to evaluate the efficacy of the initial dose employed, and there remains some confusion about the appropriate starting dose for term newborns who have PPHN because of the lack of appropriate dose-response studies.

APPROPRIATE DOSES
The first published experience of iNO treatment in term newborns reported initial doses ranging from 6 to 20 ppm to 80 ppm. The rationale for doses used in these clinical trials was based on concentrations that had been found to be effective in animal experiments by the same investigators. Brief (30 min) inhalation of NO at 80 ppm improved oxygenation in patients who had PPHN, but the response was not sustained in some patients after NO was discontinued. Rapid improvement in oxygenation in neonates who had severe PPHN also was demonstrated, but this was achieved at lower doses (20 ppm) administered for 4 hours, and decreasing the iNO dose to 6 ppm for the duration of treatment provided sustained improvement in oxygenation. Other studies documented the relative effectiveness of low-dose iNO in improving oxygenation in patients who had severe PPHN. Thus, acute improvement in oxygenation during treatment does not appear to vary with doses of iNO ranging from 5 to 80 ppm.

These laboratory and clinical studies established the boundaries of iNO dosing protocols for subsequent randomized, clinical trials in newborns. Increasing the dose to 40 ppm generally does not improve oxygenation among patients who do not respond to the lower dose of 20 ppm. The initial dose in the Neonatal Inhaled Nitric Oxide Study (NINOS) was 20 ppm, but the dose was increased to 80 ppm if the improvement in Pao2 was less than 20 torr. In this study, only 3 of 53 infants (6%) who had little response to 20 ppm had an increase in Pao2 of greater than 20 torr when treated with 80 ppm iNO. Whether a progressive increase in Pao2 would have occurred with continued exposure to 20 ppm could not be determined with this study design. Others initiated treatment with 80 ppm NO and subsequently weaned the iNO concentration if oxygenation improved, which precluded an evaluation of the effects of lower initial iNO doses. These studies did not evaluate individual doses systematically in a method that could be interpreted. However, a recent randomized, controlled, dose-response study...

ABBREVIATIONS
CLD: chronic lung disease
ECMO: extracorporeal membrane oxygenation
ICH: intracranial hemorrhage
iNO: inhaled nitric oxide
PPHN: persistent pulmonary hypertension of the newborn
PVR: pulmonary vascular resistance

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trial in term newborns who had hypoxemic respiratory failure evaluated the effects of sustained exposure to different doses of iNO in different treatment groups. Patients were randomized to treatment with either 0 (placebo), 5, 20, or 80 ppm NO. Each iNO dose improved oxygenation compared with placebo, but there was no difference in responses among treatment groups. However, at 80 ppm, methemoglobinemia (>7%) occurred in 13 of 37 patients (35%), and high inspired NO2 concentrations were measured in 7 of 37 patients (19%). Thus, 80 ppm iNO was no more effective in improving oxygenation than 5 or 20 ppm, but it was associated with adverse effects. Unfortunately, this trial was limited by early termination due to slow enrollment and the exclusion of lung recruitment approaches to optimize iNO efficacy.

Available evidence supports the use of doses of iNO beginning at 20 ppm in term newborns who have PPHN. Although brief exposures to higher doses (40 to 80 ppm) appear to be safe, sustained treatment with 80 ppm NO increases the risk of methemoglobinemia. The lowest effective initial dose for iNO in term newborns who have PPHN has not been determined, but sustained improvement in oxygenation (after >4 h of treatment) has been demonstrated for doses of less than 10 ppm.

USE OF ECMO

Overall, clinical trials of iNO in term newborns have demonstrated an approximately 40% reduction in the use of ECMO. However, not all treated patients experience a sustained improvement in oxygenation; some still require treatment with ECMO. With impending regulatory approval, this raises an important concern about the use of iNO in centers that do not employ ECMO.

Published reports on the use of iNO in ECMO centers have not substantiated early concerns that iNO would affect outcome adversely by delaying use of ECMO. In one study, the median time from randomization to treatment with ECMO was 4.4 and 6.7 hours for the control and iNO groups, respectively. Although this difference was statistically significant, there were no apparent adverse consequences caused by the delay. Patients treated with iNO did not have longer ECMO courses, increased rates of intracranial hemorrhage, or other bleeding complications compared with the control group. Indeed, iNO treatment may play an important role in stabilizing patients before ECMO is initiated. iNO may attenuate pulmonary vasodilatability even without marked increases in PaO2, thus improving the chances that ECMO cannulation may proceed without progressive clinical deterioration.

The potential dissemination of iNO therapy to non-ECMO centers, however, warrants a cautious approach. Whether the use of iNO for PPHN in non-ECMO centers will cause undue delays in initiation of transport to an ECMO center, increase the risks of transport, or significantly delay ECMO cannot be determined from the currently available evidence. It is likely that promising new therapies for severe hypoxemic respiratory failure will not be limited to centers that provide all modes of rescue treatment. Although marked improvement in oxygenation occurs in many term newborns who have severe PPHN, sustained improvement may be compromised in some patients by the nature of the underlying disease that leads to progressive atelectasis or systemic hemodynamic disturbances caused by overwhelming sepsis. When the clinical course is complicated by progression in the severity of the cardiopulmonary disease, withdrawal of NO during transport to an ECMO center may lead to acute deterioration. In such cases, iNO may provide an important therapeutic bridge to assure stability during transport. When progressive deterioration in oxygenation occurs during iNO treatment in institutions that cannot offer more advanced rescue therapy, provisions must be in place to transport the patient to the ECMO center without interrupting iNO treatment.

iNO in Preterm Newborns

ENDOGENOUS NO

Another area of investigation that is of vital clinical importance is iNO therapy in preterm newborns who have hypoxemic respiratory failure. The role of endogenous NO production in vasoregulation of the preterm pulmonary circulation and the effects of iNO in the preterm newborn have received less attention than in the term infant. In the late-gestation ovine fetus, endogenous NO modulates basal pulmonary vascular tone and contributes to the normal fall in pulmonary vascular resistance (PVR) at birth. In addition, iNO causes potent, selective, and sustained pulmonary vasodilation in the normal term newborn lamb. In the preterm lamb at 78% of term (115 d gestation or about 31 wk of human gestational age), inhibition of endogenous NO production increases fetal PVR. Further, when endogenous NO production is blocked during delivery of the preterm lamb, the normal increase in pulmonary blood flow associated with mechanical ventilation and lung inflation is attenuated markedly.

The preterm lamb is an excellent model of respiratory distress syndrome and has been studied extensively. Survival with exogenous surfactant treatment and mechanical ventilation at delivery varies, depending on the gestational age of the lamb and the type of surfactant administered. In very immature lambs (78% of term gestation), gas exchange worsens and PVR increases during mechanical ventilation beyond 60 to 90 minutes after birth, despite treatment with exogenous surfactant at delivery. Intermittent mandatory ventilation over 2 hours in the extremely preterm sheep fetus (115 d gestation, 78% of term) causes progressive worsening of gas exchange and increased PVR. After 2 hours of ventilation, brief NO treatment lowers PVR and improves gas exchange. Moreover, early and continuous treatment with iNO (20 ppm) causes sustained improvement in gas exchange and pulmonary hemodynamics over 3 hours of mechanical ventilation. Lung recruitment strategies employ-
ing high-frequency oscillatory ventilation have been shown to augment the response to low-dose iNO in preterm lambs that have hyaline membrane disease, emphasizing the critical role of adequate lung inflation during inhalational vasodilator therapy.

In addition to its effects on pulmonary hemodynamics and gas exchange during inhalation, endogenous NO may regulate vascular permeability and neutrophil adhesion in the microcirculation. Moreover, in preterm lambs delivered at 78% of term, low-dose iNO (5 ppm) increases pulmonary blood flow and improves gas exchange without increasing pulmonary edema and decreases accumulation of lung neutrophils. In another recent study, lambs delivered at 130 days (90% of gestation) and mechanically ventilated for 5 hours with 20 ppm iNO showed no evidence of lung oxidative stress injury (lung malondialdehyde, reduced glutathione, glutathione reductase) compared with controls.

iNO THERAPY IN HUMANS

Preliminary studies in human preterm neonates who had severe hypoxic respiratory failure support the potential role of low-dose iNO as adjuvant therapy. Low-dose inhaled NO markedly improved oxygenation in a preterm neonate who had group B streptococcal sepsis and severe pulmonary hypertension, allowing reduction in ventilator pressure and inspired oxygen concentration and complete clinical recovery. Preterm neonates who had severe hypoxemia associated with prolonged oligohydramnios and suspected pulmonary hypoplasia showed marked improvement in response to iNO therapy. Five patients survived in this trial, three of whom had severe intracranial hemorrhage (ICH). Another dose-response study in preterm infants concluded that 5 ppm of iNO was as effective as 20 ppm in improving oxygenation. In a small, unmasked, randomized trial of iNO (20 ppm) and dexamethasone treatment, no differences were documented in survival or incidence of chronic lung disease (CLD) or ICH between iNO-treated infants and controls. In yet another dose-response study of iNO in 11 preterm newborns, 5 ppm was shown to be as effective as 20 ppm. Seven (64%) of these infants had ICH, and 5 (45%) had ICH of grade 3 to 4. However, when these results were compared with the NICHD Neonatal Network database (for historical controls matched for severity of illness), the incidence of ICH in preterm newborns not treated with iNO was identical (64%). These observations illustrate the limitations of determining toxicity without appropriately designed clinical trials.

SAFETY AND EFFICACY

To begin to address the potential safety and efficacy of iNO in preterm newborns, we recently conducted a randomized controlled trial of iNO in preterm neonates who had severe hypoxic respiratory failure. We hypothesized that low-dose iNO (5 ppm) would improve survival in affected preterm newborns who were unresponsive to conventional therapies, including surfactant, and would not increase the incidence or severity of ICH or CLD. We randomized 80 preterm newborns (gestational ages <34 wk) who had severe hypoxic respiratory failure in 12 perinatal centers that provide tertiary care. Forty-eight patients were treated with iNO and 32 served as controls. Treatment assignment was masked. The primary outcome variable was survival to discharge. Secondary outcome variables included incidence and severity of ICH and pulmonary hemorrhage, duration of mechanical ventilation, and incidence of CLD at 36 weeks’ postconceptional age. The groups did not differ in baseline characteristics or severity of disease (PaO₂/FiO₂ = 42±18 mm Hg for iNO; 42±16 mm Hg for control; *P*=NS). iNO improved oxygenation acutely after 60 minutes of treatment (PaO₂/FiO₂ = 88±12 mm Hg for iNO; 56±9 mm Hg for control; *P*<0.05). Survival to discharge was 52% in the iNO group and 47% in controls (*P*=NS). Causes of death were related primarily to extreme prematurity and were similar between groups. Total ventilator days for survivors was less for the iNO group (*P*=0.046). In contrast to uncontrolled pilot studies, there was no difference in the incidence of ICH between the control and iNO-treated groups (Figure).

Thus, low-dose iNO resulted in acute improvement in oxygenation in preterm newborns who had severe hypoxic respiratory failure without increasing the risk of bleeding complications, including ICH. Low-dose iNO may be effective as a lung-specific anti-inflammatory therapy to diminish lung neutrophil accumulation and the attendant inflammatory injury that contributes to the evolution of CLD. Sufficient evidence now may be available to warrant a controlled trial of low-dose iNO in preterm newborns who have less severe disease.

Summary

iNO improves oxygenation and decreases use of ECMO in term newborns who have PPHN. From the available information, a reasonable recommendation for the initial dose of iNO in the term infant is 20 ppm, with the dose reduced over time. Toxicity is apparent at 80 ppm, causing increases in methemoglobinemia and inspired NO₂. High doses (>20 ppm) of iNO also may prolong bleeding time, but clinically significant increases in bleeding complications have not been reported in term newborns. Finally, there is increasing evidence for the potential role of low-dose iNO (5 ppm) in preterm newborns who...
have hypoxemic respiratory failure. This therapy causes acute improvement in oxygenation and may prove to be useful as a lung-specific anti-inflammatory treatment. However, clinical application currently should be limited to controlled trials that target outcomes of both safety and efficacy.

**SUGGESTED READING**


Suhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. *Arch Dis Child.* 1997;77:F185–F190


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**RESPIRATORY DISEASE**

**Inhaled Nitric Oxide Therapy**
Clinical Trials of Inhaled Nitric Oxide Therapy in the Newborn
John P. Kinsella

Pediatr. Rev. 1999;20;110
DOI: 10.1542/pir.20-11-e110

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The Role of High-Frequency Ventilation in Neonates: Evidence-Based Recommendations

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Respiratory failure in neonates, commonly defined as retention of carbon dioxide with a resultant decrease in the arterial blood pH and accompanied by hypoxemia, has multiple etiologies. It remains the most common complication of premature birth and the number one reason that neonates require assisted mechanical ventilation. Respiratory failure is a result of impaired pulmonary gas exchange mechanisms, such as can be seen with surfactant deficiency, atelectasis, or obstructive airway disease. Less common causes of respiratory failure may be a result of airway, musculature, or central nervous system abnormalities. The specific etiology of neonatal respiratory failure can, at times, be unclear and potentially multifactorial. Nonetheless, insights into the potential etiologies and pathophysiology of respiratory failure weigh heavily in the clinician’s decisions regarding initiation of assisted mechanical ventilation.

Much progress has been made in the treatment of neonatal respiratory failure over the past few decades. In particular, antenatal steroids and exogenous surfactant replacement have decreased neonatal mortality and morbidity in premature infants [1–3]. However, lung injury and pulmonary morbidities secondary to mechanical ventilation remain an ongoing problem in the care of premature infants. Of most concern, chronic lung disease (CLD) develops in up to one third of preterm infants who have respiratory
distress syndrome (RDS) who receive positive pressure mechanical ventilation [4]. Dilemmas still remain regarding optimization of both timing and mode of mechanical ventilation to decrease neonatal pulmonary morbidities.

High-frequency ventilation (HFV) is a form of mechanical ventilation that uses small tidal volumes and extremely rapid ventilator rates. It first came to the attention of the medical community during the 1970s, when a number of scattered reports appeared. Lunkenheimer and colleagues [5] reported the use of high-frequency oscillatory ventilation (HFOV) in apneic dogs, Sjöstrand [6] used high-frequency positive pressure ventilation in adults who have respiratory failure, and Carlon and colleagues [7] used a type of jet ventilation in adults who have bronchopleural fistula. Early reports of neonatal use came from Frantz and colleagues [8] in Boston, Massachusetts, and Pokora and colleagues [9] in St. Paul, Minnesota. In an attempt to clarify how it is possible to maintain pulmonary gas exchange when the tidal volumes used are often smaller than the anatomic dead space, Chang [10] described the multiple modes of gas transport that occur during HFV, including bulk convection, high-frequency “pendulluft,” convective dispersion, Taylor-type dispersion, and molecular diffusion. There are various high-frequency ventilator designs, including HFOV, high-frequency jet ventilation (HFJV), as well as “mixed” forms of HFV (eg, flow interrupters, high-frequency positive pressure ventilation). In the United States, the most commonly used high-frequency ventilators include the SensorMedics 3100A (SensorMedics Inc., Yorba Linda, California), which provides HFOV; the LifePulse high-frequency jet ventilator (Bunnell Inc., Salt Lake City, Utah), which provides HFJV; and the Infant Star ventilator (InfraSonics Inc., San Diego, California), which is a high-frequency flow interrupter (HFFI).

Potential advantages of HFV over conventional mechanical ventilation (CMV) include the use of small tidal volumes, the ability to independently manage ventilation and oxygenation, and the safer use of mean airway pressure that is higher than that generally used during CMV [11]. Animal studies suggest that HFV works at lower proximal airway pressures than CMV, reduces ventilator-related lung injury, improves gas exchange in the face of air leaks, and decreases oxygen requirements [12–17]. Most causes of neonatal respiratory insufficiency requiring mechanical ventilation are amenable to treatment with HFV or CMV. For either technique to be successful, lung volumes need to be optimized for the underlying condition, and pressure exposures must likewise be similarly regulated. Only by the careful application of the chosen technique can ventilator-induced lung injury be avoided. The question remains, however: is one form of ventilation better than the other?

Despite the wealth of laboratory and clinical research on HFV, there are no established guidelines for prioritizing the use of HFV versus CMV in neonatal respiratory failure. Since 1997, approximately 25% of infants
born at 1500 g or less reported to the Vermont–Oxford Network have been treated at some time with HFV [18]. Some clinicians choose to use HFV as the primary mode of mechanical ventilation for small infants. Others elect to only use HFV as a “rescue” method when CMV is failing. Most clinicians stand somewhere in the middle of this spectrum. This article is not a “how to” guide for the use of HFV. Rather, it reviews and evaluates the available literature to determine the evidence base for the use of HFV in neonatal respiratory failure.

Evidence review

An evidence review was performed to answer the following questions:

1. In the presence of acute neonatal respiratory failure or respiratory distress syndrome, does elective use of HFV provide benefit over the use of CMV?
2. In the presence of ongoing, severe neonatal respiratory failure, does the use of HFV as a rescue mode of ventilation provide benefit over the continued use of CMV?
3. Are there specific etiologies to neonatal respiratory failure in which HFV has been superior to CMV?

An electronic search of Medline and the Cochrane Database of Systematic Reviews was performed to identify relevant studies to these questions. The key words used for the search regarding the first two questions were high frequency ventilation (including high frequency oscillatory ventilation and high frequency jet ventilation) and respiratory insufficiency. The time frame searched was from 1985 to 2006, with limitation of studies related to the age range “birth to 23 months.” The search produced the following number of citations: high frequency ventilation 657 articles, respiratory insufficiency 4090 articles, HFV and respiratory insufficiency 118 articles. Selected articles, in particular controlled clinical trials and meta-analyses, were reviewed and presented in this article regarding the current role of HFV in neonates.

Elective high-frequency ventilation

Literature review

To date, there have been 15 randomized controlled clinical trials of elective use of HFV versus CMV for the treatment of premature neonates who have respiratory insufficiency or RDS. One additional study compares the use of HFV versus CMV in term and near-term infants. These trials and their pulmonary outcomes are summarized in Table 1 [19–34]. The data from these 16 randomized controlled trials of HFV have yielded conflicting results. Five of the 16 trials demonstrated that early elective use of HFV improved pulmonary outcomes, in particular, decreased the incidence of
<table>
<thead>
<tr>
<th>References</th>
<th>Infants in trial</th>
<th>Eligibility criteria</th>
<th>Type of HFV</th>
<th>Pulmonary-related results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HiFi [19]</td>
<td>673</td>
<td>Respiratory failure, 750–2000 g</td>
<td>HFOV (Hummingbird, Senko Medical)</td>
<td>No difference in CLD or death. Increased air leaks in HFOV-treated group.</td>
</tr>
<tr>
<td>Carlo et al [20]</td>
<td>42</td>
<td>RDS, 1000–2000 g</td>
<td>HFJV (not stated)</td>
<td>No difference in death, air leaks, or CLD.</td>
</tr>
<tr>
<td>Clark et al [21]</td>
<td>83</td>
<td>RDS, &lt;35 wk, ≤1750 g</td>
<td>HFOV (SensorMedics 3100A)</td>
<td>HFOV-only decreased CLD compared with CMV only. HFOV x 72 h followed by CMV did not decrease CLD.</td>
</tr>
<tr>
<td>Ogawa et al [22]</td>
<td>92</td>
<td>RDS, 750–2000 g</td>
<td>HFOV (Hummingbird, Senko Medical)</td>
<td>No difference in death, duration of mechanical ventilation, CLD, or air leaks.</td>
</tr>
<tr>
<td>Wiswell et al [23]</td>
<td>73</td>
<td>RDS, &lt;33 wk, &gt;500 g</td>
<td>HFJV (Bunnell Life Pulse)</td>
<td>No difference in air leaks, duration of mechanical ventilation, or CLD. Increased poor outcomes (grade 4 ICH, cystic PVL, or death) in HFJV group.</td>
</tr>
<tr>
<td>Gerstmann et al [24]</td>
<td>125</td>
<td>RDS, &lt;35 wk</td>
<td>HFOV (SensorMedics 3100A)</td>
<td>HFOV decreased oxygen use, days on mechanical ventilation, and CLD. No difference in air leaks.</td>
</tr>
<tr>
<td>Keszler et al [25]</td>
<td>130</td>
<td>RDS, &lt;36 wk, 700–1500 g</td>
<td>HFJV (Bunnell Life Pulse)</td>
<td>HFJV decreased oxygen use and CLD. No difference in air leaks.</td>
</tr>
<tr>
<td>Rettwitz-Volk et al [26]</td>
<td>96</td>
<td>RDS, &lt;32 wk</td>
<td>HFOV (Stephan SHF 3000)</td>
<td>No difference in duration of mechanical ventilation, air leaks, CLD or death.</td>
</tr>
<tr>
<td>Plavka et al [27]</td>
<td>43</td>
<td>RDS, 500–1500 g</td>
<td>HFOV (SensorMedics 3100A)</td>
<td>HFOV reduced CLD. No difference in air leaks or duration of mechanical ventilation.</td>
</tr>
<tr>
<td>Study</td>
<td>No.</td>
<td>Condition</td>
<td>Ventilation Type</td>
<td>Findings</td>
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<tr>
<td>Thome et al [28]</td>
<td>284</td>
<td>RDS, ≥24–&lt;30 wk</td>
<td>HFFI (Infant Star HFV)</td>
<td>HFFI was associated with more air leaks. No difference in duration of mechanical ventilation, death, or CLD.</td>
</tr>
<tr>
<td>Moriette et al [29]</td>
<td>273</td>
<td>RDS, 24–29 wk</td>
<td>HFOV (OHF1)</td>
<td>HFOV decreased need for surfactant. No difference in air leaks or CLD.</td>
</tr>
<tr>
<td>Courtney et al [30]</td>
<td>500</td>
<td>RDS, 601–1200 g, one dose of surfactant</td>
<td>HFOV (SensorMedics 3100A)</td>
<td>HFOV decreased age to extubation and CLD. No difference in death.</td>
</tr>
<tr>
<td>Johnson et al [31]</td>
<td>797</td>
<td>RDS, 23–28 wk</td>
<td>HFOV (Dräger Babylog 8000, SensorMedics 3100A, SLE 2000HFO)</td>
<td>No difference in CLD, air leaks, or death.</td>
</tr>
<tr>
<td>Van Reempts et al [32]</td>
<td>300</td>
<td>RDS, &lt;32 wk</td>
<td>HFOV (SensorMedics 3100A) or HFFI (Infant Star HFV)</td>
<td>No difference in CLD, air leaks, duration of mechanical ventilation, or death.</td>
</tr>
<tr>
<td>Craft et al [33]</td>
<td>46</td>
<td>Respiratory insufficiency, 23–34 wk, &lt;1000 g</td>
<td>HFFI (Infant Star HFV)</td>
<td>No difference in CLD, air leaks, duration of mechanical ventilation, or death.</td>
</tr>
<tr>
<td>Rojas et al [34]</td>
<td>119</td>
<td>Respiratory failure, &gt;35 wk CGA, ≥1750 g</td>
<td>HFOV (SensorMedics 3100A)</td>
<td>No difference in CLD, air leaks, duration of mechanical ventilation, or death.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CGA, corrected gestational age; ICH, intracranial hemorrhage; PVL, periventricular leukomalacia.
chronic lung disease, as compared with CMV [21,24,25,27,30]. The 11 remaining trials showed no difference in pulmonary outcomes when using HFV versus CMV [19,20,22,23,26,28,29,31–34]. Differences in high-frequency ventilators, ventilation strategies, definitions of chronic lung disease, study populations, and study center experiences over time, as well as the inability to blind the treatment intervention, may be the derivation of such incongruent results regarding early use of HFV versus CMV. Likewise, some of the studies were conducted before routine use of exogenous surfactant. Nonetheless, HFV is routinely used in many neonatal ICUs, and we need to glean as much knowledge as possible from the current body of evidence in the literature.

The HiFi trial [19], published in 1989, was the first controlled trial of HFV versus CMV in neonates and the second largest study of its kind to date. In the HFV group, the Hummingbird HFOV (Metran Co. Ltd., Saitama, Japan) was used at mean airway pressures comparable to those delivered by CMV. The study demonstrated no significant differences in the incidence of death (HFV, 18%; CMV, 17%) or chronic lung disease (HFV, 40%; CMV, 41%), defined as oxygen requirement and abnormal chest radiographic findings at 28 days between the two groups. Of concern, the study found significantly increased air leaks and severe intracranial pathology, including grade 3 and 4 intracranial hemorrhage and periventricular leukomalacia (PVL), in the HFV group. In a smaller study using the same Hummingbird HFOV and the same criteria for defining chronic lung disease but implementing a lung volume recruitment strategy, Ogawa and colleagues [22] demonstrated no significant differences in death or chronic lung disease in HFV- versus CMV-treated groups. In contrast to the HiFi study, however, this study did not show any significant difference as air leaks or severe intracranial pathology between the groups.

Although small in size, two studies by Carlo and colleagues [20] and Wiswell and colleagues [23] comparing HFV delivered by a HFJV versus CMV did not demonstrate any significant differences in pulmonary outcomes or mortality between each group. The studies did have conflicting results regarding intracranial pathology. Carlo and colleagues demonstrated no significant difference in the incidence of grade 2 through 4 intraventricular hemorrhage (IVH) between the two groups, whereas Wiswell and colleagues showed significantly more severe intracranial pathology (grade 3–4 IVH and PVL) in those treated with HFJV.

Ventilation with high-frequency flow interrupters versus CMV has been looked at in a large trial of 284 patients by Thome and colleagues [28] in 1999, and in a smaller, more recent study, the Sy-Fi study, by Craft and colleagues [33]. Thome’s study included babies 24 to 30 weeks, whereas the Sy-Fi study included similarly aged babies but added a weight criterion of less than 1000 g. Both studies demonstrated no difference in chronic lung disease, mortality, or severe IVH. Both demonstrated increased air leaks in the HFFI-treated groups. In the Sy-Fi study, however, it was a select group
of infants, those treated with HFFI and weighing more (751–1000 g), that had a higher incidence of air leaks.

The vast majority of controlled trials of HFV versus CMV have employed HFOVs. However, the types of oscillator, some of which are not commercially available in the United States, varied from study to study, and one must be cognizant of this variable when comparing studies. In the largest trial of HFV versus CMV to date, Johnson and colleagues [31] included 797 preterm infants and used multiple different types of HFOV in the HFV arm. This trial demonstrated no difference in air leaks, CLD, or death in the HFV-treated group compared with the CMV-treated group. Unlike the concerning findings of the initial large HiFi study, Johnson and colleagues did not demonstrate any differences in severe IVH or PVL between the two treatment groups. Similarly, trials conducted by Rettwitz-Volk and colleagues [26] and Moriette and colleagues [29], using oscillators that are not commercially available in the United States, did not document an advantage of HFOV over CMV, with the exception of decreased exogenous surfactant requirements in the HFOV arm of the Moriette trial. Lastly, a recent prospective controlled trial of HFV versus CMV by Van Reempts and colleagues [32] revealed information on short-term endpoints as well as long-term follow-up results. They employed either HFOV or HFFI to provide HFV. The trial demonstrated no difference in duration of ventilation, air leaks, CLD, or mortality between the HFV and CMV groups. Looking at short- and long-term neurologic findings, they found no differences in the incidence of severe intracranial hemorrhage, PVL, or in the scores of more long-term assessment of motor and cognitive function at approximately 1 year of age.

To date, five controlled trials of HFV versus CMV have shown a benefit in pulmonary outcomes in the HFV groups. Favorable pulmonary results in the HFV-treated groups have occurred in less than one third of the total number of controlled trials of HFV versus CMV, and it is worth noting that most of these “positive” trials used HFOV (SensorMedics 3100A) as the means to provide HFV. Clark and colleagues [21] published the first positive trial in 1992. This single center study had three arms: HFOV only, HFOV for 72 hours followed by CMV, and CMV only. Babies in the HFOV-only arm had a decreased incidence of CLD. None of the three groups differed significantly in the incidence of air leaks, IVH, or death. Subsequently, Gerstmann and colleagues [24], in a multicenter controlled trial, demonstrated similar results of beneficial pulmonary outcomes with HFV, including a decreased need for multiple doses of surfactant and decreased incidence of CLD. Plavka and colleagues [27], in a smaller, single-center study, concluded similar results of decreased need for exogenous surfactant and decreased CLD in HFOV-treated babies. By far the most notable of the positive trials comes from Courtney and colleagues [30] and the Neonatal Ventilation Study Group. They published the largest controlled trial to date that demonstrates a benefit of HFV in pulmonary outcomes. This study included 500 preterm neonates who received at least
one dose of surfactant. The neonates randomized to the HFOV arm had significantly fewer days of mechanical ventilation as well as a decreased incidence of CLD compared with those treated with CMV. There was no difference in mortality, IVH, or PVL between the groups.

There is only one controlled trial of HFJV versus CMV that has ever demonstrated a beneficial pulmonary effect from using early, elective HFJV. Keszler and colleagues [25], in a multicenter controlled trial of 130 babies who had RDS, demonstrated a decreased incidence of CLD at 36 weeks corrected gestational age, as well as a decreased need for home oxygen therapy in the HFJV-treated group. Furthermore, there were no differences in air leaks, IVH, or death between the two groups.

Evidence-based recommendations

There is no evidence from the authors’ current review of the literature or other meta-analyses that elective use of HFV, in the form of HFOV or HFFI, provides any greater benefit to premature infants who have RDS than CMV [35]. The data are limited and the results are mixed as to whether HFJV may reduce the incidence of CLD [36]. At this time, preferential use of HFV as the initial mode of ventilation to treat premature infants who have RDS is not supported.

Gaps in knowledge

Ventilation strategies play a potentially significant role in pulmonary outcomes. There are no standardized criteria for the optimal use of HFV, nor are there sufficient data to determine the best techniques for lung recruitment. Similarly, though recruitment and maintenance of lung volume is an important component of treatment for many conditions, there are no easy-to-use techniques for accurate clinical measurement of lung volumes at the bedside. Finally, the use of so-called “high-volume ventilation strategies” versus “low-volume ventilation strategies” is incompletely defined, and the issue of which ventilator to use to provide HFV is unknown. In the same light, standardized strategies have not been defined for the optimal use of CMV, which today has many different ventilation modes and modalities available for clinical use. Lastly, and perhaps most important, long-term neurodevelopmental outcomes are of particular interest to physicians treating premature infants; these are lacking in most published studies.

Rescue high-frequency ventilation

Literature review

The body of literature regarding the use of HFV as a rescue technique is small and incomplete. In particular, there are only two controlled trials to date that explore this issue in premature infants who have severe respiratory distress. If controlled trials comparing rescue HFV versus CMV in term and
near-term infants are included, the total number of studies only increases to four. These trials and their pulmonary outcomes are summarized in Table 2 [37–40].

The HIFO trial investigated whether the use of rescue HFOV provides any benefit over continued CMV in preterm infants who have severe respiratory insufficiency, in particular with regard to pulmonary air leaks [38]. The HIFO trial randomized 176 preterm infants (<35 weeks, >500 g) who had severe respiratory distress, and had or were at increased risk of developing pulmonary air leak to HFOV versus continued CMV. This trial demonstrated a reduction in new pulmonary air leaks in the HFOV arm; however, there was no significant difference in the incidence of ongoing pulmonary interstitial emphysema, pneumomediastinum, or pneumothorax overall. There was also no difference in duration of mechanical ventilation or death between the two groups. IVH rates were increased in the HFOV-treated group compared with the CMV-treated group. This is a potentially worrisome finding, and unfortunately, there is no long-term neurologic or developmental follow-up described in this study.

In a more select population, Keszler and colleagues [37] randomized 144 preterm infants (<35 weeks, ≥750 g and <2000 g) who had severe respiratory failure and pulmonary interstitial emphysema to ventilation with the Bunnell HFJV device versus continued CMV at high rates. The study did allow for crossover if an infant met criteria for failure of the initially allocated ventilation mode. A significant number of patients in both groups met failure criteria (39% HFJV, 63% CMV) and crossed over to the alternate ventilation strategy. This being said, the patients treated with HFJV had more rapid improvement of their pulmonary interstitial emphysema. However, there were no differences in chronic lung disease, new air leaks, severe IVH, or mortality between the two groups. When the crossover population was excluded, the study demonstrated a lower mortality rate in the HFJV-treated group compared with the CMV-treated group.

The two aforementioned controlled studies of rescue HFV versus CMV in preterm infants were completed at a time when exogenous surfactant and antenatal steroids were not necessarily administered on a routine basis. Therefore, the generalization of specific results to today’s neonatal ICU population can potentially be called into question. The controlled studies of rescue HFV versus CMV in term or near-term infants by Clark and colleagues [39] and Engle and colleagues [40] are somewhat more applicable because they were performed more recently, and the infants studied are of a gestational age that antenatal steroids and exogenous surfactant are not obligatory. Nonetheless, since the time of their publication, exogenous surfactant and other interventions, such as inhaled nitric oxide (iNO), are used with increasing frequency and are not accounted for in these studies.

Clark and colleagues [39] randomized 79 term or near-term infants (>34 weeks, ≥2000 g) who had severe respiratory failure from various etiologies (meconium aspiration, RDS, pneumonia, congenital diaphragmatic hernia,
Table 2
Summary of randomized controlled trials of rescue use of high-frequency ventilation versus conventional mechanical ventilation

<table>
<thead>
<tr>
<th>References</th>
<th>Infants in trial</th>
<th>Eligibility criteria</th>
<th>Type of HFV</th>
<th>Pulmonary-related results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keszler et al [37]</td>
<td>144</td>
<td>Pulmonary interstitial emphysema on CMV, ≥750 g</td>
<td>HFJV (Bunnell Life Pulse)</td>
<td>Increased treatment success in HFJV group. Decreased mortality in HFJV group is crossover excluded. No difference in CLD, new air leaks, airway obstruction, or necrotizing tracheobronchitis.</td>
</tr>
<tr>
<td>HIFO Study Group [38]</td>
<td>176</td>
<td>Severe RDS, ≥500 g, &lt;48 h old</td>
<td>HFOV (SensorMedics 3100A)</td>
<td>Decreased new air leaks in HFOV group. No difference in ongoing air leak syndrome, duration of mechanical ventilation, or death.</td>
</tr>
<tr>
<td>Clark et al [39]</td>
<td>79</td>
<td>Severe respiratory failure, &gt;34 wk, ≥2000 g, &lt;14 d old</td>
<td>HFOV (SensorMedics 3100A)</td>
<td>Improved gas exchange and increased treatment success in HFOV group. No difference in CLD, air leaks, duration of mechanical ventilation, need for ECMO, or death.</td>
</tr>
<tr>
<td>Engle et al [40]</td>
<td>24</td>
<td>Severe respiratory failure and pulmonary hypertension, ≥35 wk, &gt;2000 g</td>
<td>HFJV (Bunnell Life Pulse)</td>
<td>Improved gas exchange in HFJV group. No difference in CLD, air leaks, duration of mechanical ventilation, need for ECMO, or death.</td>
</tr>
</tbody>
</table>

Abbreviation: ECMO, extracorporeal membrane oxygenation.
other) to HFOV versus continued CMV. The average age at randomization was 37 to 40 hours, and crossover to the alternate form of ventilation was allowed if preset criteria for treatment failure were achieved. The study demonstrated improved gas exchange and less treatment failure with HFOV, both in the patients initially allocated to rescue HFOV as well as in those that failed continued CMV and crossed over to HFOV. There was no difference in the incidence of chronic lung disease, IVH, or death between the two groups.

Engle and colleagues [40] randomized a more specific population of term and near-term infants (≥35 weeks, >2000 g) who had severe persistent pulmonary hypertension to HFJV versus CMV. The average age at randomization was 22 to 25 hours and crossover for treatment failure was not allowed in this study, because those who failed their allocated form of ventilation were referred for extracorporeal membrane oxygenation (ECMO). In this study, the HFJV-treated patients had improved oxygenation and ventilation versus the CMV-treated group; however, there were no long-term differences in the duration of mechanical ventilation or the incidence of chronic lung disease, air leaks, IVH, patients requiring ECMO, or death.

Evidence-based recommendations

Although limited in nature, there is no evidence from the authors’ current review of the randomized controlled trials or other meta-analyses that use of rescue HFV provides any long-term benefit over continued CMV in the preterm, near-term, or term patient who has respiratory failure [41–43].

Gaps in knowledge

Although there is a significant amount of data from nonrandomized uncontrolled trials regarding the use of rescue HFV in babies who have an inadequate response to CMV, such as that by Davis and colleagues [44], few randomized controlled trials of HFV versus CMV in conditions other than acute RDS in the preterm infant exist. Similarly, the few randomized trials that have been published regarding rescue HFV were performed when the administration of exogenous surfactant and antenatal steroids were not the norm. Current randomized clinical trials of rescue HFV are necessary.

High-frequency ventilation for conditions other than respiratory distress syndrome—management of bronchopleural or tracheoesophageal fistula, and high-frequency ventilation plus inhaled nitric oxide

Literature review

Because of the low occurrence rates of bronchopleural and tracheoesophageal fistulas in neonates, there are no randomized controlled trials
evaluating their management with HFV versus CMV. However, a few studies have formally evaluated the amount of air leak through these types of fistulas using HFV versus CMV. In the management of infants who had bronchopleural fistula, Gonzales and colleagues [45] showed a decrease in chest tube air leak when using HFJV versus CMV. Goldberg and colleagues [46] and Donn and colleagues [47] reported similar experiences in managing infants who had tracheoesophageal fistulas with HFJV. Furthermore, case reports, such as that by Bloom and colleagues [48], and animal studies, such as that by Orlando and colleagues [49], relay findings of an observed benefit to the use of HFV in the ventilatory stabilization of patients who have tracheoesophageal or bronchopleural fistula.

Another common use for HFV in the neonatal population is in conjunction with iNO for severe hypoxemic respiratory failure, often as a result of persistent pulmonary hypertension. In a randomized controlled trial, Kinsella and colleagues [50] looked at the effects of combining HFOV with iNO compared with either therapy used alone in infants who have persistent pulmonary hypertension. This study enrolled 205 neonates who had pulmonary hypertension from various underlying etiologies and demonstrated maximal treatment success (better arterial oxygenation) with the simultaneous use of HFOV and iNO. When looking at the premature population, Schreiber and colleagues [51] did not find such a benefit from ventilation modality. They enrolled 207 infants born at less than 34 weeks gestation into a randomized, double-blind, controlled study of iNO and differing ventilation strategies with CMV versus HFOV. There was no difference in pulmonary outcomes or death directly related to ventilation mode. In a randomized study of pediatric patients who had hypoxemic respiratory failure, Dobyns and colleagues [52] found similar results to Kinsella’s study with maximally improved oxygenation when using the combination of HFOV plus iNO as compared with HFOV alone, CMV plus iNO, or CMV alone. Although iNO is a new therapy and its potential synergy with HFV is similarly rather new, bench research further confirmed adequate and accurate delivery of iNO with both the HFOV and HFJV systems [53,54].

**Evidence-based recommendations**

Review of the literature supports the use of HFV with iNO to maximize oxygenation and treatment effects in hypoxemic respiratory failure, in particular in babies who have pulmonary hypertension. The current literature lacks any randomized trials to support the use of HFV over CMV in the treatment bronchopleural or tracheoesophageal fistula. That being said, the data do merit consideration, as the use of HFV in this population appears to diminish the amount of continuous air leak and improve patient stabilization.
Gaps in knowledge

Ideally, randomized trials are needed to elucidate the optimal ventilatory strategy in infants who have bronchopleural or tracheoesophageal fistula. However, because of the small number of patients who have these problems, it is unlikely that a randomized controlled trial will ever be feasible.

Summary

High-frequency ventilation is a form of mechanical ventilation that uses small tidal volumes and extremely rapid ventilator rates. It allows for pulmonary gas exchange at lower mean airway pressures than conventional mechanical ventilation. When HFV was first introduced on the menu of respiratory therapies for sick babies, hope abounded that HFV would be the universal remedy for most forms of neonatal respiratory insufficiency. In particular, clinicians were optimistic that HFV could be particularly useful in decreasing the incidence of chronic lung disease of prematurity. After almost 20 years of data gathering, this does not appear to be the case. When looked at as a whole, the currently available randomized controlled trials comparing HFV versus CMV have not demonstrated any clear benefit of HFV either as a primary mode or as a rescue mode of ventilation in neonates who have respiratory insufficiency. However, the current literature does support the preferential use of HFV over CMV in conjunction with iNO to maximize oxygenation in hypoxemic respiratory failure, in particular, as a result of persistent pulmonary hypertension.

Clearly, HFV has become a reliable and useful addition to the various modes of mechanical ventilation in neonates. Nonetheless, as most causes of neonatal respiratory insufficiency requiring mechanical ventilation are amenable to treatment with HFV or CMV, clinical judgment still dictates the choice of one form or the other, because the high-quality evidence currently available is still inconclusive. Ongoing studies will ideally elucidate the optimal lung volume and ventilatory strategy for specific disease states as well as provide clinicians with long-term follow-up data regarding neurologic and developmental outcomes of children treated with the various forms of ventilation.

References


FLUID/ELECTROLYTE MANAGEMENT IN THE NEONATAL ICU

I. Guidelines for Initiation and Advancement of Parenteral Nutrition in the NICU
II. Starter TPN Information
III. Standard IV Fluid Orders
IV. Lab Monitoring Guidelines for Parenteral Nutrition
V. Enteral Feeding Guidelines
VI. Neonatal Nutrition Reference
VII. Guidelines for Milk Selection in the NICU
VIII. Guidelines to Prevent Osteopenia
IX. References
I. GUIDELINES FOR INITIATION AND ADVANCEMENT OF PARENTERAL FEEDING IN THE NEONATAL INTENSIVE CARE UNIT

1. **Introduction:**
   Early aggressive nutrition in premature infants has been shown to improve growth outcomes, neurodevelopment and resistance to infection. Timely intervention with TPN begins with the provision of glucose as soon as possible after birth and amino acids within 12 hours and intravenous lipids within 24 hours.

2. **Goal:**
   - To minimize the interruption of nutrient delivery and prevent catabolism, especially in premature infants with limited nutritional reserves.
   - Aggressive use of amino acids to prevent “metabolic shock” that triggers endogenous glucose production and catabolism and stimulate insulin secretion to improve glucose tolerance.
   - To attempt to achieve intrauterine growth and nutrient accretion rates in preterm infants.
   - To optimize nutritional status to help both term and preterm infants resist the effects of trauma and disease and improve overall morbidity rates and responses to medical and surgical therapy.
   - To define minimal and maximal acceptable intakes.

This document and the following best practices are based on a review of current literature, recommended evidence-based better practices and recently revised advisable intakes on protein and energy for pre-term and term infants. Please see a list of reviews, studies and references at the end of the document to support the following recommendations.
### Initiation and Advancement Guidelines:

<table>
<thead>
<tr>
<th></th>
<th>Starter TPN</th>
<th>Initiation</th>
<th>Advancement</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premature Infant &lt; 30 weeks, &lt; 1000 grams DOL: 0</strong></td>
<td>Dextrose</td>
<td>7.5%</td>
<td>4 – 6 mg/kg/min</td>
<td>1 – 2 mg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Amino Acids</td>
<td>3 g/kg/d</td>
<td>3 – 3.5 g/kg/d&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.5 - 1g/kg/d</td>
</tr>
<tr>
<td></td>
<td>Lipids</td>
<td>0.5 g/kg/d (If total fluids and GIR allow)</td>
<td>1 g/kg/d</td>
<td>0.5 - 1g/kg/d</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;sup&gt;a&lt;/sup&gt;Non-Protein Calories</td>
<td>30 -40 cals/kg/d&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50 – 60 cals/kg/d</td>
<td>85 – 95 cals/kg/d</td>
</tr>
<tr>
<td></td>
<td>Total Calories</td>
<td>40 – 50 cals/kg/d</td>
<td>60 – 70 cals/kg/d</td>
<td>95 – 110 cals/kg/d</td>
</tr>
<tr>
<td><strong>Premature Infant &lt; 30 – 36 weeks, &gt; 1000 grams DOL: 0</strong></td>
<td>Dextrose</td>
<td>7.5%</td>
<td>4 – 6 mg/kg/min</td>
<td>1 – 2 mg/kg/min</td>
</tr>
<tr>
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<td>Amino Acids</td>
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</tr>
<tr>
<td></td>
<td>Total Calories</td>
<td>40 – 50 cals/kg/d</td>
<td>60 – 70 cals/kg/d</td>
<td>95 – 110 cals/kg/d</td>
</tr>
<tr>
<td><strong>Term Infant &gt; 37 weeks, &gt; DOL: 1-2</strong></td>
<td>Dextrose</td>
<td>7.5%</td>
<td>6 – 8 mg/kg/min</td>
<td>1 – 2 mg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Amino Acids</td>
<td>3 g/kg/d</td>
<td>2 – 3 g/kg/d&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.5 - 1g/kg/d</td>
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<td>50 – 60 cals/kg/d&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60 – 70 cals/kg/d</td>
<td>70 – 80 cals/kg/d</td>
</tr>
<tr>
<td></td>
<td>Total Calories</td>
<td>50 – 60 cals/kg/d</td>
<td>60 – 70 cals/kg/d</td>
<td>80 – 90 cals/kg/d</td>
</tr>
</tbody>
</table>

<sup>a</sup> Goal is to supply ~25 calories of energy/gm of amino acid intake. Use a combination of glucose and lipid as the energy source. **Non-protein calories are used to calculate energy needs in the NICU.**

<sup>b</sup> Minimum calorie and amino acid intake for “zero balance” (i.e. not catabolic) can be achieved with ~40 - 50 kcal/kg/day (basal metabolic energy needs) and 1.5 g/kg/d protein. Note: a GIR of ~6 - 8 mg/kg/min with 1 g/kg lipids will provide ~40 - 50 non-protein kcal/k/d in ELBW infants.

<sup>c</sup> Do not exceed the maximal oxidative glucose capacity of ~12.5 mg/kg/min or 18 g/kg/d of carbohydrate (for cholestatic jaundice keep at ~15 g/kg/d of carbohydrate). Usual maximum concentration: 12.5% peripheral route, 25% central route.

<sup>d</sup> Fluid restricted (≤150 ml/kg/d), growth compromised patients limited by peripheral access may require lipid infusion as high as 4 g/kg/d. However, this should not routinely be the end goal of intravenous lipids.

*To prevent essential fatty acid deficiency, provide a minimum of 0.5 g/kg/d of intravenous lipids.

<sup>e</sup> There is no evidence that gradually increasing amino acid intake improves “tolerance” to amino acids. Order 3 – 3.5 g/kg/d amino acids with the first regular TPN following starter TPN.

<sup>f</sup> Use starter TPN for term infants to be NPO for 1-2 days or complex surgical patients.
II. STARTER TPN INFORMATION

Rationale:
Newborn infants who do not receive protein have negative nitrogen balance and lose up to 1% of their protein stores daily. Catabolism is a particular problem of the very low birth weight infant who may have minimal nutritional reserves. Additionally, recent studies have indicated that when there is a shortage of amino acids, insulin levels fall, resulting in hyperglycemia and hyperkalemia. Parenteral intakes of 1.5 grams/kg/day of protein appear to be sufficient to prevent catabolism in newborn infants, and to maintain normal serum glucose and potassium levels.

Target Patient:
- Newly admitted patients <1500 grams
- Newly admitted patients 1500-1800 grams who are NPO for 24 hours
- Term infants NPO >1-2 days or complex surgical patients.

Recipe:
D7.5W + 8.4 grams protein/100 ml (peripheral)
D7.5W + 8.4 grams protein/100 ml + 4 mEq Calcium/100 ml (central)

Procedure:
Run at (1.5 ml x patient’s weight in kg)/hr, for example:

Birth Weight = 500 grams, run at 0.75 ml/hr
Birth Weight = 3 kilograms, run at 4.5 ml/hr
This gives 24 ml/kg/day fluid, 3 grams protein and 1 mEq/kg/day of calcium (central)
*** Order 0.5 grams of lipid per kg to run with starter TPN if total fluids and glucose infusion rate allow.

Order Writing for Starter TPN:
- On admission, 7 days a week, 24 hours per day for target patients
- Under orders in Cerner, enter “starter,” select “central” or “peripheral,” select rate.
- Order “starter TPN – peripheral at X ml/hr” or “starter TPN – central at X ml/hr”
- Check glucose 4 hours after starting
- Order another maintenance fluid to maintain an adequate glucose infusion rate and fluid intake
- Start regular TPN the next scheduled interval and order 3 – 3.5 grams of amino acids per kg per day (for term infants order 3 grams).
- Do not discontinue the starter TPN if the baby is hyperglycemic or hyperkalemic as it may make the situation worse. Consider changing the piggyback maintenance fluids to decrease the dextrose delivery.
III. STANDARD FLUID ORDERS

**UAC fluids:**
For infants > 1 kg:
½ NS with 0.25 units of heparin/ml @ 0.8 ml/hr. (minimum rate)
*If an infant is hypernatremic, consider changing to D5W with 0.25 units heparin/ml @ 0.8 ml/hr. (Note: it is difficult to obtain accurate glucose measurements from UAC line if D5W infusing).

For infants ≤ 1 kg:
⅓ Na Acetate with 0.25 units of heparin/ml at 0.8 ml/hr

**Peripheral arterial line fluids:**
½ NS with 0.5 units heparin/ml and 12 mg Papaverine/100 ml at 0.8 ml/hr.

**Pre-Op Fluids:**
Standard pre-op and post-op IVF for infants with normal hydration and electrolyte balance: D10W ¼ NS @ ~100-120 ml/kg/day.

If TPN/maintenance fluids will be running at a rate > 2 ml/hr omit the heparin.

As a general rule, for the first week of life use the infant’s birth weight for all fluid calculations. On day of life #8 begin using the infant’s daily weight. During rounds and sign-outs, specify what weight is being used for calculations.
IV. NUTRITIONAL STATUS LABORATORY EVALUATION GUIDELINES

**Infants on TPN (< 1 week of TPN therapy)**
EP + glucose on days 1, 3, 4, 6 and 7
BMP, Mg, Phos on days 2 & 5
T/D Bilirubin on day 5

Prealbumin – start on week two of life and check weekly
Alkaline phosphatase – start on week two of life and check weekly

For babies born < 1500 gm: triglyceride level should be assessed when on lipids of 2.5 gm/kg/day (goal < 150) and assessed again once on full goal lipids of 3.5 – 4 g/kg/day

** Lab frequency may always be adjusted based on clinical needs. **

**Infants on long-term TPN (> 1 week of TPN therapy)**
BMP, Ca, Mg, Phos q Monday and Thursday
T/D bilirubin q Monday
Prealbumin q Monday
Alkaline Phosphatase q Monday
Triglyceride level every two weeks
AST/ALT once per month

** Lab frequency may always be adjusted based on clinical needs. **

**Infants on diuretic therapy**
Infants on stable diuretic therapy should have a BMP, MG, Phos and iCa q Monday

**Infants on full feedings**
Infants who are “feeding and growing” (i.e., 75 – 100% enteral feedings) should have Prealbumin and alkaline phosphatase q Monday until acceptable for two consecutive evaluations, and then stop checking.

**Infants with high total direct bilirubin**
If infant has a direct bilirubin > 1.0 mg/dL, it should be followed weekly until < 1.0 mg/dL
V. ENTERAL FEEDING GUIDELINES

The ultimate goal of our feeding protocols is to establish demand ad libitum breast or bottle-feeding, with adequate weight gain, given entirely by the parents. For our small preterm babies our first goal is to initiate enteric feeding within a few days of birth, but advance slowly to avoid feeding intolerance and necrotizing enterocolitis. For these infants, parenteral nutrition must be initiated first and continued as a supplement until full enteric feedings can be given. Adequate weight gain is approximately 15 grams/kg/day, similar to that achieved in-utero. Babies < 32 weeks corrected gestational age (CGA) do not have the neurologic maturity to successfully handle suck/swallow/breathing. Therefore these babies are exclusively gavage fed. From 32 weeks CGA to ≤ 34 weeks CGA oral feeding can be initiated but persistent immaturity will require a gradual advancement dependant on individual readiness. Babies > 34 weeks can be tried on all oral feedings, although even these more mature infants may still require gavage supplements due to immaturity or medical condition.

Oral feedings should be initiated after a baby reaches 32 weeks CGA if the baby is off ventilatory support, on <0.35 L O₂ with RR < 70 bpm and RDS score <3, and without significant neurologic impairment or gastrointestinal disease. Feedings should be given on q 2-3 hour schedule by gavage, without feeding intolerance, before beginning oral feeds. An indwelling nasogastric tube is left in place for gavage supplementation. Infant wakefulness or restlessness, especially in response to nonnutritive sucking (NNS), should be determined before each feeding. Whenever the behavioral state is favorable, oral feeding can be attempted. The length of the feeding should be determined by the infant’s tolerance. Even if the feeding is not completed, oral feeding should be stopped if the baby falls asleep or will not suck after a pause, or develops significant clinical instability (desaturation, apnea or bradycardia). Incomplete feedings are completed by gavage. Breast fed infants should establish several good breast feedings per day before bottle feedings are added, if the parents wish to have a combined breast/bottle schedule. Once a few oral feedings per day are initiated, a baby who is not awake at the desired feeding time can be allowed to sleep an additional 30 min. and assessed again. If still unable to orally feed at that time, the baby is gavage fed. When full oral feeding is attained for 24 hours (oral ingestion of all feedings at full volume without any gavage), the nasogastric tube is removed. This is usually followed by a 24 hour period of ad libitum demand feedings, given solely or predominately by the parents, prior to discharge.
Birth weight ≤1500 grams

Initiation of feeding: Begin with minimal enteric feeding (MEF) or “trophic” feeds when hemodynamically stable. Contraindications to MEF's: conditions associated with decreased gut blood flow such as significant asphyxia events, ongoing hypotension, diastolic intestinal blood flow ‘steal’ secondary to a PDA and rapid Indocin administration; high pressor support (> 10 ug/kg/min dopamine); sepsis & significant clinical instability; GI contraindications (large or bilious aspirates, recurrent abdominal distension with feeds).

Choice of food: Breast Milk or EPF 20/SSC 20. When half to full volume feedings are tolerated, breast milk is fortified with HMF to make 24 kcal/oz. Formula is changed to EPF 24/SSC 24.

These are continued until the baby progresses to nursing ad lib or the last week before discharge. If discharged on formula, change to Enfacare or Neosure during the last week. If babies are discharged on pumped breast milk, adding powdered Enfacare or Neosure to make 22-24 calories/oz can boost the caloric, protein and mineral intakes. As much as possible, powdered infant formulas should be avoided in the NICU, but may be used at discharge.

Mode of feeding: while on trophic feeding, q 2-4 hr. After that, 2 hour bolus, given slowly over ~30- 45 minutes. If slower feeding is desired, selected patients can be fed by continuous drip. However, slow bolus feeds are more physiological and some of the fat calories may be lost in breast milk fed infants on drip feedings. After 32 -33 weeks GA or weight is >1250 grams, advance to a 3 hour bolus schedule before beginning attempts to breast/bottle feed.

Route: NG or OG, usually through a soft, indwelling tube. Begin breast or bottle feeding attempts daily beginning at 32+ weeks gestation. If a combination of breast and bottle feeding is desired, do not begin bottles until breast feeding is established 2-3 times/day.

Volume: See table below. When calculating volumes, round to the nearest ½ to 1 ml. Trophic feeds = 12 – 24 ml/kg/day. Trophic feeds should be continued about a week, or longer, until the baby is stable enough to tolerate more substantive feeding. The rate of advancement is 20-35 ml/kg/day. Full feeding = 120 cals/kg/day or more. Prefeeding aspirates can be as large as 30-50% of the feeding volume if the baby is otherwise free of signs of feeding intolerance. However, with aspirates greater than 30% of feeding volumes (except when taking very small trophic feeding volumes) feedings should not be advanced until aspirates decrease.
Sample Feeding Schedule:

<table>
<thead>
<tr>
<th>Day of Feeding</th>
<th>Volume per Feeding</th>
<th>Volume per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 – 3 (minimum time)</td>
<td>1 ml/kg/feed (trophic) q 2-4 hr</td>
<td>12 ml/kg/day</td>
</tr>
<tr>
<td>Day 4 – 6 (minimum time)</td>
<td>2 ml/kg/feed (trophic) q 2 hr</td>
<td>24 ml/kg/day</td>
</tr>
<tr>
<td>Day 7</td>
<td>3 ml/kg x 6 feeds q 2 hr</td>
<td>42 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>4 ml/kg x 6 feeds q 2 hr</td>
<td></td>
</tr>
<tr>
<td>Day 8</td>
<td>5 ml/kg x 6 feeds q 2 hr</td>
<td>66 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>6 ml/kg x 6 feeds q 2 hr</td>
<td></td>
</tr>
<tr>
<td>Day 9</td>
<td>7 ml/kg x 6 feeds q 2 hr</td>
<td>90 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>8 ml/kg x 6 feeds q 2 hr</td>
<td></td>
</tr>
<tr>
<td>Day 10</td>
<td>9 ml/kg x 6 feeds q 2 hr</td>
<td>114 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>10 ml/kg x 6 feeds q 2 hr</td>
<td></td>
</tr>
<tr>
<td>Day 11</td>
<td>11 ml/kg x 6 feeds q 2 hr</td>
<td>138 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>12 ml/kg x 6 feeds q 2 hr</td>
<td></td>
</tr>
<tr>
<td>Day 12</td>
<td>Adjust volume, add fortifier to breast milk feedings.</td>
<td>150 ml/kg/day</td>
</tr>
</tbody>
</table>

Monitoring Growth:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Frequency</th>
<th>Desired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Daily</td>
<td>18 – 20 gms/kg/day</td>
</tr>
<tr>
<td>Length</td>
<td>Weekly</td>
<td>1 cm/week</td>
</tr>
<tr>
<td>Head Circumference</td>
<td>Weekly</td>
<td>0.7 – 1 cm/week</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Weekly until stable without transfusion. Also obtain before discharge.</td>
<td>Depends on clinical condition.</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>Weekly when Hgb &lt; 11 g/dL</td>
<td></td>
</tr>
</tbody>
</table>

Poor Growth: If weight gain is inadequate, especially in combination with low prealbumin, depending on fluid tolerance feeding volumes can be increased up to 180 ml/kg/day to give additional calories and protein. Alternatively, beneprotein can be added to increase protein content to a maximum of 4 gms/kg/day. Caloric density may be increased with SSC 30 cal by mixing with 24 cal SSC or fortified breastmilk to provide various higher caloric concentrations. These patients should receive a Nutrition Consult. In older/larger infants term formula concentrate can be added to increase caloric density.

Anemia: After full feedings are tolerated, enteral Fe can be considered to treat anemia when a baby is at least 2 weeks of age. Recommended total dose of iron for premature infants is 2 – 4 mg/kg/day. Premature infant formulas and Enfamil HMF added to breast milk will provide ~2 mg/kg/day of enteral iron at 120 kcals/kg/day. Similac HMF added to breast milk does not provide iron. The maximum safe dose for supplemental iron for premature infants is 6 mg/kg/day.
Birth weight 1500 – 1750 grams

**Choice of Food:** Day 1 is breast milk or EPF 20/SSC 20. When half to full volume feedings are tolerated, fortify breast milk to 24 cal/oz with HMF. Formula is changed to 24 cal EPF/SSC 24. If discharged on formula, give Enfacare or Neosure.

**Mode of Feeding:** 3-hour bolus given slowly.

**Route:** NG or OG, usually through a soft indwelling tube. Begin breast or bottle-feeding attempts daily beginning at 32+ weeks gestation. If a combination of breast and bottle-feeding is desired, do not begin bottles until breast feeding is established 2-3 times daily.

**Volume:** See table below. Trophic feeds = 12 – 24 ml/kg/day, given for at least several days. The rate of advancement is 20 – 35 ml/kg/day. Full feeding = 150 ml – 180 ml/kg/day. Prefeeding aspirates can be as large as 30 – 50% of the feeding volume if the baby is otherwise free of signs of feeding intolerance. However, with aspirates greater than 30% of feeding volumes, feedings should not be advanced until aspirates decrease.

**Sample Feeding Schedule:**

<table>
<thead>
<tr>
<th>Day of Feeding</th>
<th>Volume of feeding q 3 hr</th>
<th>Volume per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 – 2 (minimum time)</td>
<td>3 ml/kg/feed</td>
<td>24 ml/kg/day</td>
</tr>
<tr>
<td>Day 3</td>
<td>5 ml/kg x 4 feeds</td>
<td>48 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>7 ml/kg x 4 feeds</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>9 ml/kg x 4 feeds</td>
<td>80 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>11 ml/kg x 4 feeds</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>13 ml/kg x 2 feeds</td>
<td>112 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>15 ml/kg x 4 feeds</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>17 ml/kg x 8 feeds</td>
<td>136 ml/kg/day</td>
</tr>
<tr>
<td>Day 7</td>
<td>19 ml/kg</td>
<td>152 ml/kg/day</td>
</tr>
</tbody>
</table>

**Monitoring Growth:**
As above for ≤ 1500-gram infants.
Birth weight 1750 – 2000 grams

Choice of Food:  Day 1 is breast milk or EPF 20/SSC 20. When half to full volume feedings are tolerated, fortify breast milk to 24 cal/oz with HMF. Formula is changed to 24 cal EPF/SSC 24. If discharged on formula, give Enfacare or Neosure.

Mode of Feeding:  3 hour bolus given slowly

Route:  NG or OG, usually through a soft, indwelling tube. Begin breast or bottle feeding attempts daily beginning at 32+ weeks gestation. If a combination of breast and bottle feeding is desired, do not begin bottle feeding until breast feeding is established 2-3 times daily.

Volume:  See table below. All fluids may be provided enterically "IF" the baby is medically stable and not on overhead phototherapy (which requires 15-20% extra fluid to avoid dehydration).

Sample Feeding Schedule:

<table>
<thead>
<tr>
<th>Day of Feeding</th>
<th>Volume per Feeding q 3 hrs</th>
<th>Volume per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Up to 5 ml/kg/feed</td>
<td>40 ml/kg</td>
</tr>
<tr>
<td>Day 2</td>
<td>10 ml/kg/day</td>
<td>80 ml/kg/day</td>
</tr>
<tr>
<td>Day 3</td>
<td>12 ml/kg/day</td>
<td>96 ml/kg</td>
</tr>
<tr>
<td>Day 4</td>
<td>14 ml/kg x 4 feeds</td>
<td>124 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>16 ml/kg x 4 feeds</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>18 ml/kg x 2 feeds</td>
<td>148 ml/kg/day</td>
</tr>
<tr>
<td></td>
<td>19 ml/kg x 2 feeds</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>19 ml/kg/day</td>
<td>152 ml/kg/day</td>
</tr>
</tbody>
</table>

Monitoring Growth:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
<th>Desired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Daily</td>
<td>18 – 20 gms/kg/day</td>
</tr>
<tr>
<td>Length</td>
<td>Weekly</td>
<td>1 cm/week</td>
</tr>
<tr>
<td>OFC</td>
<td>Weekly</td>
<td>0.7 – 1 cm/week</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Weekly if &lt;12 g/dL</td>
<td>also at discharge</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>Weekly if Hgb &lt; 11 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>
VI. NEONATAL NUTRITION REFERENCE CARD

**Parenteral Intake Goals:**
- Preterm: 90-100 Total kcal/kg
  - (85-95 non-protein kcal/kg)
  - 3.5-4 g/kg Protein

- Term: 80-90 Total kcal/kg
  - (70-80 non-protein kcal/kg)
  - 2.3 g/kg protein

**Starter TPN = D5, 2 g amino acid/kg**
- Run hourly rate at patient’s weight in kg, i.e., 500 g = 0.5 ml/hr
- Never adjust Starter TPN

**Initiating after Starter TPN:**
- Preterm:
  - Initiation: GIR 4–6 mg/kg/min Dextrose
  - 3–3.5 g/kg/d AA
  - 1 g/kg/d Lipids

  - Advancement: GIR 1.2 mg/kg/min Dextrose
  - 0.5–1 g/kg/d AA
  - 1 g/kg/d Lipids

- Term:
  - Initiation: GIR 6–8 mg/kg/min Dextrose
  - 2–3 g/kg/d AA
  - 2 g/kg/d Lipids

  - Advancement: GIR 1.2 mg/kg/min Dextrose
  - 0.5–1 g/kg/d AA
  - 1 g/kg/d Lipids

**Calculating TPN**
- Example: 750 g infant

  1. Determine the total fluids allowed
     - i.e., 80 ml/kg/d x 0.75 g/kg = 60 ml/day

  2. Determine Lipid intake
     - We use 20% lipids (1 g = 5 ml)
     - i.e., 1 g/kg/d x 0.75 g/kg x 5 ml = 3.75 ml/day
     - (rate = 3.75 ml/20 hr = 0.19 ml/hr)
     - Subtract Lipids from Total Fluids
     - 60 ml/day – 3.75 ml = 56 ml left (for Dextrose and AA)
     - 56 ml / 24 hours = 2.3 ml/hr

  3. Determine Dextrose Concentration
     - Calculate % Dextrose from GIR
     - (GIR x wt in kg x 0) / rate per hour
     - (5 mg/kg/min x 0.75 g/kg x 6) / 2.3 ml/hr = 9.8% Dextrose

  4. Determine AA
     - Pick AA goal i.e., 3 g/kg/day

  5. Calculating Calories from TPN
     - Dextrose 3.4 kcal/g
     - (2.3 x 24) x (9.8/100) x 3.4 kcal/g = 18.4 kcal from Dextrose
     - Amino Acids 4 kcal/g
     - 3 g/kg x 0.75 x 4 kcal/g = 9 kcal from AA
     - Lipids 2 kcal/ml
     - 3.75 ml/day x 2 kcal/ml = 7.5 kcal
     - Add calories together and divide by wt in kg
     - 18.4 (D) + 9 (AA) + 7.5 (L) = 34.9 kcal
     - 34.9 kcal / 0.75 g/kg = 46.5 kcal/kg

**Taper TPN**
- EN @ 50 ml/kg: ↓ AA to 3 g/kg, Lipids 2.5 g/kg
- EN @ 75 ml/kg: ↓ AA to 2.5 g/kg, Lipids 2 g/kg
- EN @ 100 ml/kg: ↓ AA & Lipids to 1.5 g/kg

**Fluid Requirements**
- Fluid needs depend on:
  1. Urine water loss
  2. Evaporative water loss
  3. Unusual loss in special situations (gastric drainage, chest tube drainage, etc.)
  4. Environmental humidity and skin maturation vary per infant during first 10-14 DOL
  5. Overhead phototherapy requires 15-20% extra fluid

<table>
<thead>
<tr>
<th>Typical Parenteral fluids</th>
<th>&gt;1500 g</th>
<th>ml/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>60-75</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>70-80</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>80-90</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>100-120</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>140-150*</td>
<td></td>
</tr>
</tbody>
</table>

**References**
2. Newborn and nursing reviews. 4(3):133-5

**Electrolytes**
- Sodium: 3-5 mEq/kg/d of NaCl
  - ELBW 5-8 mEq/kg/d
- Potassium: Start when K+ < 3.8 mEq/L and urine output is good
- Magnesium: Do Not Give Mg if mother was given dose of Mg SO4 to suppress labor
**Growth Goals**
- DOL 1-7: Wt loss of 10-20% of birth wt due to diuresis – to regain by 10-14 DOL
- After Regain to Birth wt:
  - <2000 gm: 18-20 g/kg/day
  - >2000 gm: 25-35 g/kg/day
- Length: 0.8-1.1 cm/wk
- OFC: 0.6-1.0 cm/wk

**Nutrition Lab Monitoring**
- Electrolytes
  - Reviewed daily in rounds
  - Depends on form of nutrition (PN/EN), diuretics and supplements
- Liver Function Labs
  - D. Bili if on TPN >2 weeks
  - Get 1st levels when on full EN or after 2 weeks of life
  - Ionized Calcium by request if on supplements
- BUN > 5 mg/dL
- Pre-Alb >10 mg/dL
  - Will be elevated if on steroids
- Alk Phos, Phos, Pre-Albumin weekly until stable x 2
- Get 1st levels when on full EN or after 2 weeks of life
- Ionized Calcium by request if on supplements

**Lab Goals**
- HMF
- SHMF
- Sim Special Care
- Enfamil
- Premature
- EPF
- NeoSure
- Enfamil
- Simulac
- Enfamil
- Advance
- Premium Lipid

**Discharge Guidelines**
- Children’s does not use any powders in the unit except HMF, so before discharge infants on:
  1. Formula – change to transitional formula (Enfacare/Neosure) 22-24 cal/oz when put on an ad lib demand schedule.
  2. Breast Milk – continue to use HMF until discharge or until the pt. weighs 3.5 kg. At D/C, MBM will be fortified with formula powder. If still inpatient, MBM should be fortified with concentrate if >3.5 kg.
- Sample Order – 33 ml every 3 hours of MBM + SHMF 24 cal/oz and if no breast milk SCF 24 cal/oz.

**Discharge Formula Plans**
- Preterm (<2000 gm BW, <35 weeks)
  - Formula: Enfacare or Neosure 22 cal/oz (may need >22 cal/oz if poor wt gain and/or intake)
  - Breast Feeding: 2-4 bottles per day of 24 cal/oz MBM + transitional formula
- Term (>2500 gm BW, >35 weeks)
  - OK for discharge on unfortified breast milk or term formula if taking adequate volumes

**Progressing Enteral Nutrition**
- Minimal Enteral Feedings/Trophic (MEF)
  - Initiate unless not able 1-2 days after birth
  - Infants <1500 gm, start with 10-20 ml/kg/day
  - Infants >1500 gm, can start 20-50 ml/kg/day
  - Trophic feedings are typically every 2-4 hours and don’t usually advance for 3-5 days per s of infant

- Preterm EN
  - <1250 gm feeds are bolus every 2 hours
  - 1250-1500 gm feeds are bolus every 3 hours
  - >1250 gm feeds are bolus every 3 hours

**Vitamin D and Iron Supplement**
- Iron: Preterm on MBM + SHMF 4 mg/kg
  - Term infant on MBM 2 mg/kg
- Vitamin D: Added at D/C or per RD request
  - 1 mL/day ADEK may be requested for cholestasis

**Discharge Vitamin Supplements:**
- MVI needed for iron (goal of 2 mg/kg/day) and Vitamin D (goal of 400 IU daily)
- *1 mL of MVI with iron – 10 mg Fe, 400 IU Vit D*
- *1 mL of MVI no iron – 400 IU Vit D*
- All Formula Fed Infants:
  - 0.5 mL/day of Tri-vi-sol without iron

**Breast Feed Infants or Combo Formula/MBM**
- 1 mL/day of Poly-vi-sol with iron

(Poly-vi-sol is bitter due to B-vitamins; if pt is having trouble with taking MVI try Tri-vi-sol instead)
### VII. GUIDELINES FOR MILK SELECTION IN THE NICU AND DISCHARGE

<table>
<thead>
<tr>
<th>Indication</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human Milk Fortifier or Premature Formula</strong></td>
<td>When maternal breast milk (MBM) @ 100 ml/kg/day, add HMF to = 24 kcal/oz.</td>
<td>36 – 37 weeks corrected gestational age AND &gt;2000 grams weight AND alk phos &lt;500 units/L AND prealbumin &gt; 10 mg/dL</td>
</tr>
<tr>
<td>Birth &lt;34 wks. gest. and/or Birth wt. &lt;2000 grams</td>
<td>If MBM not available, change from 20 cal to 24 cal premature formula.</td>
<td>36 – 37 weeks corrected gestational age AND &lt;2000 grams weight AND alk phos &lt;500 units/L AND prealbumin &gt; 10 mg/dL</td>
</tr>
</tbody>
</table>

### Indication for use at Discharge

<table>
<thead>
<tr>
<th>Indication for use at Discharge</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transitional Formula</strong></td>
<td><strong>Formula:</strong> Enfacare 22 Neosure 22 <strong>Breastmilk:</strong> switch to breast milk + concentrate to = 22 cal/oz.</td>
<td>Generally at 9 -12 mo. CGA. Based on birthweight and growth after discharge:</td>
</tr>
<tr>
<td>Birth &lt;34 wks. and/or Birth wt. &lt;2000 grams (regardless of gestational age) Babies 2000 – 2500 grams • With ↑ alk phos • Poor wt. gain &amp; difficulty meeting volume goals on ad lib feedings IUGR at any age Elevated alk phos &gt; 500 units/L Long-term inability to use HMF Chronic use of medications that waste minerals &amp; prolonged TPN Growth Delays wt. and/or wt for length &lt; 3rd%ile</td>
<td>(may be o.k. to use unfortified human milk if consistently taking volumes &gt;165 – 180 ml/kg/day and gaining weight)</td>
<td></td>
</tr>
<tr>
<td><strong>Formula:</strong> Enfacare 24 Neosure 24 <strong>Breastmilk:</strong> switch to breast milk + concentrate to = 24 cal/oz.</td>
<td></td>
<td>Birthweight</td>
</tr>
<tr>
<td>&lt;750 gms</td>
<td>to 12 mo. CGA</td>
<td></td>
</tr>
<tr>
<td>&lt;1500 gms</td>
<td>to 9 mo. CGA</td>
<td></td>
</tr>
<tr>
<td>&lt;2000 gms</td>
<td>3-6 mo CGA</td>
<td></td>
</tr>
</tbody>
</table>

If breastfeeding, how many bottles? Recommend 2-4 bottles/day of breastmilk fortified to 24 cal/oz with transitional formula or if milk supply is low, use transitional formula for the supplemental feedings. **HMF should be discontinued at 3 kg, or at discharge.**
VIII. GUIDELINES TO PREVENT OSTEOPENIA

Background:

Preterm infants, particularly those with birth weights <1 kg, miss the period of most rapid in utero accretion of minerals. The intrauterine accretion rates of calcium and phosphorus are ~100 mg and ~60 mg/kg/day, respectively, beyond 24 weeks gestation, and reach peaks of approximately ~130 mg of calcium and ~75 mg/kg/day of phosphorus between 28 to 36 weeks gestation.

I. Criteria for Participation

- All infants ≤ 1000 grams at birth.
- Infants with two or more of the following risk factors:
  - Severely growth restricted (IUGR)
  - NPO/TPN for > 3 weeks
  - Chronic Lung Disease
  - Cholestasis
  - Infant born < 1500 grams unable to tolerate premature formula or fortified breast milk (i.e. on elemental feedings such as Neocate).
  - Infant on chronic Ca+ wasting diuretics, i.e. lasix
  - Long-term steroid use
  - AP levels > 900 u/L with serum P < 5 mg/dL.

II. Parenteral Requirements – optimizing calcium & phos delivery

<table>
<thead>
<tr>
<th>Mineral</th>
<th>mg/kg</th>
<th>mMol/kg</th>
<th>mEq/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>80 – 100</td>
<td>2 – 2.5</td>
<td>4 – 5</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>43 – 62</td>
<td>1.5 – 2</td>
<td>2.8 – 4</td>
</tr>
<tr>
<td>Magnesium</td>
<td>6 – 10</td>
<td></td>
<td>0.25 - 1</td>
</tr>
</tbody>
</table>

- 1 mMol P = 31 mg P and/or 1.47 mEq P
- 0.5 mMol Ca = 1 mEq Ca or 1 mEq Ca = 20 mg Ca

The maximum content/goal for parenteral calcium and phosphorus for preterm infants in the NICU, St. Paul Campus, is for 4 – 5 mEq/kg of calcium and 1.5 – 2 mMol/kg of phosphorus. A stepwise increase in the Ca and P content over the first 3 days of PN minimizes the risk of biochemical disturbance.
Introduction of calcium and phosphorus in TPN should be started at ~70-75% maximum content/goal. The Ca & P may be increased daily by ~10% until maximum content/goal is achieved.

**Example:** Maximum content/goal = 4 mEq/kg calcium & 2 mMol/kg P
Day 1 TPN (*after starter), order 2.5 - 3 mEq/kg Ca and 1 - 1.5 mMol/kg P or write to “max P”
Day 2 TPN, order 3 - 3.5 mEq/kg Ca & 1.5 - 1.75 mMol/kg P.
Day 3 TPN, order 4 mEq/kg Ca & 2 mMol/kg P.
*starter TPN (central line) provides ~1 mEq/kg Ca.

***Note, pharmacy cannot add P to TPN solutions until Na+ and K+ are required in the TPN. Most premature infants are on electrolyte free TPN for the first ~48 hours of life. However, calcium should still be added to prevent early hypocalcemia. Thus, in instances where only small amounts of e’lytes are in the TPN, it may not be feasible to fit goal amounts of P in the TPN. In an attempt to maximize P, order the desired amount, i.e. 1.5 mMol/kg P. The pharmacist may be required to adjust this amount to accommodate the limits of the PN’s electrolyte ratios.

There is no calcium in peripheral TPN solutions. The maximum P content added to peripheral TPN is 1 mMol/kg. *additional P may be added if the infant has depleted serum stores (P < 4 mg/dL).

The calcium-to-phosphorus ratio that allows for the highest retention of both minerals with minimal intolerance is 2-2.5 mEq Ca: 1 mMol P.

Cysteine lowers the pH of the TPN solution, increasing calcium and phosphorus solubility and allowing for higher delivery of minerals in TPN without precipitation. Add cysteine to parenteral nutrition solution if you are unable to maximize intakes (this usually occurs in lower protein intakes or fluid restricted TPN). *In ELBW infants with acidosis requiring >50% acetate, cysteine HCL will not be added.

**Serum Ca & P should be measured 2-3 x/week initially until maximum content/goal is reached. Thereafter, measure serum Ca & P at weekly intervals.**
**Phosphorus may need to be decreased if serum levels are >7.5 mg/dL.**
III. Enteral Requirements

<table>
<thead>
<tr>
<th>Nutrients per kg</th>
<th>&lt;1000 gm*</th>
<th>AAP/CON*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium, mg</td>
<td>120-230</td>
<td>210</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>60 – 140</td>
<td>110</td>
</tr>
<tr>
<td>Magnesium, mg</td>
<td>7.9 - 15</td>
<td>---</td>
</tr>
<tr>
<td>Vitamin D, IU</td>
<td>150 – 400</td>
<td>325</td>
</tr>
</tbody>
</table>

*Based on Tsang et al. Nutritional Needs of the Preterm Infant, 2005
AAP/CON: American Academy of Pediatrics, Committee on Nutrition

- Human milk fortifier (24 cal/oz) for breast milk fed infants and Premature Formula (24 cal/oz) is indicated for all infants weighing less than 2000 grams.
- Human milk fortifier (24 cal/oz) should be initiated when the infant is tolerating ~80 – 100 ml/kg/day of breast milk.
- Use HMF and preterm formulas up through 2.5 – 3 kg in infants born <1000 grams and with a hx of chronic lung disease requiring diuretics and steroids.
- Preterm infants unable to tolerate premature formula or breast milk fortified with HMF (i.e. preterm infant on nutramigen) may require calcium and phosphorus supplementation. Please consult the dietitian for recommendations on the addition of calcium and phos to enteral feedings in these cases.
- Mineral loss of 30-40% has been reported from sedimentation in milk, especially during continuous enteral infusion. Therefore, intermittent bolus feedings are preferred as well as pointing the syringe tip down or agitation of the milk during drip feedings to redistribute minerals and ensure they get to the infant.

**Calcium and Phosphorus Intake for Preterm Infants – Milk Choices**

<table>
<thead>
<tr>
<th>Formula – 150 ml/kg/day</th>
<th>Calcium</th>
<th>Phosphorus</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSC 24</td>
<td>~219 mg/kg/day</td>
<td>~122 mg/kg/day</td>
<td>~180 IU/kg</td>
</tr>
<tr>
<td>EPF 24</td>
<td>~196 mg/kg/day</td>
<td>~99 mg/kg/day</td>
<td>~288 IU/kg</td>
</tr>
<tr>
<td>MBM + SHMF</td>
<td>~212 mg/kg/day</td>
<td>~119 mg/kg/day</td>
<td>~178 IU/kg</td>
</tr>
<tr>
<td>MBM + EHMF</td>
<td>~172 mg/kg/day</td>
<td>~96 mg/kg/day</td>
<td>~228 IU/kg</td>
</tr>
</tbody>
</table>

Estimated Calcium and Phosphorus needs for infants with documented osteopenia and/or elevated AP levels > 900 u/dL along with serum P levels below 5.5 mg/dL = ~200 – 230 mg/kg/day of calcium and ~110-140 mg/kg/day of P to optimize bone mineralization. Thus, these infants would require MBM + SHMF or SSC 24 to meet these needs.
IV. Monitoring

**Alkaline phosphatase (AP) -**
An abnormally high circulating AP level in preterm infants can be indicative of osteopenia of prematurity, especially if other risk factors exist. Total AP levels > 900 mg/dL along with serum P < 5.5 mg/dL in preterm infants suggests low bone mineral content with high sensitivity. AP can be normal.

**Serum Phos (P) —**
Preterm infants may have limited P stores and increased needs with rapid growth. Serum P values < 5 mg/dL in preterm infants suggests inadequate intakes. Consider decreasing intakes if serum P is > 7.5 mg/dL.

Serum calcium is not a good indicator of calcium intakes and serum calcium may be low, normal or high with bone demineralization.

If you have any questions regarding parenteral or enteral calcium and phosphorus intakes in the preterm infant, please contact the NICU dietician or Pharm D.
References:


Miller ME. (2003). The Bone Disease of Preterm Birth:


X. NUTRITION REFERENCES


PHARMACOLOGY

I. NICU Medications

II. Protocols
   A. Methadone Withdrawal Protocol
   B. Caffeine
   C. Chronic Lung Disease Protocol
   D. Gentamycin Dosing
   E. Hyperkalemia
   F. Rapid Sequence Intubation Medications
   G. Narcotics
   H. Vitamin D Supplementation to Prevent Osteopenia of Prematurity
   I. Indomethacin for IVH Prevention in ELBW's

III. Appendix
   A. Antibiogram
## Neonatal Dosing Guidelines 2008

**NEONATAL DOSING GUIDELINES**

(All values listed are PER DOSE unless specified per day)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide (Diamox)</td>
<td>5mg/kg IV q6-12h</td>
</tr>
<tr>
<td>Acetylcysteine (Muconyst)</td>
<td>1-2mL/kg PO q8-12h</td>
</tr>
<tr>
<td>Acetaminophen (Tylenol)</td>
<td>10-15mg/kg PO/PR q4-6h</td>
</tr>
<tr>
<td>Adenosine (Adenocard)</td>
<td>50-100mcg/kg rapid IV (max of 300mcg over 3 doses)</td>
</tr>
<tr>
<td>Albumin</td>
<td>5% 10mL/kg (0.5g/kg) -hypovolemia 5-19g/kg - hypoproteinemia</td>
</tr>
<tr>
<td>Albuterol (Ventolin/Proventil)</td>
<td>1.25-2.5mg Neb q2-8h</td>
</tr>
<tr>
<td>Alprostadil</td>
<td>initial maintenance 0.05-0.1mcg/kg/min</td>
</tr>
<tr>
<td>Aminophylline (load)</td>
<td>6mg/kg/dose IV/PO 1.4mg/kg/day IV/PO q8h</td>
</tr>
<tr>
<td>Atropine</td>
<td>0.02mg/kg (0.1mg min dose) IV/SQ</td>
</tr>
<tr>
<td>Budesonide (Pulmicort)</td>
<td>0.25-0.5mg Neb q12-24h</td>
</tr>
<tr>
<td>Bicitra (Na Citrate/Citric Acid)</td>
<td>0.75-1mg/kg PO q8h</td>
</tr>
<tr>
<td>Bumetanide (cont. infusion)</td>
<td>0.01-0.05mg/kg q6-24h</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>10-20mg/kg/dose IV (over 1 hr)</td>
</tr>
<tr>
<td>Captopril (Capoten)</td>
<td>0.01-0.05mg/kg PO q8-12h</td>
</tr>
<tr>
<td>Chloral Hydrate</td>
<td>20-75mg/kg/dose PO/PR q6-8h</td>
</tr>
<tr>
<td>Chlorothiazide (Diural)</td>
<td>10-20mg/kg/dose PO q12h</td>
</tr>
<tr>
<td>Caffeine (load)</td>
<td>30mg/kg IV/PO x 1</td>
</tr>
<tr>
<td>Caffeine (maintenance)</td>
<td>6mg/kg IV/PO q24h</td>
</tr>
<tr>
<td>Ciclesoporin (stim test)</td>
<td>1mcg/kg IV</td>
</tr>
<tr>
<td>Dextrose 10%</td>
<td>2mL/kg IV</td>
</tr>
<tr>
<td>Dexamethasone (Decadron)</td>
<td>0.25mg/kg IV/IM/PO q12h</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>0.02-0.3mg/kg IV q6-8h</td>
</tr>
<tr>
<td>Diphenhydramine (Phenergan)</td>
<td>8-60mg/kg PO q8h</td>
</tr>
<tr>
<td>Digoxin (preterm)</td>
<td>IV - 15-25mcg/kg</td>
</tr>
<tr>
<td>Digoxin (load)</td>
<td>PO - 20-30mcg/kg</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2.5-20mcg/kg/hr</td>
</tr>
<tr>
<td>Domperidone (Pulminex)</td>
<td>1.25 mcg Neb q12-24h</td>
</tr>
<tr>
<td>Enalapril (PO)</td>
<td>0.1-0.5mg/kg q24h</td>
</tr>
<tr>
<td>Enalaprilat (IV)</td>
<td>5-10mcg/kg q8-24h</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>1.5mg/kg subQ/IV q8-12h</td>
</tr>
<tr>
<td>Epinephrine (1:10,000)</td>
<td>resus HOTN 0.01-0.03mg/kg=0.1-0.3mL/kg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>intermittent cont. infusion 1-4mcg/kg IV q2-4h</td>
</tr>
<tr>
<td>Flumazenil (Romazicon)</td>
<td>5-10mcg/kg over 15 sec; may repeat q45 sec</td>
</tr>
<tr>
<td>Fosphenytoin/Phenytoin (load) (Dilantin)</td>
<td>maintenance 2.5-3.5mcg/kg q12h</td>
</tr>
<tr>
<td>Furosemide (Lasik)</td>
<td>0.5-1mg IV q12-24h</td>
</tr>
<tr>
<td>Glucagon</td>
<td>0.03mg/kg (max 1mg/kg)</td>
</tr>
<tr>
<td>Glycopyrrolate (Robinul)</td>
<td>40-100mcg/kg PO 3-4x/day 4-10mcg/kg IV/IM q3-4h</td>
</tr>
<tr>
<td>Heparin load maintenance</td>
<td>75 units/kg</td>
</tr>
<tr>
<td>Heparin maintenance</td>
<td>28 units/kg</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>150 units (1ml) divide into 5 0.2ml injections</td>
</tr>
<tr>
<td>Hydrocortisone stress</td>
<td>preterm - 0.5mg/kg/IV/PO q12h term - 0.5mg/kg/IV/PO q6-8h</td>
</tr>
<tr>
<td>Ibuprofen (IV) (Neoprofen)</td>
<td>10mg/kg x 1 then 24 hrs later 5mg/kg q24h x 2 (may repeat with 2nd course - 5mg/kg q24h x3</td>
</tr>
<tr>
<td>Ibuprofen (PO)</td>
<td>(3+ months) 5-10mg/kg/dose q6-8h</td>
</tr>
<tr>
<td>Indomethacin (Indocin)</td>
<td>&lt;48 hrs old 0.2mg/kg IV x 1, then 0.1mg/kg q12x 2 doses</td>
</tr>
<tr>
<td>Insulin</td>
<td>Bolus Continuous Drip 0.05-0.1 unit/kg IV</td>
</tr>
<tr>
<td>Ipratropium (Atrovent)</td>
<td>0.25 mg Neb q6-12h</td>
</tr>
<tr>
<td>Iron (Ferrous Sulfate) MBM</td>
<td>Formula and Fortified MBM 2mg/kg q12h PO</td>
</tr>
<tr>
<td>Kayexalate</td>
<td>1-2g/kg PO/PR q2-4h, decanting K from formula 0.6G/1mEq K+ in feeds</td>
</tr>
<tr>
<td>Lactobacillus granules</td>
<td>0.25 packet PO q12h</td>
</tr>
<tr>
<td>Lansoprazole (Prevacid)</td>
<td>1mg/kg IV/PO q12-24h</td>
</tr>
</tbody>
</table>
### Antimicrobial Dosing Guidelines (IV meds)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levetiracetam (Keppra)</strong></td>
<td>5-10mg/kg/day (divide 2-3x/day) Max of 60mg/kg/day (5-10mg/kg/day per week)</td>
</tr>
<tr>
<td><strong>Levothyroxine (Synthroid)</strong></td>
<td>10-14 mcg/kg PO q24h 5-7 mcg/kg IV q24h</td>
</tr>
<tr>
<td><strong>Loperamide (Imodium)</strong></td>
<td>0.3-0.5mg/kg PO q6-8h</td>
</tr>
<tr>
<td><strong>Lorazepam (Ativan)</strong></td>
<td>0.05-1.0mg/kg IV/PO q6-8h</td>
</tr>
<tr>
<td><strong>Metadone</strong></td>
<td>0.1mg/kg IV/PO</td>
</tr>
<tr>
<td><strong>Metronidazole (IV/PO)</strong></td>
<td>Max of 60mg/kg/day (inc 10mg/kg/day per week)</td>
</tr>
<tr>
<td><strong>Metoprolol (IV) / metoprolol (PO)</strong></td>
<td>(Oprad)</td>
</tr>
<tr>
<td><strong>Midazolam (Versed)</strong></td>
<td>0.05-0.1mg/kg IV/PO q2-4h</td>
</tr>
<tr>
<td><strong>Morphine</strong></td>
<td>0.1mg/kg IV/IM q3-6h</td>
</tr>
<tr>
<td><strong>Methylprednisolone (IV) / prednisolone (PO)</strong></td>
<td>(Oprad)</td>
</tr>
<tr>
<td><strong>Methamphetamine</strong></td>
<td>0.25-1mg/kg IV q24h &lt; 7 days old 7 days old</td>
</tr>
<tr>
<td><strong>Minocycline</strong></td>
<td>3-5mg/kg IV q24h</td>
</tr>
<tr>
<td><strong>Oxycodone</strong></td>
<td>25mg/kg q12h</td>
</tr>
<tr>
<td><strong>Penicillin G (IV)</strong></td>
<td>250,000 units IV q6-8h</td>
</tr>
<tr>
<td><strong>Phenobarbital</strong></td>
<td>1.25-1.75mg/kg q6h &gt;2000g - 50mg/kg q8-12h &gt;2000g - 50mg/kg q6h</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td>1mg/kg IV q12h (airway inflam)</td>
</tr>
<tr>
<td><strong>Piperacillin</strong></td>
<td>1200-2000g - 7.5mg/kg q12h 1200-2000g - 15mg/kg q12h</td>
</tr>
<tr>
<td><strong>Piperacillin/Tazobactam (Zosyn)</strong></td>
<td>50-100mg/kg/dose q8h</td>
</tr>
<tr>
<td><strong>Prednisone (IV) / methylprednisolone (PO)</strong></td>
<td>(Orapred)</td>
</tr>
<tr>
<td><strong>Prednisone (IV) / methylprednisolone (PO)</strong></td>
<td>(Unasyn) (use ampicillin dosing regimen) &gt;2000g - 25mg/kg q6h</td>
</tr>
<tr>
<td><strong>Protamine Sulfate</strong></td>
<td>&gt;1250g - 500 units q12h &gt;1250g - 250 units q12h</td>
</tr>
<tr>
<td><strong>Rifampin (IV)</strong></td>
<td>&gt;1250g - 50mg/kg q12h</td>
</tr>
<tr>
<td><strong>Rifampin (IV)</strong></td>
<td>1200-2000g - 25mg/kg q12h</td>
</tr>
<tr>
<td><strong>Rifampin (IV)</strong></td>
<td>&gt;2000g - 25mg/kg q12h</td>
</tr>
<tr>
<td><strong>Rifampin (IV)</strong></td>
<td>&gt;2000g - 25mg/kg q12h</td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td>3.5-4mg/kg q24-48h (see protocol)</td>
</tr>
<tr>
<td><strong>Vincristine</strong></td>
<td>0.05-0.1mg/kg IV/IM q2-4h</td>
</tr>
<tr>
<td><strong>Vincristine</strong></td>
<td>&gt;2000g - 25mg/kg q12h</td>
</tr>
<tr>
<td><strong>Vincristine</strong></td>
<td>&gt;2000g - 25mg/kg q12h</td>
</tr>
<tr>
<td><strong>Vincristine</strong></td>
<td>&gt;2000g - 25mg/kg q12h</td>
</tr>
</tbody>
</table>

### Antimicrobial Dosing Guidelines (Oral meds)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin (prophylaxis)</strong></td>
<td>25mg/kg q24h</td>
</tr>
<tr>
<td><strong>Cefdinir</strong></td>
<td>15-20mg/kg IV/IM/PO q24h</td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td>1200-2000g - 50mg/kg q12h 1200-2000g - 50mg/kg q8h</td>
</tr>
<tr>
<td><strong>Cefuroxime (Cefuroxime axetil)</strong></td>
<td>2000g - 50mg/kg q12h 2000g - 50mg/kg q8h</td>
</tr>
<tr>
<td><strong>Cefuroxime (Cefuroxime axetil)</strong></td>
<td>2000g - 50mg/kg q12h 2000g - 50mg/kg q8h</td>
</tr>
<tr>
<td><strong>Cefuroxime (Cefuroxime axetil)</strong></td>
<td>2000g - 50mg/kg q12h 2000g - 50mg/kg q8h</td>
</tr>
<tr>
<td><strong>Cefuroxime (Cefuroxime axetil)</strong></td>
<td>2000g - 50mg/kg q12h 2000g - 50mg/kg q8h</td>
</tr>
<tr>
<td><strong>Cefuroxime (Cefuroxime axetil)</strong></td>
<td>2000g - 50mg/kg q12h 2000g - 50mg/kg q8h</td>
</tr>
<tr>
<td><strong>Cefuroxime (Cefuroxime axetil)</strong></td>
<td>2000g - 50mg/kg q12h 2000g - 50mg/kg q8h</td>
</tr>
<tr>
<td><strong>Cefuroxime (Cefuroxime axetil)</strong></td>
<td>2000g - 50mg/kg q12h 2000g - 50mg/kg q8h</td>
</tr>
<tr>
<td><strong>Cefuroxime (Cefuroxime axetil)</strong></td>
<td>2000g - 50mg/kg q12h 2000g - 50mg/kg q8h</td>
</tr>
</tbody>
</table>

### NI CU Gentamicin/ Tobramycin Dosing Protocol

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gentamicin</strong></td>
<td>3.5-4mg/kg q24-48h (see protocol)</td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
<td>3.5-4mg/kg q24-48h (see protocol)</td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
<td>3.5-4mg/kg q24-48h (see protocol)</td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
<td>3.5-4mg/kg q24-48h (see protocol)</td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
<td>3.5-4mg/kg q24-48h (see protocol)</td>
</tr>
</tbody>
</table>

---

* adjust for renal impairment

(All values listed are ‘PER DOSE’ unless specified)
II. PROTOCOLS
   a. Methadone Withdrawal Protocol

If three consecutive abstinence scores are > 8

Start methadone 0.15 mg/kg DOSE po q 6h

If abstinence scores remain > 8 after initial dosing, give 0.05 mg/kg/DOSE q3h. Add extradoses to the daily dose the next day.

Decrease dose by half po q 6h

After 24 hrs or when three consecutive abstinence scores are < 8

Same dose po q 8h

After 24 hrs or when three consecutive abstinence scores are < 8

Same dose po q 12h

After 24 hrs or when three consecutive abstinence scores are < 8

Decrease dose by half po q 12h

After 24 hrs or when three consecutive abstinence scores are < 8

Same dose po q day

Discontinue methadone when abstinence scores consistently < 8 or by daily assessment of needs
b. CAFFEINE

**CAFFEINE CITRATE USE IN VLBW INFANTS**

<1250 GRAMS OR <30 WEEKS

---

Caffeine Citrate (must specify *citrate*)

Load: 30 mg/kg IV or PO maintenance: 6 mg/kg/day (one dose/24 hrs)

- **Apnea of Prematurity**
  - Facilitate Extubation
  
  Load with caffeine citrate and start maintenance

  - Significant apnea or doubtful efficacy
    - Obtain level.
      - Wait 4-5 days until steady steady obtained
      - Wide therapeutic range (8-20 mcg/ml)
    
    - Reload and/or increase maintenance

  - Therapeutic response
    - 31-33 weeks PCA and no apnea or significant intervention
    
    - Stop caffeine
      
      Goal: sub-therapeutic level by 33 wks PCA

  - Significant apnea recurs
    
    Consider starting Aminophylline

  - Apnea resolves
    
    DC Aminophylline

  - Apnea persists at discharge

---

**Discharge plan**

- Stop Aminophylline
- ½ loading dose of caffeine citrate
- Enroll in infant apnea program
- Monitor training for caretakers
- Discharge with home monitor and caffeine citrate

**Outpatient management**

- Stop caffeine in 2 weeks if no significant events
- Document mature respiratory pattern with event recording at one month
- Stop monitor if recording mature

---

**Note:**
Because of its long half-life, caffeine should be discontinued at 1500 grams.

Theophylline can be prescribed if needed
c. CHRONIC LUNG DISEASE PROTOCOL

Recommendations for the use of steroids and diuretics in chronic lung disease at ≥ 34 weeks CGA

AIMS
1. Reduce incidence of chronic lung disease (as defined by supplemental O₂ need at 36 weeks CGA).
2. Provide consistency in diuretic and steroid use among neonatology providers in infants with CLD and relatively low oxygen requirements.

RECOMMENDATIONS
Infants at 34 weeks CGA with persistent oxygen need of an effective FiO₂ < 0.3 on low flow blended nasal cannula will have consideration of the following interventions in attempt to wean off oxygen. Prior to initiation, a discussion with parents regarding the speculative benefits of these treatments should occur.

1. At 34 weeks postmenstrual age: institute a trial of furosemide (Lasix) a 2 mg/kg/day po daily x 7 days.
   If trial results in reduction of oxygen need, consideration should be given to initiation of long-term chlorothiazide (Diuril) at 40 mg/kg/day (+/- sodium and potassium supplements.

AND/ OR
2. At 34 weeks postmenstrual age for persistent supplemental oxygen need +/- diuretic trial: institute prednisolone at 1 mg/kg/dose q 8 hours x 72 hours.
   Infants should be observed for rebound oxygen need for 5-7 days post steroid use.

RELATIVE CONTRAINDICATIONS
1. Lasix: hypokalemia or nephrocalcinosis
2. Prenisolone/methylprednisolone: hypertension

These clinical practice recommendations should be considered as suggested clinical practice and the choice to pursue these treatment options will remain at the discretion of rounding neonatologist or fellow.

Suggested reading:
d. GENTAMYCIN DOSING

NICU GENTAMICIN DOSING

<table>
<thead>
<tr>
<th></th>
<th>&lt; 1250 grams</th>
<th>&gt; 1250 grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 days of age</td>
<td>4 mg/kg/dose q 48 hrs</td>
<td>4 mg/kg/dose q 24 hrs</td>
</tr>
<tr>
<td></td>
<td>Levels if treating &gt; 72 hrs</td>
<td>Levels if treating &gt; 72 hrs</td>
</tr>
<tr>
<td></td>
<td>Contact Pharmacy to set up levels</td>
<td>Contact Pharmacy to set up levels</td>
</tr>
<tr>
<td>ANY Neonate with</td>
<td>4 mg/kg/dose – one dose only</td>
<td>4 mg/kg/dose – one dose only</td>
</tr>
<tr>
<td>renal dysfunction</td>
<td>Contact Pharmacy for gentamicin levels and</td>
<td>Contact Pharmacy for gentamicin levels and</td>
</tr>
<tr>
<td>or asphyxia at</td>
<td>maintenance dosing</td>
<td>maintenance dosing</td>
</tr>
<tr>
<td>birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 7 days of age</td>
<td>3 mg/kg/dose q 12 - 24 hrs</td>
<td>No gentamicin levels until after culture results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>are known</td>
</tr>
</tbody>
</table>

Gentamicin Dosing Table for infants < 7 days old (round to nearest 0.5 mg):

<table>
<thead>
<tr>
<th>Weight (grams)</th>
<th>Dose (mg)</th>
<th>Interval (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>4</td>
<td>48</td>
</tr>
<tr>
<td>1100</td>
<td>4.5</td>
<td>48</td>
</tr>
<tr>
<td>1200</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>1300</td>
<td>4.5</td>
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</tr>
<tr>
<td>1400</td>
<td>5.5</td>
<td>24</td>
</tr>
<tr>
<td>1500</td>
<td>6</td>
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<td>1600</td>
<td>6.5</td>
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</tr>
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<td>7</td>
<td>24</td>
</tr>
<tr>
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<td>7.5</td>
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</tr>
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<td>7.5</td>
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<td>2100</td>
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<td>9</td>
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<tr>
<td>2300</td>
<td>9.5</td>
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</tr>
<tr>
<td>2400</td>
<td>9.5</td>
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</tr>
<tr>
<td>2500</td>
<td>10</td>
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</tr>
<tr>
<td>2600</td>
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</tr>
<tr>
<td>2700</td>
<td>11</td>
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<tr>
<td>2800</td>
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<tr>
<td>2900</td>
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<tr>
<td>3000</td>
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<tr>
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</tr>
<tr>
<td>3400</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>3500</td>
<td>14</td>
<td>24</td>
</tr>
</tbody>
</table>

1 Children’s Hospitals and Clinics 09/97 – Based on data collected at St Paul 1996
e. HYPERKALEMIA

MANAGEMENT OF HYPERKALEMIA IN VLBW INFANTS

1. Maintenance fluids: 80 – 100 cc/kg/day D5W. If blood sugar is > 100 mg%, begin regular insulin normal saline, 0.1 units/kg/hour. Titrate infusion rate to keep blood sugar 100 – 200 mg%.

2. Blood sugar should be monitored every hour until stable, then every two hours. If blood sugar or if serum potassium continues to rise, increase insulin infusion rate by .05 cc/kg/hr. If blood sugar is < 100 mg%, insulin infusion should be stopped. Any changes in insulin infusion rate should be blood sugar within one hour.

3. Additional treatment for hyperkalemia:
   Sodium bicarbonate, 1 – 3 mEq/kg IV over 3 – 5 minutes;
   Calcium gluconate (10%), 0.2 – 0.5 cc/kg IV over 2 – 5 minutes.
   NOTE: Calcium gluconate is not compatible with sodium bicarbonate.
f. RAPID SEQUENCE INTUBATION MEDICATIONS

Rapid sequence intubation medications should be given as a push in the following order for all NON-EMERGENT intubations in the NICU.

1. Atropine 0.01 mg/kg (minimum dose 0.1 mg)
2. Morphine 0.1 mg/kg
3. Rocuronium 1 mg/kg

The rocuronium typically takes two minutes to go into effect, so do not give a second dose until you have waited at least two minutes to see any effect.
g. NARCOTICS

Individual clinical circumstances may require a change from the suggested guidelines.

NARCOTICS for PAIN or SEDATION

Narcotics should be prescribed for pain control according to our guidelines for postoperative analgesia and for procedures. There is no concerted effort to not treat pain, particularly post-operatively. However, we should administer analgesics according to guidelines and be mindful of the side effects of prolonged exposure to narcotics.

Narcotics should not routinely be used for sedation of infants receiving mechanical ventilation. Alternative drugs for sedation include Ativan and chloral hydrate.

Morphine may be a better choice than fentanyl because of less chance of chest wall rigidity or laryngospasm following rapid administration. One study comparing continuous infusions of morphine and fentanyl in neonates found an average 9.6-day delay in discharge of infants who received fentanyl.

Intermittent doses of narcotics are generally preferable to continuous infusions. Continuous infusions predispose an infant to more complications/side effects, including gut hypomotility, urinary retention, and addiction. Infusions may be more practical in certain conditions, such as postoperative gastroschisis where both paralysis and prolonged narcotic administration may be needed. High frequency oscillatory ventilation and congenital diaphragmatic are examples where sedation rather than pain control are important.
h. VITAMIN D SUPPLEMENTATION TO PREVENT OSTEOPENIA OF PREMATURITY

**Recommendation**
All infants born at < 34 weeks gestation should be started on Vitamin D 400 IU/day PO/NG at the time of birth.

** This should be initiated regardless if the patient is otherwise NPO **

**Screening Labs**
Vitamin D panel should be assessed after one month of therapy, and monthly thereafter (goal 25 (OH)-D level > 50 nmol/L). Alkaline phosphatase should be assessed per NICU practice.

** Vitamin D supplementation will be discontinued if the infant is receiving > 16 ounces/day of formula, the alkaline phosphatase is < 400, or the vitamin D laboratories indicate excessive levels. **

**Rationale**
55% of ELBW infants and 23% of VLBW infants have low bone mineralization due to premature birth. It is reported that up to 25% of VLBW infants have overt fractures during their hospitalization. Inadequate calcium and phosphorus as well as inadequate vitamin D levels are major contributors to premature infant metabolic bone disease (rickets/osteopenia). Many pregnant mothers are vitamin D deficient. Infants receive their vitamin D supply via the mother in utero and get approximately 50 – 70% of the level of the mother.

i. INDOMETHACIN FOR I VH PREVENTION IN ELBWS

Recommendation

All infants born < 1000 gm should have indomethacin prophylaxis initiated at 3 – 6 hours of life for the prevention of intracranial hemorrhage. Dosing is indomethacin 0.1 mg/kg/dose q 24 hrs x 3 doses. First dose should be given between 3 – 6 hours of life.

** Routine echocardiogram at 72 hrs of life is no longer warranted and should be obtained only if the infant is having signs/symptoms of a patent ductus arteriosus. **

** If the infant requires hydrocortisone, dosing should be delayed by 24 hours from the most recent indomethacin dose.

Rationale

### III. APPENDIX

#### a. 2008 ANTIBIOGRAM

<table>
<thead>
<tr>
<th>Gram Positive Organisms</th>
<th>2008 Percent Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>~</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>Methicillin Sensitive, Methicillin Resistant **</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Enterococcus faecalis and other species</td>
</tr>
<tr>
<td>Streptococcus agalactiae (group B Streptococcus)</td>
<td>Streptococcus pneumoniae (all except blood and CSF)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae (blood and CSF)</td>
<td>Streptococcus pneumoniae (blood and CSF isolates only)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. Tested</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>448</td>
<td>91 15 0 100</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>915</td>
<td>67 8 100 33</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>678</td>
<td>18 245 24 38 91</td>
</tr>
<tr>
<td>Enterococcus faecalis and other species</td>
<td>18</td>
<td>245</td>
</tr>
<tr>
<td>Streptococcus agalactiae (group B Streptococcus)</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>Streptococcus pneumoniae (all except blood and CSF)</td>
<td>91</td>
<td>33</td>
</tr>
<tr>
<td>Streptococcus pneumoniae (blood and CSF)</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae (blood and CSF isolates only)</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

**MRSA prevalence = 38% (of all patients with a positive S. aureus isolate)**

Vancomycin indications: 1) Vancomycin-requiring organism. 2) Empiric (<72 hours) in: a critically ill child with a suspected Vancomycin-requiring organism, meningitis or other serious infection caused by resistant *Streptococcus pneumoniae*; patients with prosthetic cardiac devices and/or CNS shunts; or febrile, neutropenic patients with at least one blood culture for gram positive cocci in clusters. 3) Treatment or prophylaxis of a serious gram-positive organism in a patient who is allergic to penicillins or cephalosporins. 4) A febrile neutropenic patient who continues to have fevers on standard antibiotics for >72 hours without a positive blood culture. 5) Treatment of *Clostridium difficile* colitis resistant to metronidazole or is life threatening. 6) Endocarditis prophylaxis as recommended by the American Heart Assn. 7) Treatment of known or suspected necrotizing enterocolitis in the NICU.

### 2008 Antibiogram & Antibiotic Cost Data

| Pat Ackerman, Laboratory x56004 Pharmacy x66962 (STP); x57259 (Mpls) |

<table>
<thead>
<tr>
<th>Comparative Daily Drug Costs for Typical (10 kg Patient) Doses of IV Antibiotics on Formulary *</th>
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</thead>
<tbody>
<tr>
<td><strong>Daily Dose</strong></td>
</tr>
<tr>
<td><strong>mg/kg/day</strong></td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
</tr>
<tr>
<td>Gentamicin</td>
</tr>
<tr>
<td>Tobramycin</td>
</tr>
<tr>
<td>Amikacin</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
</tr>
<tr>
<td>Cefazolin</td>
</tr>
<tr>
<td>Cefuroxime</td>
</tr>
<tr>
<td>Cefotaxime</td>
</tr>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Ceftazidime</td>
</tr>
<tr>
<td><strong>Penicillins</strong></td>
</tr>
<tr>
<td>Ampicillin</td>
</tr>
<tr>
<td>Amp/Sulbactam</td>
</tr>
<tr>
<td>Oxacillin</td>
</tr>
<tr>
<td>Penicillin (units)</td>
</tr>
<tr>
<td>Pip/Tazobactam</td>
</tr>
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<td><strong>Miscellaneous</strong></td>
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</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Meropenem</td>
</tr>
<tr>
<td>TMP/SMX</td>
</tr>
<tr>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

* Dose & frequency may vary due to infection type and severity
### Children's Hospitals & Clinics of Minnesota 2008 Antibiogram

<table>
<thead>
<tr>
<th>Gram Negative Organisms</th>
<th>Acinetobacter calcoaceticus baumanii complex</th>
<th>Achromobacter xylosoxidans</th>
<th>Citrobacter freundii</th>
<th>Enterobacter aerogenes</th>
<th>Enterobacter cloacae</th>
<th>Eschericia coli *</th>
<th>Haemophilus influenzae</th>
<th>Klebsiella oxytoca</th>
<th>Klebsiella pneumoniae</th>
<th>Proteus mirabilis *</th>
<th>Pseudomonas aeruginosa mucoid strains (with Cystic Fibrosis)</th>
<th>Pseudomonas aeruginosa, matte strains (without Cystic Fibrosis)</th>
<th>Salmonella typhimurium</th>
<th>Shigella sonnei</th>
<th>Stenotrophomonas maltophilia</th>
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<tbody>
<tr>
<td><strong>No. Tested</strong></td>
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<td>58</td>
<td>125</td>
<td>86</td>
<td>19</td>
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<tr>
<td><strong>% Susceptible</strong></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
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<tr>
<td>Ceftriaxone **</td>
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<td>90</td>
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<td>96</td>
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</tr>
<tr>
<td>Meropenem</td>
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<td>Piperacillin-Tazobactam</td>
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<td>96</td>
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<tr>
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<td>100</td>
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<td>94</td>
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<tr>
<td>TMP/SMX</td>
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<td>100</td>
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<td>74</td>
<td>100</td>
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<td>39</td>
<td>1</td>
<td>100</td>
<td>94</td>
<td>77</td>
</tr>
</tbody>
</table>

* nitrofurantoin susceptibility (Escherichia coli – 97% and Proteus mirabilis – 0%)
** cefotaxime susceptibility is similar

Revised 6/09 by Pat Ackerman (Laboratory) and David Hoff, PharmD (Pharmacy)
DI SC HARGE FRO M T H E NI CU

I. Discharge Planning
II. ROP Screening Guidelines
I. DISCHARGE

Notify one of the discharge coordinators as soon as you have a tentative discharge date set for a NICU patient. They will schedule all needed tests, parent teaching, home nursing visits, home supplies and equipment, and follow-up appointments.

Discharge coordinators are:
1) Karleen Maeurer, RN: Phone: 67930
   Voicemail: 66218
2) Deborah Sullivan, RN: Phone: 67931
   Voicemail: 66208

I. BACK TO SLEEP POSITIONING PROTOCOL:
Talk to parents and staff when infant is bottle/breast feeding at least ½ of feedings (in order to model appropriate positioning for home).

II. BILIRUBIN:
Every infant admitted to the NICU should have had at least one bilirubin level checked during its hospitalization.

III. CAR BED:
Discharge coordinator will arrange for car beds when indicated. Most infants < 1800 grams will be too short (from shoulders to hips) to fit the car seat straps. Rental car beds are available M-F 8am – 4pm in the family resource center on 4th floor of Garden View.

IV. CAR SEAT TRIAL:
   a. For all infants < 37 weeks gestation at birth
   b. Usually done the day the MMU/CR scan is read. If infant fails MMU, CR scan, then car seat trial will not be done. If monitor is d/c’d, notify the discharge coordinator to arrange for car seat trial.

V. CIRCUMCISION:
   a. Parents must check with insurance re: inpatient/outpatient coverage for circumcisions. Medical Assistance and other carriers may not cover inpatient circs.
   b. Discharge coordinator will arrange with primary MD. If primary MD doesn’t do circumcisions for newborns at Children’s, the discharge coordinator will check with the Children’s Group who will usually perform circumcisions if their schedule allows. Outpatient circumcisions can also be arranged.
VI. TRAINING FOR PARENTS:
   a. CPR: up to 6 adults in class. Discharge coordinator can arrange with RCP for individual family class when requested by parents.
   b. Reflux Class: a 2-hour class that teaches infant CPR and reflux precautions. Available M-F 8 am - 2pm (class ends at 4 pm). Allow extra time if using interpreter.
   c. Monitor class: A 4-hour class that teaches infant CPR, use of home monitor, and caffeine administration.
   d. Other equipment training: (oxygen/nebulizer/home equipment for GT/Trach) will be arranged by discharge coordinator.

VII. FEEDINGS:
   a. Change to 22 calorie if infant is > 2 kg and discontinue HMF if infant is > 35 wks corrected age. (Transition is usually done when infant is feeding full bottles/breast 4-5 feedings per day)
   b. Discontinue supplemental protein before discharge
   c. 22 cal/oz: (in-house may NOT use powder)
      Use Enfacare 22/Neosure 22 OR
      MBM + Enfamil/Similac concentrate (to = 22 cal/oz)
   d. **If infant is < 2kg discharge home on 24 calorie/oz. feedings

VIII. F/U TESTING:
   a. Echocardiogram (? needed before discharge)
   b. HUS: If gestational age < 30 weeks or birth weight < 1500 grams get a HUS at 1 week of life. Check with Neonatologist at 1 month to determine if second HUS is indicated at one month or at discharge.
   c. Renal U/S: Check diagnosis to determine need for follow up renal u/s.
   d. Hemoglobin: Obtain hemoglobin week of discharge
   e. Eye exam: (See ROP Screening attachment)
   f. Do any consultants need to see infant prior to discharge?

IX. HEARING TEST:
   OAE in hospital, usually done when car seat trial is done. If infant fails OAE a BAER is done in the hospital. If infant fails BAER will need to have audiology follow-up scheduled.

X. IMMUNIZATIONS:
   a. Per federal law, parental permission must be obtained prior to giving immunizations.
   b. Current immunization information can be downloaded from www.immunize.org (bedside RN can download this info and give to parents).
   c. Give Engerix-B (0.5ml) IM at discharge or at one month of age if infant is thriving.
XI. MEDICATIONS:
Change from iron to Poly-vi-sol with Iron or Tri-vi-sol with Iron
* If infant is on iron at 35 weeks gestation, see Nutrition handout for specifics

XII. MMU vs. CR SCAN:
a. MMU for all infants < 34 weeks gestation and any infant (regardless of gestational age) who has experienced clinical apnea
b. CR scan for all infants being discharged home on oxygen or if there is concern over oxygenation, as in infant with BPD.
c. For both MMU and CR scan, specify whether head of bed should be elevated or flat.

XIII. NEWBORN SCREENS: (order on day of admission)
a. If birth weight < 1800 grams newborn screen should be obtained:
   - DOL # 2
   - DOL # 14
   - DOL # 30
   - If infant is discharged BEFORE day # 30, the 3rd newborn screen must be drawn on day of discharge (call unit coordinator to arrange)
b. Phone number for the Minnesota Department of Health for Newborn Screens: 612-676-5260
c. Repeat newborn screen before discharge if initial screen was invalid secondary to blood transfusions (metabolic diseases can be picked up). Repeat newborn screen 3-4 months after last transfusion (hemoglobinopathies can be detected at this time).

XIV. NICU NEURODEVELOPMENTAL FOLLOW-UP CLINIC:
Eligibility:
a. ≤ 30 weeks and/or 1500 grams
b. Neonatal seizures or significant neurologic problem
c. Hypoxic-ischemic encephalopathy treated with total body cooling.
d. Complicated or prolonged mechanical ventilator course
e. Other situations will necessitate NICU F/U Clinic referral and eligibility should be determined with attending
II. ROP SCREENING GUIDELINES

EVIDENCE BASED/BEST PRACTICE ROP SCREENING

ROP screening criteria:

- All infants weighing 1500 grams or less at birth
  
  OR
  
- Gestational age less than 31 weeks (30 6/7 weeks and less).
- No infants > 2000 grams at birth
- 1500 grams to 2000 grams birth weight and considered high risk for ROP with at least one of the following occurring at <28 days of age:
  - Surgical necrotizing enterocolitis
  - Confirmed sepsis with significant cardiovascular (high dose pressors) or respiratory instability (ventilated with pneumothoraces, significant instability)
  - Intraventricular hemorrhage > grade 2
  - Use of inhaled nitric oxide for PPHN
  - High frequency ventilation with significant PO2 or PCO2 lability
- Additional selected infants believed to be high risk by their treating neonatologist and are > 30 weeks gestation
- Retinal exams to classify, diagram and record, will be performed by an experienced ophthalmologist using the “International Classification of Retinopathy of Prematurity Revisited”.
- The initial exam will be based on gestational age at birth plus chronological age

**Recommended Schedule for Initial Exams**

<table>
<thead>
<tr>
<th>Gestational Age at Birth (weeks)</th>
<th>Corrected Age (weeks)</th>
<th>Chronological Age (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22a</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>23a</td>
<td>31</td>
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<td>4</td>
</tr>
<tr>
<td>30</td>
<td>34</td>
<td>4</td>
</tr>
</tbody>
</table>

a Tentative guideline; small number of survivors at this GA

GA 31 – 32 weeks will be seen at 4 weeks of age, when indicated.
• Follow-up exams and any necessary treatment will be determined by the ophthalmologist based on findings of the exam
• Parents of infants with ROP should be educated about ROP and the possible consequences of the disorder. They should be updated on an ongoing basis and understand the need for follow-up care even after discharge
• Services for follow-up ROP eye care needs to be available for each infant discharged or transferred. The accepting physician must be informed of the plan for the follow-up eye care.
I. Newborn Resuscitation and Intubation Guidelines
II. First Hour of Life Protocol
III. Surfactant Therapy
IV. Gestational Age Assessment
V. Group B Streptococcal Infections
VI. Blood Product Transfusion Guidelines
VII. ROP Surveillance
VIII. Intraventricular Hemorrhage
IX. 1-2-3 MN Newborn Hearing Screening Program
X. MN State Newborn Screening
XI. Osteopenia of Prematurity
XII. Cleft Lip or Palate
XIII. Organ Donation
XIV. End of Life Care
XV. Immunizations
XVI. References
I. NEWBORN RESUSCITATION AND INTUBATION GUIDELINES

All house staff will be NRP certified (5th Edition, 2006 NRP Textbook). House staff will become NRP competent by attending neonatal simulations and supervised deliveries.

Over 90% of newborns make the transition from intrauterine to extra-uterine life without little or no assistance. Approximately 10% require some assistance, and 1% require intensive resuscitative measures to restore their cardiopulmonary function.

“ABCs” of resuscitation are the same for neonates as for adults. Interactive Apgar scoring is documented at one and five minutes after birth. When five-minute Apgar is less than 7, additional scores should be assigned every five minutes for up to 20 minutes.

<table>
<thead>
<tr>
<th>SIGN</th>
<th>0</th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>Color</td>
<td>Blue or Pale</td>
<td>Acrocyanotic</td>
<td>Completely Pink</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Absent</td>
<td>&lt; 100 minute</td>
<td>&gt; 100 minute</td>
</tr>
<tr>
<td>Reflex</td>
<td>No Response</td>
<td>Grimace</td>
<td>Cry or Active Withdrawal</td>
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<tr>
<td>irritability</td>
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<tr>
<td>Muscle Tone</td>
<td>Limp</td>
<td>Some Flexion</td>
<td>Active Motion</td>
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<td>Respiration</td>
<td>Absent</td>
<td>Weak Cry: Hypoventilation</td>
<td>Good, crying</td>
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APGAR Score

Gestational Age __________ weeks

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</tr>
<tr>
<td>ETT</td>
<td></td>
</tr>
<tr>
<td>Chest Compressions</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
</tr>
</tbody>
</table>
Complete documentation of the events taking place during resuscitation must also include a narrative description of all interventions performed.
INTUBATION GUIDELINES FOR NEONATES

Pediatric residents, by the end of their residency training, will be proficient at neonatal airway management, including intubations, bag/mask ventilation, Neopuff ventilation, and oral airway placement. Intubation attempts should not compromise patient stability. Patients should maintain a heart rate greater than or equal to 100 beats/minute, and oxygen saturation greater than or equal to 90%. The most experienced provider available should perform the intubations on unstable neonates or neonates at risk for adverse outcomes. These cases include:

- extremely preterm neonates (less than or equal to 26 weeks’ gestation);
- unstable neonates (unable to establish oxygenation with positive pressure ventilation);
- and neonates requiring CPR;

and certain congenital anomalies:

- congenital diaphragmatic hernia;
- known airway obstruction;
- micrognathia;
- cleft palate;
- hydrops.

Pre-medication with atropine, morphine, and a short-acting muscle relaxant should be used for all non-emergent intubations. This has been shown to decrease the time and number of attempts needed to successfully intubate and reduce the incidence of severe desaturations.

**Endotracheal tube size for babies of various weights and gestational ages**

Select the appropriate-sized tube

<table>
<thead>
<tr>
<th>Tube size (mm) (inside diameter)</th>
<th>Weight (g)</th>
<th>Gestational Age (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>Below 1000</td>
<td>Below 28</td>
</tr>
<tr>
<td>3.0</td>
<td>1000 – 2000</td>
<td>28 – 34</td>
</tr>
<tr>
<td>3.5</td>
<td>2000 – 3000</td>
<td>34 – 38</td>
</tr>
<tr>
<td>3.5 – 4.0</td>
<td>Above 3000</td>
<td>Above 38</td>
</tr>
</tbody>
</table>

**Depth of insertion**

Estimated distance from tip of tube to baby’s lip, based on baby’s weight

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Depth of Insertion (cm from upper lip)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

* Babies weighing less than 750 g may require only 6 cm insertion.
Umbilical vein – to junction of inferior vena cava and right atrium
Umbilical artery – to bifurcation of aorta

Proper position of ETT verified clinically, CO₂ detection and radiologically. Determination of length of catheter to be inserted for appropriate arterial or venous placement. UAC (high) = 3 x BW + 9. UVC = ½ UAC + 1.

II. FIRST HOUR OF LIFE PROTOCOL

Criteria for Inserting Central Lines:
- If infant is <1kg and is intubated, place UAC/UVC.
- If infant is < 1kg and is stable on CPAP or NC, place UAC and PIV.
- If infant is > 1kg and is intubated, place UAC if frequent lab or BP monitoring is anticipated. Consider UVC if needed for medications or long term TPN.
- If infant is > 1kg and is stable on CPAP or NC place PIV only
- If attempts at placing umbilical lines are unsuccessful after 20-30 minutes, procedure should be aborted and PIV placed. However, every effort should be made to procure blood for initial lab evaluation at this time.
- For stable infants who need central IV access try to place a PICC within 3 days of life and remove UVC by day of life 3 if possible.
- If infant is unstable, requiring pressors or PGE umbilical venous catheter may be left in place longer than 3 days
- Consider double lumen UVC only if infant is >1kg and if multiple access is needed (PPHN, cardiac dz, etc)

Upon Admission to NICU:
- The infant’s initial glucose should be checked within 30 minutes of birth (not admission). It may be drawn from UVC if UVC is being inserted (NNP to insert low UVC, draw labs, wait for glucose results and then advance UVC. If glucose if low, a D10W bolus can be administered safely through a low UVC before UVC is advanced).
- Follow up glucoses should be checked at 1 hr and 1 ½ hrs of life with all high-risk infants.
- Admission nurse should draw initial labs (if no central lines placed). Use IRMA for initial blood gas, Hct and glucose. If admission nurse is uncomfortable drawing initial labs, she/he should ask for assistance.
- A mask/cap must be worn by anyone in the infant’s room during UAC/UVC insertion
- Consider pushing first dose of Ampicillin (obtain from Pyxis)
- Goal is to have infants admitted, stable and antibiotics started within 1 hour of birth
III. SURFACTANT THERAPY

Pulmonary surfactant is a complex of phospholipids, neutrolipids, and specific proteins - SB-B, -C, -A, -D. Pulmonary surfactant reduces the collapsing force in the alveolus, confers mechanical stability to the alveoli, and maintains the alveolar surface relatively free of liquid. Administration of a natural animal-derived surfactant to surfactant-deficit newborn decreases the minimum pressure required to open the lung, increases the minimal lung volume, and prevents lung collapse at low pressure.

Exogenous Surfactants
Natural surfactants (mammalian surfactant preparations) are purified and extracted with organic solvents from either lung minces or lung lavages. Their phospholipid concentration is greater than 80%, and all contain the low molecular-weight hydrophobic proteins – SP-B and SP-C.

Entirely synthetic surfactants are composed mainly of DPPC (dipalmitoylphosphatidylcholine). The current new generation of synthetic surfactants contain phospholipids and chemically or genetically engineered peptide analogs of SP-B. Example is Lucinactant (Surfaxin).

TABLE OF SURFACTANTS

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Origin</th>
<th>Characteristics</th>
<th>Protein</th>
<th>First Dose (mg/kg)</th>
<th>Additional doses (maximal number) (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natural Surfactants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infasurf</td>
<td>Calf lung lavage</td>
<td>Chloroform/methanol extracted</td>
<td>SP-B/SP-C</td>
<td>105 (3)</td>
<td>Max 2 doses at least q12h; 105 (3)</td>
</tr>
<tr>
<td>BLES</td>
<td>Cow lung lavage</td>
<td>Chloroform/methanol extracted</td>
<td>SP-B/SP-C</td>
<td>135 (5)</td>
<td>Max 2 doses at least q6h; 135 (5)</td>
</tr>
<tr>
<td>Survanta</td>
<td>Minced bovine lung extract</td>
<td>Enriched with DPPC, tripalmitolglycerol, and free fatty acids</td>
<td>SP-C/low SP-B content</td>
<td>100 (4)</td>
<td>Max 3 doses at least q6h; 100 (4)</td>
</tr>
<tr>
<td>Curosurf</td>
<td>Minced porcine lung extract</td>
<td>No neutral lipids (liquidgel chromatography)</td>
<td>SP-B/SP-C</td>
<td>100 – 200 (1.25 – 2.5)</td>
<td>Max 2 doses at least q6h; 100 (1.25)</td>
</tr>
<tr>
<td><strong>Synthetic Surfactants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exosurf*</td>
<td>Synthetic preparation</td>
<td>DPPC + hexadecanol (9%) + tyloxapol (6%)</td>
<td>0</td>
<td>67 (5)</td>
<td>Max 2 doses at least q12h; 67 (5)</td>
</tr>
<tr>
<td>Surfaxin</td>
<td>Synthetic preparation</td>
<td>DPPC/POPG 3/1 + free fatty acids (palmitic acid)</td>
<td>Sinapultide (3%)</td>
<td>175 (5.8)</td>
<td>Max 2 doses at least q6h; 175 (5.8)</td>
</tr>
</tbody>
</table>

*Not available in North America
Studies demonstrated 40% reduction in the odds of neonatal death after surfactant treatment, either natural or synthetic administered as a prophylactic or rescue treatment. Both types of surfactant and both treatment strategies have significantly reduced the risk of pulmonary air leaks by 30-50%. Chronic lung disease has not been significantly reduced because the increase in survival is mainly among extremely premature infants.

Prophylactic treatment (treatment within the first 30 minutes of birth), instilling surfactant before the onset of respiratory distress syndrome, has been shown to partially avoid barotrauma and vascular injury resulting from mechanical ventilation. Infants born at, or less than, 26 weeks’ gestation are eligible for prophylactic treatment.

Early rescue (before two hours of life) is associated with decreased risk of neonatal mortality and significant reduction in the incidence of pneumothorax. Infants born at greater than 26 weeks’ gestation, and less than 32 weeks, should receive surfactant without delay if they require supplemental oxygen with FiO₂ greater than 0.3 on nasal CPAP or mechanical ventilation at 90 minutes of life.

Inactivation of surfactant is involved in the pathogenesis of various respiratory disorders, including meconium aspiration syndrome, pneumonia, and sepsis. These disorders may represent potential targets for surfactant therapy.

**Administration**

Dosing is usually two divided aliquots and administered via a catheter in the endotracheal tube. Infants are manually ventilated during administration to ensure maximal dispersion. Each half-dose is injected over 1-2 minutes, and infant’s head and torso are rotated 30-45 degrees to the right for the first half-dose, and 30-45 degrees to the left for the second half-dose. Transient oxygen desaturation and mild bradycardia are frequently observed during administration, and may require adjustments of the ventilation and FiO₂ or interruption of surfactant administration. Improvement in gas exchange after administration is usually rapid (within a few minutes) and ventilation pressure and volume must be adjusted while monitoring tidal volume and PaCO₂. Because oxygenation improves rapidly, continuous monitoring of oxygen saturation during and after administration is mandatory. Approximately one-third of treated infants still require mechanical ventilation with an FiO₂ greater than 0.3, six hours after the first dose; these infants are eligible for retreatment. Infants less than 26 weeks’ gestation with a diagnosis of respiratory distress syndrome may receive a second dose of surfactant, if they continue intubated on mechanical ventilation, regardless of the inspired oxygen concentration. Infants greater than 26 weeks’ gestation with a diagnosis of respiratory distress syndrome should receive a second dose, if they continue on mechanical ventilation and require greater than 30% inspired oxygen. If infant remains intubated on oxygen concentration between 21-29%, consider a second dose of surfactant. There is no proven benefit to more than two additional doses.
IV. GESTATIONAL AGE ASSESSMENT

As part of the admission examination, gestational age assessment (Ballard) is performed. This is compared to gestational age determination by dating and/or early fetal ultrasound, if available. Growth measurements are plotted at established gestational age and recorded.

An example of outcomes is included.

### Survival and Neurologic Disability Rates in Prematurely Born Infants

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Severe*</td>
<td>Moderate**</td>
</tr>
<tr>
<td>&lt;23</td>
<td>&lt;2%</td>
<td>7%</td>
<td>0% (9)*</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>23 ½/7 to 23 6/7</td>
<td>15%</td>
<td>30%</td>
<td>32% (24)</td>
<td>25 – 60%</td>
<td>20 – 30%</td>
</tr>
<tr>
<td>24 ½/7 to 24 6/7</td>
<td>35%</td>
<td>57%</td>
<td>75% (23)</td>
<td>25%</td>
<td>20 – 30%</td>
</tr>
<tr>
<td>25 ½/7 to 25 6/7</td>
<td>60%</td>
<td>72%</td>
<td>66% (27)</td>
<td>20%</td>
<td>20 – 30%</td>
</tr>
<tr>
<td>26 ½/7 to 26 6/7</td>
<td>80%</td>
<td>85%</td>
<td>91% (34)</td>
<td>10 – 20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

VO Network is the Vermont Oxford Network.

* (N) = Number of patients in each gestation age category.

* Severe Disability = Developmental IQ < 70 (or 2 SD below the mean) or cerebral palsy or blind or deaf.

** Moderate Disability = Developmental IQ 70 – 84 (or 1 – 2 SD below the mean). Moderate disorders of tone, movement or vision included in some references.

** Percentages are of all survivors eligible for follow-up.

<table>
<thead>
<tr>
<th>Weeks at Birth</th>
<th>Survivors with no significant neurologic injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;23</td>
<td>?</td>
</tr>
<tr>
<td>23 ½/7 to 23 6/7</td>
<td>44%</td>
</tr>
<tr>
<td>24 ½/7 to 24 6/7</td>
<td>64%</td>
</tr>
<tr>
<td>25 ½/7 to 25 6/7</td>
<td>62%</td>
</tr>
<tr>
<td>26 ½/7 to 26 6/7</td>
<td>63%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weeks at Birth</th>
<th>Pregnancies that result in survival and no significant neurologic injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;23</td>
<td>?</td>
</tr>
<tr>
<td>23 ½/7 to 23 6/7</td>
<td>14%</td>
</tr>
<tr>
<td>24 ½/7 to 24 6/7</td>
<td>48%</td>
</tr>
<tr>
<td>25 ½/7 to 25 6/7</td>
<td>41%</td>
</tr>
<tr>
<td>26 ½/7 to 26 6/7</td>
<td>57%</td>
</tr>
</tbody>
</table>
V. GROUP B STREPTOCOCCAL INFECTIONS

Group B streptococcus remains the most common cause of neonatal bacterial infections in the United States in infants >2500 gms. The mainstay for prevention of Group B strep infections in neonates, as suggested by the CDC, is screening pregnant women for Group B strep colonization and providing intrapartum antibiotic prophylaxis (IAP).

Approximately 30% of women have asymptomatic Group B strep colonization during pregnancy. Nearly 50% of infants who pass through a colonized birth canal become colonized, and 1-2% of colonized infants developed invasive disease; 75% of cases of Group B strep infections are early onset (0-6 six days). Most infants with early onset disease become ill within the first 24 hours. Transmission is vertical in nearly all cases, and occurs shortly before or during delivery. Septicemia occurs in 25-40%, pneumonia 35-55%, and meningitis in 5-10%. Mortality is 4-6%, and higher in preterm infants.

Late onset disease occurs at 3-4 weeks with a range of 7 days-3 months. Term and preterm infants are equally susceptible. Intrapartum antibiotic prophylaxis has not decreased the incidence of late onset disease. Late onset Group B strep disease presents as bacteremia, meningitis, osteomyelitis, septic arthritis, adenitis, and cellulitis. Transmission is mainly horizontal.

Universal screening of all pregnant women at 35-37 weeks’ gestational age is a recommended standard of care. Intrapartum prophylaxis is indicated for all Group B strep carriers, except for those where cesarean section delivery is planned in the absence of labor with intact membranes.
Indications for intrapartum antimicrobial prophylaxis (IAP) to prevent early-onset group B streptococcal (GBS) disease using a universal prenatal culture screening strategy at 35 to 37 weeks’ gestation for all women.

**IAP INDICATED**
- Previous infant with invasive GBS disease
- GBS bacteriuria during current pregnancy
- Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery is performed in the absence of labor or membrane rupture)
- Unknown GBS status AND any of the following:
  - Delivery at < 37 weeks’ gestation
  - Membranes ruptured for > 18 hours
  - Intrapartum fever (temperature ≥ 38.0°C [> 100.4°F])

**IAP NOT INDICATED**
- Previous pregnancy with a positive GBS screening culture (unless a culture also was positive during the current pregnancy or previous infant with invasive GBS disease)
- Planned cesarean delivery performed in the absence of labor or membrane rupture (regardless of GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation, regardless of intrapartum risk factors

1 Exceptions: women with GBS bacteriuria during the current pregnancy or women with a previous infant with invasive GBS disease.
2 If chorioamnionitis is suspected, broad-spectrum antimicrobial therapy that includes an agent known to be active against GBS should replace GBS IAP.

When appropriate, antibiotics are administered more than four hours prior to delivery; only 1.2% (instead of 47%) of infants are colonized. Appropriate maternal antibiotics are penicillin, ampicillin, cefozolin, and vancomycin.

Incidence of early onset Group B strep disease has decreased to 0.34 cases/1,000 live births with maternal screening and intrapartum antibiotic prophylaxis. (This is down from 1-4 cases/1,000 live births before the above screening and IAP). Ninety-five (95) percent of early onset Group B strep infection presents within the first 24 hours after birth. Management of infants whose mothers received IAP remains controversial. The CDC and AAP provide algorithm for management of infants born to mothers who have received IAP. Full diagnostic work-up includes CBC, CRP, blood culture, and lumbar puncture (if sepsis is suspected). Thirty-eight (38) percent of infants with culture-proving meningitis have negative blood cultures. Chest radiograph should be obtained with respiratory symptoms. Ampicillin and gentamicin are started empirically. Length of therapy depends on the infant’s clinical course and laboratory results.
Empiric management of a neonate whose mother received intrapartum antimicrobial prophylaxis (IAP) for prevention of early-onset group B streptococcal (GBS) disease or suspected chorioamnionitis. The algorithm is not an exclusive course of management. Variations that incorporate individual circumstances or institutional preferences may be appropriate.

1 If no maternal IAP for GBS was administered despite an indication being present, data are insufficient on which to recommend a single management strategy.
2 Includes complete blood cell (CBC) count with differential, blood culture, and chest radiograph if respiratory abnormalities are present. When signs of sepsis are present, a lumbar puncture, if feasible, should be performed.
3 Duration of therapy varies depending on results of blood culture, cerebrospinal fluid findings (if obtained), and the clinical course of the infant. If laboratory results and clinical course do not indicate bacterial infection, duration may be as short as 48 hours.
4 CBC including white blood cell count with differential and blood culture.
5 Applies only to penicillin, ampicillin, or cefazolin and assumes recommended dosing regimens.
6 A healthy-appearing infant who was \( \geq 38 \) weeks' gestation at delivery and whose mother received \( \geq 4 \) hours of IAP before delivery may be discharged home after 24 hours if other discharge criteria have been met and a person able to comply fully with instructions for home observation will be present. If any one of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until criteria for discharge are achieved.
VI. BLOOD PRODUCT TRANSFUSION GUIDELINES

The decision to treat anemia should be based on etiology, severity, and condition of the infant. If infant is born with signs of hypovolemia, shock, or anemia, immediate volume expansion is indicated with saline and plasma, followed by blood if indicated. Packed red blood cells are used routinely. If coagulation factors are needed, use packed red blood cells and fresh frozen plasma. Begin with 20 ml/kg over 30-60 minutes. More may be required, but care must be taken to accurately assess the need for further volume support. Uncross-matched O negative red blood cells are available in an emergency.

If infant develops severe anemia chronically in utero, but is hemodynamically well compensated without findings of hypotension, tachycardia, or poor perfusion, packed red blood cells should be given without delay. Smaller increments should be given – 10 ml/kg – in separate transfusion until hemoglobin normalizes.

If infant is hydropic with severe anemia and variable hemodynamic decompensation, an isovolumetric partial exchange transfusion, using packed red blood cells, should be accomplished without delay.

Pretransfusion work-up: Requires newborn work-up during current admission period.

Surgical RBC ordering recommendations: Newborn open cavity, 20 ml/kg; PDA ligation, 50 ml/kg.

Indications For Transfusion - typically transfuse 10 - 15 ml/kg PRBC
Transfuse for hemoglobin less than 7 gm/100 dl in an asymptomatic infant if reticulocytes are less than 100,000/ml.

Transfuse for hemoglobin less than 10 gm/100 dl with any of the following:
- Requiring oxygen, less than 35% FiO₂;
- Significant apnea and bradycardia while on methylxanthines and requiring intervention (greater than nine episodes in 12 hours, or two episodes in 24 hours requiring mask/bag ventilation);
- If heart rate greater than 180 beats/minute or respirations greater than 80/minute over 24 hours;
- Weight gain less than 10 gm/day over four days, despite adequate calories;
- Scheduled surgery;
- Sepsis.

Transfuse for hemoglobin less than 11 gm/100 dl.
- Oxygen requirement greater than 50% FiO₂;
- IMV/CPAP.
Lasix does not need to be given after routine transfusion.

Irradiated blood should be used:
- When there is a suspicion of immune deficiency (DiGeorge Syndrome, absent thymus, aortic arch abnormality, family history);
- The infant has received intrauterine transfusion and is to receive a double-volume exchange transfusion;
- The blood is from a primary family member (directed donor blood);
- Acellular blood components (fresh frozen plasma and cryoprecipitate) do not need to be irradiated.

**Guidelines For Administering Blood Products**

**Packed red blood cells:** Concentrated red blood cells, have most plasma and platelets removed. CMV safe is either leukocyte-depleted, or CMV negative. Average hematocrit = 55 – 60%. Volume of blood to be available in surgery varies with procedure: rate of transfusion, 5 cc/kg/hour; 2 ml/kg/hour if patient has insipient congestive heart failure.

**Platelets:** Platelets are suspended in a small amount of plasma. Average volume is 50-70 ml/unit. Transfusion guidelines:
- Severe thrombocytopenia (platelet count less than 20,000);
- Platelet count less than 50,000:
  - in patients who require a surgery;
  - in patients with active hemorrhage;
  - risk of eminent bleeding;
  - increased risk for intraventricular hemorrhage (less than 32 weeks post conceptual age).

Higher platelet counts may be used at discretion of neonatologist for extremely low birth-weight premature infants.

Dose is 10-20 cc/kg (one unit for every 10 kg body weight) will increase platelet count by 50,000. Full-volume platelets are preferred to volume-reduced platelets because process of volume reduction activates platelets, causing degranulation, making them less effective.

Administer no faster than 2-3 cc/minute via syringe pump. If volume overload is a problem, administer total dose over 1-2 hours.

**Fresh frozen plasma:** Fresh frozen plasma is the portion of blood that contains clotting factors and protein. Type AB plasma may be used in an emergency. Indications are:
- Massive hemorrhage;
- Multiple clotting deficiencies (liver disease, disseminated intravascular coagulation).

Dose for acute hemorrhage is 15-30 cc/kg. Clotting deficiencies 10-15 cc/kg. May be repeated up to three times each 24 hours as necessary. Monitor for congestive heart failure, secondary to volume overload. Rate of administration for hemorrhage is dependent on patient’s condition. For clotting deficiencies, administer over 2-3 hours.

**Cryoprecipitate:** Cryoprecipitate is concentrated fibrinogen, 15 ml/unit. Indication is hypofibrinogenemia, disseminated intravascular coagulation. Dosage: body weight less than 2.5 kg, give 0.4 units (6 ml/kg of body weight); 2.5-5 kg, give one unit (15 ml); 5-10 kg, give 1-2 units. Infants who can tolerate or who need extra intravascular volume, administer as much of the unit as tolerated to reduce donor exposure.
### Age-Specific Leukocyte Differential

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Leukocytes a</th>
<th>Neutrophils b</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>%</td>
<td>Mean</td>
<td>%</td>
</tr>
<tr>
<td>Birth</td>
<td>18.1 (9-30)</td>
<td>11 (6-26)</td>
<td>61</td>
<td>5.5 (2-11)</td>
<td>31</td>
</tr>
<tr>
<td>12 hr</td>
<td>22.8 (13-38)</td>
<td>15.5 (6-28)</td>
<td>68</td>
<td>5.5 (2-11)</td>
<td>24</td>
</tr>
<tr>
<td>24 hr</td>
<td>18.9 (9-34)</td>
<td>11.5 (5-21)</td>
<td>61</td>
<td>5.8 (2-11.5)</td>
<td>31</td>
</tr>
<tr>
<td>1 wk</td>
<td>12.2 (5-21)</td>
<td>5.5 (1.5-10)</td>
<td>45</td>
<td>5.0 (2-17)</td>
<td>41</td>
</tr>
<tr>
<td>2 wk</td>
<td>11.4 (5-20)</td>
<td>4.5 (1-9.5)</td>
<td>40</td>
<td>5.5 (2-17)</td>
<td>48</td>
</tr>
<tr>
<td>1 mo</td>
<td>10.8 (5-19.5)</td>
<td>3.8 (1-8.5)</td>
<td>35</td>
<td>6.0 (2.5-16.5)</td>
<td>56</td>
</tr>
<tr>
<td>2 mo</td>
<td>11.9 (6-17.5)</td>
<td>3.8 (1-8.5)</td>
<td>32</td>
<td>7.3 (4-13.5)</td>
<td>61</td>
</tr>
<tr>
<td>1 yr</td>
<td>11.4 (6-17.5)</td>
<td>3.5 (1.5-8.5)</td>
<td>31</td>
<td>7.0 (4-10.5)</td>
<td>61</td>
</tr>
<tr>
<td>2 yr</td>
<td>10.6 (6-17)</td>
<td>3.5 (1.5-8.5)</td>
<td>33</td>
<td>6.3 (3-9.5)</td>
<td>59</td>
</tr>
<tr>
<td>4 yr</td>
<td>9.1 (5.5-15.5)</td>
<td>3.8 (1-8.5)</td>
<td>42</td>
<td>4.5 (2-8)</td>
<td>50</td>
</tr>
<tr>
<td>6 yr</td>
<td>8.5 (5-14.5)</td>
<td>4.3 (1-5.5)</td>
<td>51</td>
<td>3.5 (1.5-7)</td>
<td>42</td>
</tr>
<tr>
<td>8 yr</td>
<td>8.3 (4.5-13.5)</td>
<td>4.4 (1-5.5)</td>
<td>53</td>
<td>3.3 (1.5-6.8)</td>
<td>39</td>
</tr>
<tr>
<td>10 yr</td>
<td>8.1 (4.5-13.5)</td>
<td>4.4 (1-5.5)</td>
<td>54</td>
<td>3.1 (1.5-6.5)</td>
<td>38</td>
</tr>
<tr>
<td>16 yr</td>
<td>7.8 (4.5-13.0)</td>
<td>4.4 (1-8.6)</td>
<td>57</td>
<td>2.8 (1.2.5-2)</td>
<td>35</td>
</tr>
<tr>
<td>21 yr</td>
<td>7.4 (4.5-11.0)</td>
<td>4.4 (1-8.7)</td>
<td>59</td>
<td>2.5 (1.4-8)</td>
<td>34</td>
</tr>
</tbody>
</table>

From Dallman

a Number of leukocytes are x 103/mm3; ranges are estimates of 95% confidence limits; percents refer to differential counts.
b Neutrophils include band cells at all ages and a small number of metamyeloocytes and myelocytes in the first few days of life.

### Age-Specific Coagulation Values

<table>
<thead>
<tr>
<th>Coagulation tests</th>
<th>Preterm infant 30-36 wk, day of life #1</th>
<th>Term infant, day of life #1</th>
<th>1-5 yr</th>
<th>6-10 yr</th>
<th>11-16 yr</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>15.4 (14.6-16.9)</td>
<td>13.0 (10.1-15.9)</td>
<td>11</td>
<td>10.6-11.4</td>
<td>11.1</td>
<td>11.2</td>
</tr>
<tr>
<td>INR</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.0</td>
<td>1.01</td>
<td>1.02</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>108 (80-168)</td>
<td>42.9 (31.3-54.3)</td>
<td>30</td>
<td>24-36</td>
<td>31</td>
<td>26-36</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.43 (1.5-3.73)</td>
<td>2.63 (1.67-3.09)</td>
<td>2.76</td>
<td>1.70-4.0</td>
<td>2.79</td>
<td>1.57-4.0</td>
</tr>
<tr>
<td>Bleeding time (min)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>6.2 (5-10)</td>
<td>7.25</td>
<td>5 (3-8)</td>
</tr>
<tr>
<td>Thrombin time (sec)</td>
<td>14 (11-17)</td>
<td>12 (10-16)</td>
<td>6 (2.5-10)</td>
<td>12 (2.5-3)</td>
<td>12 (3-8)</td>
<td>4 (1-7)</td>
</tr>
<tr>
<td>II (U/mL)</td>
<td>0.45 (0.20-0.77)</td>
<td>0.48 (0.26-0.70)</td>
<td>0.94</td>
<td>0.71-1.16</td>
<td>0.88</td>
<td>0.96</td>
</tr>
<tr>
<td>V (U/mL)</td>
<td>0.88 (0.41-1.44)</td>
<td>0.72 (0.43-1.08)</td>
<td>1.03</td>
<td>0.79-1.27</td>
<td>0.90</td>
<td>0.96</td>
</tr>
<tr>
<td>VII (U/mL)</td>
<td>0.67 (0.21-1.13)</td>
<td>0.66 (0.28-1.04)</td>
<td>0.82</td>
<td>0.55-1.16</td>
<td>0.85</td>
<td>0.52</td>
</tr>
<tr>
<td>VIII (U/mL)</td>
<td>1.10 (0.50-2.13)</td>
<td>1.00 (0.50-1.78)</td>
<td>0.90</td>
<td>0.59-1.42</td>
<td>0.95</td>
<td>0.58</td>
</tr>
<tr>
<td>vWF (U/mL)</td>
<td>1.36 (0.78-2.10)</td>
<td>1.53 (0.50-2.87)</td>
<td>0.82</td>
<td>0.47-1.04</td>
<td>0.94</td>
<td>0.44</td>
</tr>
<tr>
<td>IX (U/mL)</td>
<td>0.35 (0.19-0.65)</td>
<td>0.53 (0.15-0.91)</td>
<td>0.73</td>
<td>0.47-1.04</td>
<td>0.75</td>
<td>0.63</td>
</tr>
<tr>
<td>X (U/mL)</td>
<td>0.41 (0.11-0.71)</td>
<td>0.40 (0.12-0.68)</td>
<td>0.88</td>
<td>0.58-1.16</td>
<td>0.75</td>
<td>0.55</td>
</tr>
<tr>
<td>XI (U/mL)</td>
<td>0.30 (0.08-0.52)</td>
<td>0.38 (0.10-0.66)</td>
<td>0.97</td>
<td>0.56-1.50</td>
<td>0.86</td>
<td>0.52</td>
</tr>
<tr>
<td>XII (U/mL)</td>
<td>0.38 (0.10-0.66)</td>
<td>0.53 (0.13-0.93)</td>
<td>0.93</td>
<td>0.64-1.29</td>
<td>0.92</td>
<td>0.60</td>
</tr>
<tr>
<td>PK (U/mL)</td>
<td>0.33 (0.09-0.57)</td>
<td>0.37 (0.18-0.69)</td>
<td>0.95</td>
<td>0.65-1.30</td>
<td>0.99</td>
<td>0.66</td>
</tr>
<tr>
<td>HMWK (U/mL)</td>
<td>0.49 (0.09-0.89)</td>
<td>0.54 (0.06-1.02)</td>
<td>0.98</td>
<td>0.64-1.32</td>
<td>0.93</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Data from Andrew

HMWK, high-molecular-weight kininogen; PK, prekallikrein; VIII, factor VIII procoagulant

### Normal Values for Coagulation Screening Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Older Child</th>
<th>Full-Term Newborn</th>
<th>Healthy Growing Premature Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (per mm³)</td>
<td>150,000-400,000</td>
<td>150,000-400,000</td>
<td>150,000-400,000</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>10-14</td>
<td>11-15</td>
<td>11-16</td>
</tr>
<tr>
<td>Partial thromboplastin time (s)</td>
<td>25-35</td>
<td>30-40</td>
<td>35-80</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>175-400</td>
<td>165-400</td>
<td>150-325</td>
</tr>
<tr>
<td>Fibrin degradation products (µg/mL)</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

### Conditions Associated With Bleeding and Thrombocytopenia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Appearance</th>
<th>Prothrombin Time</th>
<th>Partial Thromboplastin Time</th>
<th>Other Useful Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Sick</td>
<td>1</td>
<td>1</td>
<td>Fibrinogen; fibrin degradation products</td>
</tr>
<tr>
<td>TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex)</td>
<td>Sick</td>
<td>Normal or 1</td>
<td>Normal or 1</td>
<td>Liver function tests; fibrinogen; fibrin degradation products</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Sick</td>
<td>Normal</td>
<td>Normal</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Maternal immune thrombocytopenic purpura</td>
<td>Well</td>
<td>Normal</td>
<td>Normal</td>
<td>Maternal platelet count</td>
</tr>
<tr>
<td>Allergic thrombocytopenia</td>
<td>Well</td>
<td>Normal</td>
<td>Normal</td>
<td>Maternal platelet count and platelet antigen typing (PAI-1)</td>
</tr>
<tr>
<td>Giant hemangioma</td>
<td>Well</td>
<td>Normal or 1</td>
<td>Normal or 1</td>
<td>Fibrinogen; fibrin degradation products</td>
</tr>
<tr>
<td>Defective platelet production</td>
<td>Well</td>
<td>Normal</td>
<td>Normal</td>
<td>Bone marrow examination</td>
</tr>
</tbody>
</table>

### Products Used in Treatment of Neonatal Coagulopathies

<table>
<thead>
<tr>
<th>Product</th>
<th>Contents</th>
<th>Usual Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh frozen plasma</td>
<td>All factors</td>
<td>10-20 mL/kg</td>
<td>Disseminated intravascular coagulation (DIC); liver disease; protein C deficiency</td>
</tr>
<tr>
<td>Exchange transfusion*</td>
<td>All factors; platelets</td>
<td>Double volume</td>
<td>Severe DIC; liver failure</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Factors VIII and XIII; VWF; fibrinogen</td>
<td>1 bag†</td>
<td>DIC; liver disease; factor VIII or XIII deficiency; von Willebrand disease</td>
</tr>
<tr>
<td>Factor IX concentrates</td>
<td>Factor IX</td>
<td>50-100 U/kg</td>
<td>Factor IX deficiency</td>
</tr>
<tr>
<td>Factor VIII concentrates</td>
<td>Factor VIII</td>
<td>25-50 U/kg</td>
<td>Factor VIII deficiency</td>
</tr>
<tr>
<td>Vitamin K</td>
<td></td>
<td>1-2 mg</td>
<td>Suspected vitamin K deficiency</td>
</tr>
<tr>
<td>Platelet concentrates</td>
<td>Platelets</td>
<td>1-2 units/5kg‡</td>
<td>Bleeding caused by thrombocytopenia</td>
</tr>
<tr>
<td>Intravenous gamma globulin</td>
<td>IgG</td>
<td>1-2 g/kg</td>
<td>Severs sepsis; thrombocytopenia caused by transplacental antibodies</td>
</tr>
</tbody>
</table>

* If fresh whole blood is used for exchange.  
† One bag of cryoprecipitate contains approximately 250 mg of fibrinogen and 80 to 120 units of factor VIII.  
‡Response to platelets can vary markedly, depending on underlying condition.

### Conditions Associated With Bleeding and Normal Platelet Count

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Appearance</th>
<th>PT</th>
<th>PTT</th>
<th>Other Useful Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic disease of newborn</td>
<td>Well</td>
<td>†</td>
<td>†</td>
<td>Fibrinogen; fibrin degradation products</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>Sick</td>
<td>†</td>
<td>†</td>
<td>Albumin; fibrinogen; fibrin degradation products; liver function tests</td>
</tr>
<tr>
<td>von Willebrand disease*</td>
<td>Well</td>
<td>Normal</td>
<td>Normal or 1</td>
<td>Bleeding time</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Well</td>
<td>Normal</td>
<td>†</td>
<td>Mixing tests; factor VIII and IX assays</td>
</tr>
<tr>
<td>Factor XIII deficiency</td>
<td>Well</td>
<td>Normal</td>
<td>Normal</td>
<td>Urea clot solubility</td>
</tr>
<tr>
<td>A fibrinogenemia</td>
<td>Well</td>
<td>†</td>
<td>†</td>
<td>Fibrinogen; fibrin degradation products; thrombin time</td>
</tr>
<tr>
<td>Disorders of platelet function*</td>
<td>Well</td>
<td>Normal</td>
<td>Normal</td>
<td>Bleeding time; platelet aggregometry</td>
</tr>
</tbody>
</table>

* Some patients with these disorders show mild to moderate thrombocytopenia.  
PT, Prothrombin time; PTT, partial thromboplastin time.
## Transfusion Therapy Products

<table>
<thead>
<tr>
<th>Special Requirements Components</th>
<th>Freshest Available</th>
<th>Leukocyte-reduced or CMV Seronegative</th>
<th>Lack Sickle HGB</th>
<th>Irradiated</th>
<th>Volume to Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells (packed cells)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>If directed donor from family</td>
<td>Hemorrhage: 20 mL/kg Chronic anemia: multiple transfusions of 10-15 mL/kg</td>
</tr>
<tr>
<td>Platelets</td>
<td>X</td>
<td>X</td>
<td></td>
<td>If directed donor from family</td>
<td>10 mL/kg to maintain greater than 50,000</td>
</tr>
<tr>
<td>Cryoprecipitated antihemophilic globulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 unit</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-15 mL/kg to maintain fibrinogen &gt; 100 mg/dL</td>
</tr>
<tr>
<td>Whole blood equivalent for exchange transfusion</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Double volume exchange based on infant’s weight (80-85 mL/kg/vol)</td>
</tr>
</tbody>
</table>

Access Transfusion Request Order Form [here](#).

Access Pre-Operative Blood Product Order Form [here](#).
VI I. RETINOPATHY OF PREMATURITY SURVEILLANCE

Retinopathy of prematurity (ROP) is a vasculo-proliferative disorder occurring almost exclusively in premature infants. Almost all ROP-related vision loss is associated with severe disease. Approximately 420 infants/year experience vision loss from ROP. New vessel growth regresses about 80% of the time with the other 20% progressing to neuro-vascularization, scar formation, hemorrhage, or retinal detachment. Prematurity is the greatest risk factor for ROP. Hyperoxia is a widely accepted risk factor. There is no safe level of arterial PaO2. The American Academy of Pediatrics guidelines recommends oxygen saturation monitoring if supplemental oxygen is required beyond the emergency period for newborns delivered before 36 weeks of gestation.

Premature newborns are screened according to the following guidelines. Hypertension, reflex bradycardia, apneic events can be caused by the eye exam, or the mydriatic eye drops.

The location and sequential retinal changes provide timely recognition of disease that is amendable to therapy and helps to provide prognosis. Retinopathy of prematurity is classified by location, zones I-III, and severity stage I-V. The extent of disease is measured around the retina in clock hours (1-12) with special designation for the accelerated inflammation with poor prognosis, plus disease.

(See diagram of retina)

If the ROP reaches (threshold) severity, the risk of poor retinal outcome increases to about 50%.

Complications of ROP include varying degrees of visual impairment, including retinal detachment and blindness in the worse cases. Later complications include glaucoma, strabismus, cataracts, and amblyopia.

Treatment of ROP is with cryotherapy or laser therapy. Cryotherapy freezes the avascular retina, preventing further abnormal vessel proliferation. Laser therapy, Argon, or iodide laser therapy photocoagulates the avascular periphery of the retina. This is less invasive and less traumatic to the eye than cryotherapy, and requires no anesthetics. Complications include scarring, choroidal hemorrhage, and pain.
VIII. INTRAVENTRICULAR HEMORRHAGE

Intraventricular hemorrhage occurs mainly in preterm infants (less than 32 weeks’ gestation). Incidence ranges from 13-65%, and decreases with advancing gestational age; 25-50% are asymptomatic, and are discovered by head ultrasound. Cranial ultrasound is the diagnostic method of choice to detect intraventricular hemorrhage and white matter disease (WMD) in the premature infant. White matter disease is often detectable on early ultrasound as either an echodensity or echolucency, but may not become apparent for 1-3 weeks after the initiating event when cysts begin to form. The echolucencies may then disappear after 1-3 months leaving enlarged ventricles.

The incidence of intraventricular hemorrhage in infants less than 1000 grams is 50-60%, and in infants 1000-1500 grams, the incidence is 10-20%. Approximately 90% of IVH occur by the 4th postnatal day with 50% occurring on the 1st postnatal day. Approximately 20-40% exhibit progression of hemorrhage over 3-5 days. Infants with IVH are at risk for hydrocephalus and white matter injury.

Periventricular leukomalacia (PVL) occurs in about 3-4% of infants of birth weight less than 1500 grams, and periventricular hemorrhagic infarction (PVHI) occurs in approximately 10-15% of infants of birth weights less than 1000 grams. Both PVL and PVHI have been associated with abnormal neurologic outcomes.

**Guidelines for obtaining cranial ultrasounds**

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Day of Life</th>
<th>7</th>
<th>28</th>
<th>Prior to discharge * (consider MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 grams</td>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>1000 – 1250 grams</td>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>1250 – 1500 grams</td>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

Cranial ultrasounds may need to be repeated at more frequent intervals to evaluate for developing hydrocephalus if there is evidence of hemorrhage. Additional or earlier ultrasounds may be needed at the discretion of the attending physician.
IX. “1-2-3” MINNESOTA NEWBORN HEARING SCREENING PROGRAM

All newborns will have hearing screening by “1” month of age, audiologic assessment by “3” months of age, and intervention by “6” months of age. All newborns discharged from the NICU are screened for hearing loss by (EOAE) Evoked Audio Acoustic Emissions as recommended by the American Academy of Pediatrics.

Significant bilateral hearing loss is present in 1-3/1,000 newborns in well-baby nursery population and in 2-4/1,000 newborns in newborn ICU population. In Minnesota, four infants are born per week with congenital hearing loss. One of every 1,000 children is born deaf; 3-5 of every 1,000 children have a mild-moderate hearing loss.

EOAE measures sound waves generated in the inner ear (cochlea) in response to clicks or tone bursts emitted and recorded via miniature microphones placed in the external ear canals of the infants. EOAE screening may be affected by debris or fluid in the external and middle ear.

Special Diagnostics Lab performs EAOE on all infants when a car seat evaluation is performed before discharge. If EAOE is abnormal, referral is made for ABR/BAER with Audiology.

ABR/BAER, Auditory Brainstem Response, is a non-invasive electrophysiologic method for the determination of hearing sensitivity and neuro-maturational status. Surface electrodes are taped to the forehead and earlobes or mastoid area, and acoustic clicks are generated by standard earphones or small ear-canal receivers. Hearing sensitivity is determined by the presence or absence of a typical and intact waveform (wave V). Neurologic and maturational status is determined from the measurement of peak latency (neural conduction time from the cochlea to upper medulla and lower mid brain).
X. MINNESOTA STATE NEWBORN SCREENING

All newborns are screened for 53 disorders by Minnesota law, unless a parent objects in writing. Approximately 60 (out of 65,000) infants each year are born with one of these disorders. If these rare disorders are diagnosed and treated early, mental retardation, developmental delays, severe illness, and death can be prevented. Amino acid, fatty acid oxidation, organic acid, endocrine disorders, hemoglobinopathies, other metabolic disorders, cystic fibrosis, and hearing loss are screened.

http://www.health.state.mn.us/divs/phl/newborn/factsheets.html

Minnesota Department of Health
2006 Newborn Screening Panel

Amino Acid Disorders
Arginemia (ARG, Arginase deficiency)
Argininosuccinate acidemia (ASA)
Defects of bioppterin cofactor biosynthesis (BIOPT-BS)
Defects of bioppterin cofactor regeneration (BIOPT-REG)
Citrrullinemia type I (CIT-I, argininosuccinate synthetase)
Citrrullinemia type II (CIT-II, citrin deficiency)
Homocystinuria (HCY, cystathionine beta synthase)
Hyperphenylalaninemia (H-PHE)
Hypermethioninemia (MET, I/III deficiency)
Maple Syrup Urine Disease (MSUD, branched-chain ketoacid dehydrogenase)
Phenylketonuria
Tyrosinemia type I (TYR-1)
Tyrosinemia type II (TYR-II)
Tyrosinemia type III (TYR-III)

Endocrine Disorders
Congenital adrenal hyperplasia (CAH)
Congenital hypothyroidism (CH)

Hemoglobinopathies
Sickle cell disease (HB S/S)
Sickle-C disease (HB S/C)
S-βeta thalassemia
Variant hemoglobinopathies

Others
Biotinidase deficiency (BIO)
Classic galactosemia (GALT)
Galactose epimerase deficiency (GALE)
Galactokinase deficiency (GALK)
Cystic fibrosis
Hearing - Voluntary

Fatty Acid Oxidation Disorders
Carnitine acylcarnitine translocase deficiency (CACT)
Carnitine uptake defect (CUD, carnitine transport defect)
Carnitine palmitoyltransferase deficiency I (CPT-1a)
Carnitine palmitoyltransferase deficiency II (CPT-II)
Dienoyl-CoA reductase deficiency (DE-RED)
Glutaric acidemia type II (GA-II)
Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT)
Medium/Short chain L-3-hydroxy acyl-CoA dehydrogenase deficiency (M/SCHAD)
Short-chain acyl-CoA dehydrogenase deficiency (SCAD)
Trifunctional protein deficiency (TFP)
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
**Organic Acid Disorders**

2-Methyl-3-hydroxybutyric aciduria (2M3HBA)
2-Methylbutyryl-CoA dehydrogenase deficiency (2MBG, SBCAD)
3-Hydroxy 3-methylglutaric aciduria (HMG, 3-Hydrox 3-methylglutaryl-CoA lyase)
3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC)
3-Methylglutaconic aciduria (3MGA, Type I hydratase deficiency)
Beta ketothiolase (BKT, mitochondrial acetoacetyl-CoA thiolase, short-chain ketoacyl thiolase)
Glutaric acidemia type I (GA-1)
Isobutyryl-CoA dehydrogenase deficiency (IBG)
Isovaleric acidemia (IVA, Isovaleryl-CoA dehydrogenase deficiency)
Malonic acidemia (MAL, Malonyl-CoA decarboxylase)
Methylmalonic acidemia (CBL A,B; Vitamin B12 Disorders)
Methylmalonic acidemia (CBL C,D)
Methylmalonic acidemia (MUT, methylmalonyl-CoA mutase)
Multiple carboxylase deficiency (MCD, holocarboxylase synthetase)
Propionic acidemia (PROP, propionyl-CoA carboxylase)
XI. OSTEOPENIA OF PREMATURITY

Osteopenia of prematurity occurs when bone mineral content in an infant is significantly decreased compared with that seen in the fetus or infant of comparable size or gestational age. Osteopenia occurs in up to 30% of very low-birth-weight infants less than 1500 grams, and up to 50% in extremely low-birth-weight infants less than 1000 grams. Additional risk factors for osteopenia of prematurity, besides low birth weight, are small for gestational age, multiples, chronic lung disease, long-term total parenteral nutrition, diuretic and corticosteroid therapy, short gut disease, and hepatic disease.

Body distribution and regulation of serum concentration of minerals of calcium, phosphorus, and magnesium, determines overall bone mineralization. Renal regulation of these minerals is also essential to the ability of the infant to prevent bone demineralization. Movement of calcium from the GI tract and bone determines serum calcium concentrations. Loop diuretics (Lasix, chronic administration of thiazide diuretics) increase urinary excretion of calcium by inhibiting calcium reabsorption. Lasix and theophylline are all calciuretic. Diuril, short-term, may be calcium sparing.

Serum calcium concentration decreases over the first days of life, followed by a gradual increase to adult concentrations by the 2nd or 3rd week of life. Serum phosphorus concentrations in the newborn are maintained at concentrations greater than adults. Serum magnesium concentrations are maintained within tight limits at all ages.

Osteopenia of prematurity can generally be suspected when there is an elevated alkaline phosphatase greater than 900 IU/L, and lowered serum phosphorus less than 5.5 mg/dl. Moderate increases in alkaline phosphatase (400-800 IU/L) can be commonly seen in rapidly growing premature infants and warrant careful monitoring of the infant’s mineral intake. Metabolic bone disease can be suspected with radiologic changes suggesting poor mineralization, ricketic changes or fractures together with raised alkaline phosphatase levels. Detection of bone demineralization in at-risk premature infants is a late finding in long bones, wrist, and knee radiographs. Clinical findings can be decrease in long bone growth, cranial tabies, nontraumatic palpable swelling of costochondral junctions of the rib cage, rib fractures and callus, splaying of metaphyseal ends of long bones.

Perinatal mineralization deficiencies can result in preterm infants being shorter and lighter. Ex-preterm infants have significant reductions in bone mineral mass commensurate with their reduced growth and reduced bone mineral density.

A critical factor in the development of osteopenia is lack of adequate phosphorus. Normalization of bone mineral content is usually seen by one year of life in infants fed preterm formulas. Normalization of bone mineral content is delayed to two years in breast-fed, premature infants. At-risk infants should be followed through the first 1-2
years with monitoring growth parameters, possibly alkaline phosphatase, phosphate, and vitamin D levels during and after switching from premature nutrition.

The stability of bones is adapted to local muscle forces. This has been shown in very low-birth-weight infants, who had greater gains in body weight, fat-free mass, forearm length, and bone mineral content with an exercise program, consisting of passive resistance and compression of all extremity joints, starting when stable. Fetuses have had resistance training against the uterine muscle. Sick preterm infants tend to be very inactive, naturally or iatrogenically.

Prevention of osteopenia of prematurity is the best approach. Osteopenia of prematurity nutritional therapy protocol should be followed from birth. Calcium and phosphorus content and ratio should be optimized in hyperalimentation. Initiate enteral feedings and optimize calcium, phosphorus content by adding human milk fortifier or premature formula. If premature infant is on unfortified breast milk for a prolonged period of time, consider calcium, phosphorus supplementation or feeding some premature formula. Switch from Lasix to an anti-calciuretic diuretic (chlorothiazide) as soon as possible. Limit use of aminophylline and steroids. Maintain vitamin D intake, especially with GI, hepatic, or renal dysfunction. More would be required with cholestasis, direct bilirubin level greater than 2. In cases of severe cholestasis, consider the use of 25-hydroxy vitamin D supplements.

Initiate occupational therapy, passive range of motion and compression of joints to enhance bone mineralization and bone mineral content in very low-birth-weight infants when stable.
XI. CLEFT LIP OR PALATE

Affected infants will have a number of medical issues and potential complications requiring multidisciplinary evaluation and care. A child with a cleft lip/palate, or other craniofacial abnormalities, has multiple and complex problems, including early feeding and nutritional concerns, middle ear disease, hearing deficiencies, deviations in speech and resonance, dental, facial, and orthodontic abnormalities, and psycho-social adjustment problems. Appropriate consultation should be obtained from Plastic Surgery (Dr. Robert Wood), Genetics, Audiology and/or Pediatric Otolaryngology, and Speech Pathology, with follow-up with Dr. Wood at Gillette Children’s Hospital.

Cleft lip with or without cleft palate, and cleft palate alone, have a combined incidence of 1-2/1,000. They are the 4th most common birth defect. Cleft lip and palate incidence is 1 in 700 births with cleft palate alone occurring 1 in 2500 births. Native Americans have the higher incidence in the United States.

Cleft lip with cleft palate is the most common presentation. The etiology of cleft lip and/or cleft palate is largely unknown. It is believed to be of multifactorial etiology with genetic and environmental factors interacting to shift a complex process of morphogenesis, resulting in clefting. Development of the face and upper lip occurs between the 5th and 9th weeks of pregnancy. Palatal development occurs between the 6th and 11th weeks of pregnancy. Patients with oral clefts exhibit other anomalies 21-37%, such as cardiovascular, musculoskeletal, facial dysmorphia, and genitourinary system disturbances. Numerous syndromes and chromosomal abnormalities have been associated with oral cleft.

Cleft lip with cleft palate is the most common presentation. More males are affected than females. More males have complete clefts. The unilateral clefts are most common on the left side. Infants with associated anomalies are more likely to have combined cleft lip/palate, or cleft palate rather than a cleft lip alone. They are also more likely to be small for gestational age.
XIII. ORGAN DONATION

Organ and tissue donations provide hope for people with organ failure or tissue disease and injuries. A person who is an organ donor can potentially help up to eight people. A person who is a tissue donor can potentially help up to 50 people. Donations can occur after brain death or cardiac death. Organs that can be donated are heart, lungs, pancreas, intestines, kidneys, and liver. Tissues to be donated are corneas, heart valves, veins/arteries, bone, connective tissue, and skin.

Life Source is the not-for-profit organ procurement organization for our four-state region. They are our bridge between donation and transplantation. They identify potential donors, matching donors with recipients, coordinating clinical donation activities, arranging surgical recovery, support donor families, and increasing public awareness about donation.

All patient deaths (imminent brain death and cardiac death) must be referred to Life Source. Call Life Source when brain death is imminent, cardiac death or asystole occurs, or family mentions donation. Do not mention donation to the family. A donation coordinator will evaluate your patient to determine donor designation and possible procurement. A Life Source coordinator will collaborate with the healthcare team to develop an appropriate communication plan if the family mentions or has questions about donation. Call Life Source when the patient has expired for possible tissue and eye donation, even if the patient has been previously referred.
XI V. END OF LIFE CARE

More infants die in the neonatal period than at any other time in childhood. Pediatric residency provides neonatal end-of-life training and supportive care if needed in these situations. Caring for terminally ill children is a multidisciplinary task. At Children’s Hospitals and Clinics of Minnesota - St. Paul, notify Social Work, bereavement team, and chaplaincy.

Appropriate end-of-life care is palliative comfort care. Parents will need to understand their infant’s condition and the reason for palliative care. Bereavement process for parents starts before the termination of active medical treatment. Encourage parents to touch, care, and obtain items (pictures, blankets, clothes) that they can remember their infant after death. Private rooms provide a quiet private location for end-of-life care. Staff (nursing and medical) presence and involvement is important for parents.

Autopsy request should be discussed at an appropriate time before or after death - not at the time of death. Consent for autopsy, or denial, needs to be documented on the hospital Autopsy Consent Form.

Follow-up with parents, with or without an autopsy, is important to the parents.

It is acceptable to attend funerals of your patients, if you would like.

Always consider cultural norms with the death of your patients.
XV. IMMUNIZATIONS

All medically stable infants should be given vaccines as recommended for their age. A medically stable infant is defined as one who does not require on-going management for serious infections, metabolic disease, acute renal, cardiovascular, or respiratory tract illness, and who demonstrates a clinical course of sustained recovery and pattern of steady growth. To avoid multiple injections and superimposed local reactions, two-week intervals of recommended vaccines may be reasonable.

Consistent weight gain by a preterm infant is important before receipt of the first dose of hepatitis B vaccine, as this is predictive of immune responsiveness. Medically stable, thriving infants, weighing less than 2000 grams, demonstrate predictable, consistent, and sufficient hepatitis B antibody responses, and should receive the first dose of hepatitis B vaccine as early as 30 days of chronologic age, regardless of gestational age or birth weight. Starting the hepatitis B series at one month of age, regardless of the weight of the preterm infant, offers more options for implementing the immunization schedule in the NICU setting, lessens the number of simultaneous injections at two months of age, provides earlier protection to vulnerable preterm infants, more likely to receive multiple blood products and undergo surgical interventions, and decreases the risk of horizontal transmission from occult hepatitis B chronic carriers among family members, hospital visitors, and other caregivers. Medically stable preterm infants, weighing more than 2000 grams, born to hepatitis B, surface antigen negative mothers, may receive the first dose of hepatitis B vaccine at birth, or shortly thereafter. Only monovalent hepatitis B vaccine should be used for infants from birth-six weeks of age.

Because all preterm infants are considered at increased risk for complications of influenza, two doses of an inactivated influenza vaccine, given one month a part, should be offered for these infants, beginning at six months of chronologic age before the onset of influenza season. Household contacts should also receive inactivated influenza vaccine.

RSV pneumonia is a major cause of serious pediatric respiratory disease from November - April, especially among infants who have chronic lung disease and those born prematurely. Palivizumab (Synagis TM), a recombinant monoclonal antibody against RSV, is effective in decreasing the incidence of RSV pneumonia in high-risk infants. Palivizumab use does not interfere with the provision of routine childhood immunizations to preterm or low-birth-weight infants. Infants at risk for RSV will be given Synagis, 15 mg/kg IM monthly, from November-April. Patients who are to be given this treatment include: gestational age less than 28 weeks, and less than 12 months postnatal age at start of RSV season; gestational age 29-32 weeks and postnatal age less than or equal to six months at start of RSV season; gestational age 33-35 weeks and additional risk factors, who are younger than six months of age at the start of the RSV season; childcare attendants; school age siblings; exposure to environmental air pollutants, congenital abnormality of the airway, or severe
neuromuscular disease; and patients up to the age of 24 months with chronic lung disease and requiring oxygen, steroids, or bronchodilators in the six months prior to the start of RSV season. Children less than 24 months of age with hemodynamically significant cyanotic and acyanotic congenital heart disease need consultation with Cardiology.

Unless contraindicated, all patients should received acetaminophen 1-2 hours prior to DTaP immunizations, and every 4-6 hours after for 24 hours.

New pentavalent Rotavirus vaccine was licensed for use among U.S. infants in February 2006. Immunizations were recommended with three doses administered orally at 2, 4, and 6 months of age. The first dose should be administered between 6-12 weeks of age. Subsequent doses should be administered at 4-10 week intervals. This has not yet been initiated in the NICU setting.

The State of Minnesota is establishing an immunization database for recording all administered immunizations. This will facilitate accurate record keeping of childhood immunizations.

<table>
<thead>
<tr>
<th>Age</th>
<th>Mother’s HBsAg Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Birth</td>
<td>HBV #1 (by age 12h)</td>
</tr>
<tr>
<td></td>
<td>HBIG (by age 12h)</td>
</tr>
<tr>
<td>1 month</td>
<td>HBV #2</td>
</tr>
<tr>
<td>2 months</td>
<td>IPV #1</td>
</tr>
<tr>
<td></td>
<td>DTaP #1</td>
</tr>
<tr>
<td></td>
<td>COMVAX #1</td>
</tr>
<tr>
<td></td>
<td>PCV7 #1</td>
</tr>
<tr>
<td>4 months</td>
<td>IPV #2</td>
</tr>
<tr>
<td></td>
<td>DTaP #2</td>
</tr>
<tr>
<td></td>
<td>COMVAX #2</td>
</tr>
<tr>
<td></td>
<td>PCV7 #2</td>
</tr>
<tr>
<td>6 months</td>
<td>DTaP #3</td>
</tr>
<tr>
<td></td>
<td>PCV7 #3</td>
</tr>
<tr>
<td></td>
<td>HIB #3</td>
</tr>
<tr>
<td></td>
<td>HBV #3</td>
</tr>
<tr>
<td>12-15 months†</td>
<td>IPV #3</td>
</tr>
<tr>
<td></td>
<td>COMVAX #3</td>
</tr>
</tbody>
</table>

* Determine maternal HBsAg status after birth; if positive, give HBIG by age 7 days for full term infants; for preterm, give HBIG within 12h after birth.
† Consider giving influenza vaccine to infants with chronic lung disease or cardiac disease.
<table>
<thead>
<tr>
<th>Maternal Status</th>
<th>Infant &gt; 2000g</th>
<th>Infant &lt; 2000g</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbsAg positive</strong></td>
<td>Hepatitis B vaccine + HBIG (within 12 h of birth) Continue vaccine series beginning at 1-2 mo of age according to recommended schedule for infants born to HBsAg-positive mothers (see following table)</td>
<td>Hepatitis B vaccine + HBIG (within 12 h of birth) Continue vaccine series beginning at 1-2 mo of age according to recommended schedule for infants born to HBsAg-positive mothers (see following table)</td>
</tr>
<tr>
<td><strong>HBsAg status unknown</strong></td>
<td>Test mother for HBsAg immediately after admission for delivery Hepatitis B vaccine (by 12h) Administer HBIG (within 7 days) if mother tests HBsAg positive Continue vaccine series beginning at 1-2 mo of age according to recommended schedule based on mother’s HBsAg result (see following table)</td>
<td>Test mother for HBsAg immediately after admission for delivery Hepatitis B vaccine (by 12h) Administer HBIG if mother tests HBsAg positive or if mother’s HBsAg result is not available within 12h of birth Continue vaccine series beginning at 1-2 mo of age according to recommended schedule based on mother’s HBsAg result (see following table)</td>
</tr>
<tr>
<td><strong>HBsAg negative</strong></td>
<td>Hepatitis B vaccine at birth³</td>
<td>Hepatitis B vaccine dose 1-30 days of chronologic age if medically stable, or at hospital discharge if before 30 days of chronologic age</td>
</tr>
</tbody>
</table>

HBsAg indicates hepatitis B surface antigen; HBIG, hepatitis B Immune Globulin; anti-HBs, antibody to hepatitis B surface antigen.

¹ Extremes of gestational age and birth weight no longer are a consideration for timing of hepatitis B vaccine doses.

² Test at 9 to 18 months of age, generally at the next well-child visit after completion of the primary series. Use testing method that allows determination of a protective concentration of anti-HBs (≥10 mIU/mL).

³ The first dose may be delayed until after hospital discharge for an infant who weighs ≥ 2000 g and whose mother is HBsAg negative, but only if a physician’s order to withhold the birth dose and a copy of the mother’s original HBsAg-negative laboratory are documented in the infant’s medical record.
Hepatitis B Vaccine Schedules for Infant, by Maternal Hepatitis B Surface Antigen (HBsAg) Status\textsuperscript{1, 2}

<table>
<thead>
<tr>
<th>Maternal HBsAg Status</th>
<th>Single Antigen Vaccine</th>
<th>Single Antigen + Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose</td>
<td>Age</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg Positive</td>
<td>1\textsuperscript{3}</td>
<td>Birth (&lt;12h)</td>
</tr>
<tr>
<td></td>
<td>HBIG\textsuperscript{4}</td>
<td>Birth (&lt;12h)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1-2 mo</td>
</tr>
<tr>
<td></td>
<td>3\textsuperscript{5}</td>
<td>6 mo</td>
</tr>
<tr>
<td>Unknown\textsuperscript{6}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg Unknown</td>
<td>1\textsuperscript{3}</td>
<td>Birth (&lt;12h)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1-2 mo</td>
</tr>
<tr>
<td></td>
<td>3\textsuperscript{5}</td>
<td>6 mo</td>
</tr>
<tr>
<td></td>
<td>4\textsuperscript{5}</td>
<td>6 mo (Pediatrix) or 12-15 mo (Comvax)</td>
</tr>
<tr>
<td>Negative</td>
<td>1\textsuperscript{3, 7}</td>
<td>Birth (before discharge)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1-2 mo</td>
</tr>
<tr>
<td></td>
<td>3\textsuperscript{5}</td>
<td>6 mo</td>
</tr>
</tbody>
</table>


\textsuperscript{2} See previous table for vaccine schedules for preterm infants weighing < 2000g.

\textsuperscript{3} Recombivax HB or Engerix-B should be used for the birth dose. Comvax and Pediatrix cannot be administered at birth or before 6 weeks of age.

\textsuperscript{4} Hepatitis B Immune Globulin (0.5 mL) administered intramuscularly in a separate site from vaccine.

\textsuperscript{5} The final dose in the vaccine series should not be administered intramuscularly in a separate site from vaccine.

\textsuperscript{6} Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than 7 days of age.

\textsuperscript{7} On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs > 2000g and whose mother is HBsAg negative, but only if a physician’s order to withhold the birth dose and a copy of the mother’s original; HBsAg-negative laboratory report are documented in the infant’s medical record.
XVI. REFERENCES

Resources
1. The Harriet Lane Handbook. Authors: Siberry and Iannone. Publisher: Mosby.
2. NeoFax. Authors: Young and Mangum. Publisher: Acorn Publishing.
6. Care of the High-Risk Neonate. Authors: Klaus and Fanaroff. Publisher: Saunders.
7. Neonatal Resuscitation Textbook by AAP/AHA.
9. Smith’s Recognizable Patterns of Human Malformations. Author: Jones. Publisher: Elsevier and Saunders.
10. Drugs in Pregnancy and Lactation. Authors: Briggs, Freeman and Yaffe. Publisher: L.W.N.W.

Web Resources
3. NICU-WEB http://neonatal.peds.washington.edu
5. Lucille Packard Children’s Hospital www.lpch.org/diseasehealthinfo/healthlibrary/hrnewborn/sitemap.html
6. Family Village library www.familyvillage.wisc.edu/specific.htm
12. Neonatal Radiology
13. Neonatal Ventilation
15. University of Pittsburgh Seminars in Newborn Medicine
   http://www.eprom.pitt.edu/34_viewFolder.asp?folderID=1225850524
16. Jordan University of Science and Technology Department of Pediatrics Fourth
    Year Newborn and Neonatology Course Presentations
   http://www.just.edu.jo/~mykhassawneh/newborn.htm
17. White/Cox: Diseases of the Skin, 2ed., chapter 19: Pediatric Dermatology
    http://www.merckmedicus.com/ppdocs/us/hcp/content/white/white-ch-019-
toc.htm
18. Yale Well Baby Nursery
    http://yalepediatrics.org/residents/PCC%20References/WBN.html