## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>General Information about the NICU at CPMC</td>
<td>7</td>
</tr>
<tr>
<td>Admission Criteria</td>
<td>10</td>
</tr>
<tr>
<td>Inborn</td>
<td>10</td>
</tr>
<tr>
<td>Outborn</td>
<td>10</td>
</tr>
<tr>
<td>Special Considerations for Transporting Infants</td>
<td>11</td>
</tr>
<tr>
<td>Accepting the referral:</td>
<td>11</td>
</tr>
<tr>
<td>Arranging the transport:</td>
<td>11</td>
</tr>
<tr>
<td>Delivery Room: NICU Attendance at Deliveries</td>
<td>13</td>
</tr>
<tr>
<td>What to Do When an Infant Dies</td>
<td>14</td>
</tr>
<tr>
<td>Stillbirth Infant</td>
<td>14</td>
</tr>
<tr>
<td>Non-viable Liveborn Infant</td>
<td>15</td>
</tr>
<tr>
<td>Neonatal Organ Donation</td>
<td>15</td>
</tr>
<tr>
<td>Donating Milk to Milk Bank</td>
<td>16</td>
</tr>
<tr>
<td>Criteria for Home Monitoring</td>
<td>17</td>
</tr>
<tr>
<td>Hearing Screens</td>
<td>18</td>
</tr>
<tr>
<td>Management of Neonatal Abstinence Syndrome (Drug Withdrawal)</td>
<td>19</td>
</tr>
<tr>
<td>Developmental Dysplasia of the Hip (DDH)</td>
<td>22</td>
</tr>
<tr>
<td>Dorsal Midline Cutaneous Findings</td>
<td>23</td>
</tr>
<tr>
<td>Management of the Newborn with Prenatal Diagnosis of Hydronephrosis</td>
<td>24</td>
</tr>
<tr>
<td>Approach to the Infant with a Single Umbilical Artery</td>
<td>26</td>
</tr>
<tr>
<td>Routine Measurements in the ICN</td>
<td>27</td>
</tr>
<tr>
<td>Assessment of Gestational Age &amp; Growth</td>
<td>27</td>
</tr>
<tr>
<td>Intrauterine Growth by Ultrasound</td>
<td>27</td>
</tr>
<tr>
<td>Ballard Exam</td>
<td>29</td>
</tr>
<tr>
<td>Postnatal Growth</td>
<td>30</td>
</tr>
<tr>
<td>Physiologic Monitoring</td>
<td>33</td>
</tr>
<tr>
<td>Arterial Blood Pressure</td>
<td>33</td>
</tr>
<tr>
<td>Umbilical Arterial Catheters</td>
<td>36</td>
</tr>
<tr>
<td>Peripheral Arterial Catheters (Radial or Posterior Tibial)</td>
<td>37</td>
</tr>
<tr>
<td>Venous Catheters and Central Venous Pressure</td>
<td>37</td>
</tr>
<tr>
<td>Environmental Control Ambient Temperature</td>
<td>38</td>
</tr>
<tr>
<td>Analgesia and Sedation</td>
<td>39</td>
</tr>
<tr>
<td>Special Considerations in the Care of the Extremely Low Birth Weight Baby</td>
<td>42</td>
</tr>
<tr>
<td>Delivery Room Management</td>
<td>43</td>
</tr>
<tr>
<td>Immediate Management in the NBICU</td>
<td>44</td>
</tr>
<tr>
<td>Special Considerations in the Late Preterm Infant</td>
<td>46</td>
</tr>
<tr>
<td>Fluid and Electrolytes</td>
<td>47</td>
</tr>
<tr>
<td>Electrolyte Disturbances and Corrections</td>
<td>51</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>51</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>51</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>52</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>52</td>
</tr>
<tr>
<td>Hypochloremia</td>
<td>53</td>
</tr>
<tr>
<td>Hyperchloremia</td>
<td>53</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>54</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>54</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>55</td>
</tr>
<tr>
<td>Topic</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>56</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>56</td>
</tr>
<tr>
<td>Feeding of Preterm Infants</td>
<td>57</td>
</tr>
<tr>
<td>Vitamin and Iron Supplementation</td>
<td>65</td>
</tr>
<tr>
<td>Probiotics</td>
<td>66</td>
</tr>
<tr>
<td>Feeding of Late Preterm Infants (35+ weeks) and Term Infants</td>
<td>67</td>
</tr>
<tr>
<td>Parenteral Nutrition</td>
<td>68</td>
</tr>
<tr>
<td>Insulin Infusion in Glucose Intolerant Infants &lt; 1000 gm</td>
<td>71</td>
</tr>
<tr>
<td>Glucose Control &amp; Hypoglycemia</td>
<td>72</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>76</td>
</tr>
<tr>
<td>Metabolic Bone Disease: Rickets/Osteopenia</td>
<td>77</td>
</tr>
<tr>
<td>Newborn Screening and Inborn Errors of Metabolism</td>
<td>78</td>
</tr>
<tr>
<td>Metabolic Disorders (Inborn Errors of Metabolism)</td>
<td>80</td>
</tr>
<tr>
<td>Characteristics of the Newborn Kidney</td>
<td>84</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>85</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>88</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus (PDA)</td>
<td>89</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>91</td>
</tr>
<tr>
<td>Use of Prostaglandin E1 (Alprostadil) for Maintaining Ductus Patency</td>
<td>93</td>
</tr>
<tr>
<td>Hypertension in the Newborn and Infant</td>
<td>94</td>
</tr>
<tr>
<td>Hospital Acquired Infections</td>
<td>97</td>
</tr>
<tr>
<td>Cascade for Evaluation and Treatment of Suspected Sepsis</td>
<td>102</td>
</tr>
<tr>
<td>Choice of Antibiotics by Site of Infection</td>
<td>105</td>
</tr>
<tr>
<td>Candidal Infections</td>
<td>106</td>
</tr>
<tr>
<td>Hepatitis B Virus Infection and Vaccine</td>
<td>108</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>109</td>
</tr>
<tr>
<td>Congenital Syphilis</td>
<td>111</td>
</tr>
<tr>
<td>Herpes Simplex Virus (HSV) Exposure and Infection</td>
<td>113</td>
</tr>
<tr>
<td>Management of Infants Born to Tuberculin Skin Test Positive Mothers</td>
<td>115</td>
</tr>
<tr>
<td>Care of Neonates at Risk for HIV Infection</td>
<td>116</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>120</td>
</tr>
<tr>
<td>Immunizations</td>
<td>121</td>
</tr>
<tr>
<td>Non-Pulmonary Causes of Respiratory Distress and Apnea</td>
<td>122</td>
</tr>
<tr>
<td>Apnea</td>
<td>123</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>125</td>
</tr>
<tr>
<td>Guidelines for Specific Diseases</td>
<td>127</td>
</tr>
<tr>
<td>Continuous Positive Airway Pressure (CPAP)</td>
<td>129</td>
</tr>
<tr>
<td>High Frequency Ventilation</td>
<td>130</td>
</tr>
<tr>
<td>Surfactant</td>
<td>132</td>
</tr>
<tr>
<td>Guidelines for Tracheal Tube Lengths</td>
<td>133</td>
</tr>
<tr>
<td>Use of Transcutaneous Monitors</td>
<td>133</td>
</tr>
<tr>
<td>Oxygen Saturation and Pulse Oximeters</td>
<td>133</td>
</tr>
<tr>
<td>Use of End-Tidal CO2 Monitor</td>
<td>135</td>
</tr>
<tr>
<td>Treatment of Meconium Aspiration</td>
<td>136</td>
</tr>
<tr>
<td>Management of Infants with Persistent Pulmonary Hypertension</td>
<td>137</td>
</tr>
<tr>
<td>Treatment of Pneumothorax</td>
<td>140</td>
</tr>
<tr>
<td>Treatment of Pulmonary Interstitial Emphysema</td>
<td>141</td>
</tr>
<tr>
<td>Care of Infants with Chronic Lung Disease</td>
<td>142</td>
</tr>
<tr>
<td>Anemia</td>
<td>145</td>
</tr>
<tr>
<td>Bleeding Newborn</td>
<td>147</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>150</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>152</td>
</tr>
<tr>
<td>Treatment of Anemia of Prematurity with Erythropoietin</td>
<td>154</td>
</tr>
<tr>
<td>Transfusion Therapy</td>
<td>155</td>
</tr>
<tr>
<td>Topic</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Neonatal Jaundice – Unconjugated Hyperbilirubinemia</td>
<td>159</td>
</tr>
<tr>
<td>Neonatal Jaundice – Conjugated Hyperbilirubinemia (Cholestatic Jaundice)</td>
<td>163</td>
</tr>
<tr>
<td>Exchange Transfusions</td>
<td>164</td>
</tr>
<tr>
<td>Abdominal Distension and/or Vomiting</td>
<td>165</td>
</tr>
<tr>
<td>Gastroesophageal Reflux Disease (GERD)</td>
<td>166</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis (NEC)</td>
<td>168</td>
</tr>
<tr>
<td>Perinatal or Neonatal Asphyxia</td>
<td>173</td>
</tr>
<tr>
<td>Whole Body Cooling for Neonatal Encephalopathy</td>
<td>176</td>
</tr>
<tr>
<td>Neonatal Seizures</td>
<td>180</td>
</tr>
<tr>
<td>Intraventricular Hemorrhage</td>
<td>183</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>186</td>
</tr>
<tr>
<td>Retinopathy of Prematurity</td>
<td>188</td>
</tr>
<tr>
<td>The Transfer of Drugs and Other Chemicals into Human Milk</td>
<td>191</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>192</td>
</tr>
<tr>
<td>Medications (non antibiotic)</td>
<td>201</td>
</tr>
</tbody>
</table>
California Pacific Medical Center

Manual of Neonatal Management

Version 7 (Jan 2010)

Introduction

This manual is designed to be a convenient reference guide for personnel in the California Pacific Medical Center NICU and our referring hospitals. It provides guidelines for the usual diagnostic and therapeutic approaches used in the CPMC NICU. It is not a substitute for larger, more complete neonatal textbooks and resources; it should be used in conjunction with other references.

The "management" protocols included in this manual should be taken as guidelines for therapy. Individual patients and clinical situations may require alterations in the suggested management. Links to the CPMC policies are included where appropriate. These links will not work if you are not on a computer with Sutter network access. Links will show if you “hover over them” or use Ctrl + click.

A number of useful web sites are available when searching for information about specific diseases, conditions or practice guidelines. The following may be of use to you for practical information regarding patient care. Most of these sites can be accessed through the CPMC library site at http://insidecpmc.org/. Click on references to take you to the library resources. Other useful web sites for neonatal topics include www.neonatology.org, http://www.neoreviews.org.

The AAP also has practice guidelines on the site www.aap.org

The California Perinatal Quality Care Collaborative CPQCC has comprehensive toolkits for neonatal issues available online (including hospital acquired infection, nutrition, late preterm infants and delivery room management)

For searches on congenital malformations and or genetics syndromes
For rare diseases - a good source for patient information.

A multitude of equations for medicine can be found at: http://www.changbioscience.com/bio/cal0.htm

Cochrane reviews offers meta-analysis of many topics. Under each of the summary reviews you can link for the full analysis at the full text option under the Cochrane Library link. You need to be a subscriber to access this site (CPMC is a subscriber so accessing the link from a hospital intranet site will give you access.)

A variety of clinical guidelines are available at the National Guideline Clearinghouse a government run site that also provides weekly updates

A concise Journal Club format of recent articles of interest to Neonatology providers.

If on line at CPMC you have access to textbooks via the library linakge:

Link to Cloherty's Manual of Neonatal Care

Link to AAP Redbook: Redbook

Link to Harriet Lane Manual

Comprehensive information sheets on congenital heart lesions can be found on Cincinnati Children’s site
A Brief History of Neonatology

600 BC  Newborns routinely salted after birth
1642  Sir Isaac Newton is born a 3# preterm infant
1741  Foundling Hospital in London opens
1749  Goethe is initially thought to be a stillbirth but is revived by hours of being rubbed with wine
1802  First hospital for infants
1815  First report of normal newborn weight curves
1829  Incubators developed
1861  Little describes link of cerebral palsy to birth asphyxia
1869  2500 gm designation of prematurity
1884  First gavage feeding
1874  Sir Winston Churchill is born preterm
1879  Crede uses silver nitrate to prevent gonococcal ophthalmia neonatorum
1881  Pablo Picasso is resuscitated at birth by his uncle
1882  Franklin Delano Roosevelt receives mouth to mouth resuscitation at birth after his mother receives a chloroform overdose
1889  First use of oxygen in neonatal care
1898  Preterm baby expositions at World's Fair
1915  First scalp vein infusion
1925  First double volume exchange transfusion for jaundice
1934  Dionne quintuplets are born – felt to be identical they ranged in size from 794-1247 grams. They were fed pooled human milk and their multiple apnea episodes were treated with a drop or two of rum and 95% oxygen
1937  Vitamin K for prevention of hemorrhagic disease of the newborn
1940  Routine use of oxygen (at level of 40-60%)
1944  First use hyperalimentation in infancy
1950  Stevie Wonder born – one of an estimated 12,000 preterms blinded by retrolental fibroplasia (now known as ROP) in the decade since routine O2 use started
1952  Virginia Apgar develops the Apgar score
1953  RDS defined (Hyaline Membrane Disease)
1958  Phototherapy
1960  Ventilation possible with endotracheal tubes
1960  Term “neonatology” coined
1963  Patrick Bouvier Kennedy (son of President Kennedy) dies of RDS after being born at 34 weeks
1963  RhoGam developed
1965  First NICU opens in New Haven
1967  BPD described
1971  CPAP utilized
1972  Transcutaneous oxygen monitoring
1973  Antenatal steroids to promote lung maturity
1975  American Board of Pediatrics establishes sub-board for neonatal medicine
1980  Early reports of survival of infants <750 grams
1985  ECMO use re-emerges
1986  Artificial Surfactant trials
1987  Pulse oximeters introduced to NICU’s
1987  NRP launched
1990  Surfactant use becomes routine
1990  High frequency ventilation becomes available
1992  Nitric oxide trials begun
1994  Liquid ventilation trials instituted
2000  Nitric oxide approved by FDA
2005  Cooling trials for hypoxic encephalopathy

More historical information can be found at Neonatology on the Web (in the diversions and classics section)
This manual is due to the combined efforts of the neonatologists at California Pacific Medical Center. We are deeply grateful for the assistance of our amazing pharmacists Andree Hest, Gina Rosito and Kitty Sum, our dedicated keen-eyed nurse practitioners Nancy Kirkpatrick and Anne Parker and all the hospitalists whose curiosity encouraged us to be more consistent. We are also grateful to our families who allowed us the extra time after a day of caring for babies to write, edit and refine this document.

Please contact one of us if you see areas that need further tweaks or to suggest ideas for the next version.

Nancy Chorne    Steve Goldman    Ghizala Kaleem    David Lee
Kathy Lewis    Chris Retajczyk    Terri Slagle
General Information about the NICU at CPMC

California Pacific Medical Center NICU has been in operation since 1968. We are designated a Level 3 Regional ICN by California Children's Services (CCS). Approximately 600 infants are admitted each year. 80% of the infants are inborn, either from within our general service area or from maternal transports. We have referral contracts with Mills-Peninsula Hospital (a level 2 nursery), Seton Medical Center, Santa Rosa Sutter Medical Center (a community ICN), Sutter Lakeside (a small level 1 center in Clear Lake). We also get referrals from the special care nursery at our St. Luke’s campus. We provide intensive care for all infants, including neonates with conditions requiring surgery and infants with cardiac disease. Infants who require ECMO are referred to ECMO centers in our geographic region.

Seven neonatologists and two nurse practitioners staff the ICN. The neonatologists and nurse practitioners provide the primary medical care for infants in the intensive care unit. Community pediatricians are included in the care of their patients. In addition to the neonatologists, board certified pediatricians who are dedicated to the neonatal intensive care unit and/or neonatal nurse practitioners provide coverage for our patients and for the delivery room.

The ICN has 36 beds in 3 units (north, east and west.) We have 19 LDRP, 3 operative delivery rooms and additional preterm labor antepartum rooms on the first floor.

Outcome from infants cared for in the NICU can be measured in many different ways. Below are some of the key data curves to help evaluate the care we give. The 2009 annual report of the quality outcomes from the NICU is available on line and in printed form in CPMC NICU. This document includes outcome data, our key quality metrics and quality improvement initiatives and our goals for the upcoming year.

(This document may not load if you are not on the CPMC Intranet.)

Survival varies by gestational age and for any 1 year data can be skewed by the number of births. A quick guide for survival by gestational age can be obtained from the Pediatrix Medical Group data set – survival is listed per 1000 infants without anomalies.
The ultimate outcome of preterms needs to include measures beyond survival. We participate in the California Perinatal Quality Care Collaborative (they compile the data in California for the international Vermont Oxford Network registry.) Below are our cumulative 2006-2008 small baby (500-1500 gm birth weight) outcomes on select measures compared to the Vermont Oxford Network. These data are risk adjusted and compared to over 50,000 infants in the international registry. The dots represent CPMC data and the bars the 5-95% confidence intervals. Our outcomes on all these key measures (the dots) are better than expected (the calculated line at 1.) A detailed description of the methodology of this data set is available on the Vermont Oxford web site: http://www.vtoxford.org/
- Pntx: Pneumothorax
- PVL: Periventricular leukomalacia
- CLD: Chronic lung disease (36 weeks, not O2 at day 28) & CLD if born <33 weeks (SGA out)
- NEC: Necrotizing enterocolitis (medical or surgical)
- IVH: Intraventricular hemorrhage – any grade in screened infant
- SIVH: grades 3 and 4 only
- ROP: Retinopathy of prematurity – any stage in screened infant
- Severe ROP: stage 3 or more
- Infections – not congenital, sepsis after 3 days of age
  - Bacterial & Coag neg staph & fungus => NOSO Nosocomial infections
- Mort EED: Mortality if lived beyond 12 hours of age
- Mortality
- Death or morbidity: Px, CLD, NEC, PVL, Severe IVH, Late infection, extremely long LOS; length of stay includes back transfer days
Admission Criteria

Inborn
- Preterm infants <35 weeks gestation
- Birth weight ≤1800 grams
- Any infant requiring continuous monitoring
- Critically ill infants requiring
  - Supplemental oxygen
  - Continuous positive airway pressure
  - Mechanical ventilation
  - Umbilical artery or venous catheters, central lines or peripheral arterial lines
  - Peripheral intravenous lines for continuous infusion of fluid or medications
  - Chest tubes
  - Apnea and bradycardia, frequent and requiring stimulation
- Infants requiring:
  - Frequent vital signs (every two hours or more often)
  - Frequent suctioning
  - Parenteral nutrition
  - Frequent or lengthy feeding
  - Isolation for infection control or immunocompromise
  - Hypoglycemia not responding to oral feedings
- Any problem requiring surgery during the neonatal period
- Infants with complex anomalies
- Neural tube defects
- Congenital heart disease
- Symptomatic or requiring treatment/monitoring
- Seizures or other neurologic problems
- Hyperbilirubinemia requiring exchange transfusion
- Sepsis
- Passively addicted infants requiring pharmacologic treatment

Outborn
Any infant regardless of age may be admitted as a direct transfer from any referring nursery or intensive care nursery. Infants may be admitted from home if less than 28 days of life and without signs of respiratory infection or gastroenteritis. By special arrangements, infants greater than 28 days of age may be admitted to the ICN for surgery or other care after consultation with the neonatologist. During the RSV season we generally recommend that all outborn infants with respiratory illnesses be admitted to pediatrics or have a rapid RSV screen before being admitted to the ICN.

Admission Criteria at CPMC Protocol
Special Considerations for Transporting Infants

The physician or nurse clinician on call accepts transport calls. Never turn down an admission without conferring with the attending neonatologist. We try very hard to accept all transports from our contracting referring sites (Luke’s, Mills-Peninsula, Seton Medical Center, Sutter Santa Rosa, Sutter Lakeside in Clear Lake.) We try to accept all direct referrals from the pediatricians or family practitioners on our staff and all surgical referrals. The following procedures ensure a smooth transport for sick babies.

Accepting the referral:
Get sufficient clinical information about the infant being transported from the referring physician and accept the transport. Refer to the transport algorithm at the front desk on how to contact the transport team. Start collecting information on the transport intake form (in binder at the front desk in North unit.) If the charge nurse has concerns about staffing for the transport, contact the neonatologist on call. If we are unable to accept the infant ourselves, we will help make arrangements for the transfer elsewhere. The decision to not accept a transport is only made by the attending neonatologist. Get the referring hospital’s telephone number and call the on-call neonatologist who will provide suggestions for interim management as necessary.

Arranging the transport:
- Consult the TRANSPORT CHECKLIST (available on the top of the transport packets and on line with the policies and procedures.) The transport cascade is posted at front desk.
- Personnel:
  - All two way transports will include two people: a physician (one of the hospitalists from the ward/PICU team) and a nurse (cross-trained for NICU/PICU.)
  - For non emergency transports, please consult the “two way transport of an infant to a neonatal intensive care unit” policy for composition of the team and which transports can be done with just the RN.

Transport vehicle
Ground transportation is almost always the method used – there is a restriction against landing a helicopter in San Francisco so air transports all need to land at the airport. Consider Air transport if greater than 100 miles or more than 2 hours away – discuss options with the neonatologist and the transport nurse on call.

Communication:
- After the team sent out is done evaluating and stabilizing the patient at the referring hospital, they should call the attending neonatologist on call to discuss the patient. They also should call the NICU to give a status report on the patient and estimated time of arrival before leaving the referring hospital.
- After arrival in the NICU, call the referring hospital and the parents to give them a report on the infant's condition.

Transporting infants with special conditions
- Diaphragmatic hernia: Place an ET tube and ventilate. Insert a replogle tube and maintain continuous suction during transport. Discuss need to divert to a center that provides ECMO.
- Omphalocele or gastroschisis: Insert a replogle tube and put on continuous suction. If the omphalocele sac is intact, take precautions to prevent rupture. Place the entire lower half of the baby into a sterile plastic bag. In general, avoid putting gauze or other material directly on the bowel.
- Tracheo-esophageal fistula with esophageal atresia: Avoid mechanical ventilation if possible, particularly mask ventilation. Place a NG tube into esophageal pouch for drainage.
- Meningomyelocele: Avoid rupturing an intact sac. Cover both ruptured or unruptured sac with sterile normal saline soaked Telfa and cover with plastic wrap or tegaderm. Keep the infant prone with a roll under the hips as much as possible. Begin I.V. antibiotic treatment if sac is ruptured. No IV antibiotics if sac is intact. Use latex precautions for all infants with meningomyelocele.
- Cyanotic heart disease: If a ductus dependent lesion is suspected or highly likely, begin prostaglandin infusion. Consider intubating the infant before transporting because of the possibility of apnea with PGE infusion. If the infant has been receiving a stable dose of PGE without apnea for greater than 1 hour and the transport time is estimated to be less than one hour, it is safe to transport without placing the infant on ventilation.
- Hypoxic-Ischemic encephalopathy: If the infant meets criteria for cooling make sure access is established (UVC – double lumen is preferred and at least 1 PIV or at least 2 PIV’s.) Passively cool the infant (set servo to aim for a temperature of 35-36 degrees.) Have center refer to the Outborn Cooling checklist.
Transport protocols:

**Check list for referring hospitals** to use to get ready for us coming out.

As part of the state mandated data collection we need to report key information on all transports. The CPETS (California Perinatal Emergency Transport System) form has elements we need to complete and the referring hospital needs to complete. All sites have copies of this form but sick babies take up all energies at referring sites so you should confirm they know about the form and are filling out their sections.

These **CPETS referral forms** are in the transport pack and available online.
Delivery Room: NICU Attendance at Deliveries

The neonatal intensive care staff must be present at the following deliveries:
- Cesarean section
- Meconium-stained fluid
- Fetal distress, cord prolapse, placental abruption
- Preterm delivery <36 weeks
- Postterm delivery >42 weeks
- Forceps or vacuum assisted deliveries:
  - All mid forceps/vacuum deliveries
  - Outlet forceps/vacuum delivery for fetal distress
  - Low or outlet forceps/vacuum if any significant fetal heart rate change such as decreased variability, tachycardia, late decelerations or severe variables. If no fetal distress, peds does not need to attend for outlet assistance
- Multiple gestation
- Vaginal breech or complex presentation
- Known polyhydramnios
- Suspected or known major anomalies
- Severe preeclampsia or eclampsia
- Severe isoimmunization or history of in utero transfusions
- Chorioamnionitis
- By request of the obstetrician because of anticipated problems

The neonatal staff should be called after delivery to evaluate:
- Infants with respiratory depression or respiratory distress
- Infants with perinatal depression
- Persistent hypotonia
- 5 minute Apgar <7
- Heart rate >180 or <100
- Any infant weighing less than 2000 gm

The pediatrician should be notified about the following conditions,
- Maternal beta strep positive status if length of maternal pre-treat less than 4 hours or any signs of infection: see guidelines for managements of beta strep positive mothers and treatment of infants
- Maternal fever ≥38˚ and diagnosis of chorioamnionitis
- Maternal drug addiction
- Fetal anomalies (e.g. unilateral hydronephrosis)

If there were sepsis risk factors present but the infant is well baby status, the OB or WBN nurse should notify the pediatrician directly, rather than a message left with the answering service. The following information should be provided when the pediatrician is notified of the delivery:
- Group B strep status of mother
- Adequate treatment prior to delivery (>4 hours)
- Number of hours of ROM
- Maximum maternal temperature
- Obstetrical diagnosis of chorioamnionitis
- Any other information which might indicate risk of infection (e.g. GBS status, presence of fetal distress, foul smelling fluid etc)

Policy on NICU Attendance at deliveries
What to Do When an Infant Dies

- Notify pediatrician, obstetrician and social worker
- Write a note giving time, cause and circumstances of death
- The following cases must be referred to the coroner (415-553-1694) by the attending physician (use a liberal interpretation to call the coroner)
  - Deaths within 24 hours of admission from unknown or unexpected causes
  - Intraoperative or immediate post-operative deaths
  - Suspicious birth circumstances
  - Unsupervised home births or those unattended by unlicensed personnel
  - Births brought on by trauma
  - Early deaths of infants whose mother’s have a history of illicit drug use
- The coroner will either release the case (most frequent) or mandate an autopsy (i.e. no parental consent needed). The coroner encourages calling if any doubt exists to assure nothing important is missed. Coroner will give a case or badge number which should be included in the death note.
- If the death is sudden, unexpected or you do not know the reason for death
  - Draw blood to send to lab to save for additional testing (recommend minimally purple top, several large green tops)
  - Collect urine (for possible metabolic testing)
  - Send cultures of blood and ET aspirate
  - Make sure newborn metabolic screen was done (this may give indications of what to test for on saved blood)
  - Leave lines in place (may remove ET tube to allow parents to see infant’s face)
  - If infant not newly born - treat the bedside like a crime scene: save all the fluid bags, keep the pumps the infant was on separate until it is determined if information is needed from their memory
- If an autopsy is to be performed
  - Get consent signed
  - You can’t legally do any invasive procedures after the infant has died without the consent – including skin biopsies or cardiac punctures for blood
  - Copy of medical record with autopsy consent goes to admitting. If it is the middle of the night keep the chart in the ICN until the next morning.
  - Notify pathology or place obvious note on the permit if you want to be called to discuss the case or to be present at the autopsy.
- The Social Worker on call will help the family with the arrangements for the body.

Stillbirth Infant

Definition: Any infant ≥ 20 weeks gestation born without signs of life at birth.

- A pediatrician or nurse practitioner will be asked to evaluate stillborn infants. The purpose of this exam is to evaluate for possible congenital anomalies. If autopsy consent has been obtained, the stillbirth exam may be deferred to the pathologist. The exam includes:
  - Full exam to be recorded in mother’s chart on the preprinted stillbirth examination form available from the L&D nurses.
  - If there is a question of chromosomal abnormality, get permission from the family for chromosomes or arrange for skin biopsy. For infants who have been dead in utero for any length of time, a skin biopsy is preferable
  - If there is any suspicion of infection, draw blood culture. (You must have informed consent before doing any invasive procedures on a still born infant.)
- Obtain photos. (R.N. will usually do). This may facilitate diagnosis.
- X-rays may be indicated if baby is dysmorphic. Both X-Rays and photos can be done in pathology for dysmorphic infants, even if parents decline an autopsy.
- Obstetrician will usually seek autopsy permission. If you are doing cultures, chromosomes or skin biopsy, you must have autopsy permission. A limited autopsy request for these procedures should be signed and expansion of the permit to include full postmortem exam can be done at a later date.
Non-viable Liveborn Infant

Definition: Infant born very prematurely or with severe, lethal anomalies.

- The neonatologist on call should be made aware of impending delivery so they are present to assist in decision-making if there has been no opportunity to discuss the family’s wishes before the delivery. No resuscitation is offered for fetuses <23 weeks gestation.
- If the family and obstetrician decide that they want no resuscitative efforts, you may be called to attend the delivery and provide comfort care or to evaluate the infant after birth or only to examine the baby (for anomalies) after they have died. If you will not be called to delivery discuss with the L&D staff comfort measures and importance of keeping the baby warm.
- All liveborn infants must be admitted into the hospital computer system as infants (given their own medical record number.) They may be cared for in the delivery area with the mother or, if the parents request, given comfort care in the ICN. If brought to the ICN, the patient is admitted to “growing care” status and a note is written in Daily Baby.
- Pain medications may be given as comfort measure.
- Evaluation of infant may include cultures, chromosomes, radiographs and photographs as indicated to assist diagnostic efforts and future counseling of the parents.
- Infant should be kept warm and hourly vital signs taken and recorded.
- Document reasons for “non-viability”, time of death, and write a short death summary in Daily Baby.
- Obtain autopsy consent, if indicated.
- Notify social worker of death

If an infant dies in the delivery room, he/she still needs a short admission note as a liveborn infant (hand written for the baby chart or done in Daily Baby.) If you have no involvement until after the infant has died you may do the exam on the stillbirth/non-viable infant form provided by the L&D staff.
Both a birth and death certificate must be completed for all liveborn infants who die.

Perinatal Loss Policy at CPMC

Neonatal Organ Donation

Organ donation can provide consolation to a dying patient's family as well as benefit the organ recipient. We are also mandated by California law to provide information about donation to potential donors' families under certain circumstances. To be considered for organ donations, the infants must be at least 36 weeks of gestation. Tissues currently donated by neonates include cornea, liver and heart.

Call the California Transplant Donor Network 1-800-553-6667:
Information needed: patient name, age, medical, surgical and social history

Brain Death

- A representative of the Transplant Bank will meet with the family, make transplant arrangements and perform the organ removal.
- Organs considered from neonates include heart, kidneys, liver
- Corneas need to be removed within 8 hours of circulatory death.
- There is no guarantee that the donor tissue will be adequate for transplant or that recipients will be available. Unused tissue will be used for transplant research.

- Criteria for Neonatal Brain Death
  - May be determined entirely on clinical grounds
  - Two licensed physicians must put in writing that the infant is brain dead by clinical criteria.
  - A ventilatory challenge test (i.e. no onset of spontaneous breathing with rise in pCO2 > 60) may be one clinical criteria
  - Clinical evaluation (in absence of metabolic or toxic CNS depression)
  - No pupillary reflex
  - No corneal reflex
  - Dolls eyes present
  - No gag or cough reflex
  - Apneic
The second physicians note documenting brain death is considered the time of death.

Donating Milk to Milk Bank

San Jose milk bank will take donations of milk from families in our unit. This comes up when an infant has died or a mother has lots of milk at time of discharge and no freezer capacity at home. The process for donating milk is:

- Call San Jose Milk Bank – 866-998-4550 to alert them if you have a donor for bereaved donor program
- Have family call milk bank to do intake screening (we may do this step for the family.) Families can designate milk for research or feeding babies.
- The milk bank will accept any amount of milk from a bereaved mother. For other donations they may refuse the donation due to medical reasons or due to costs and processing small volumes of milk.
- Maternal medical criteria for donation for feeding to babies are nationally supported by the human milk banks
- Consent for donation must be signed
- Donor information forms must be completed and can be faxed to milk bank at 408-297-9208. A consent form and a 2 page donor interview form are needed before the milk bank will pick up milk or start the donation process (call above number to get the forms.) For bereaved families the milk bank staff will take the remainder of the intake forms with the mother.
- The San Jose milk bank will come to pick up the milk at the hospital or will send a cooler for FedEx shipping.
- The milk bank will arrange for maternal blood tests (they will come to the mother if infant has died.)
Criteria for Home Monitoring

Definitions:
- Apnea of infancy: cessation of breathing for 20 seconds or longer, or shorter pause associated with bradycardia, cyanosis, pallor and/or marked hypotonia. (Infant > 37 wk gestation at birth)
- Apnea of prematurity: same as above at < 37 weeks
- Extreme apnea: apnea lasting >30 second with bradycardia <60 in infants <44 weeks, or apnea > 30 seconds with bradycardia <50 bpm ≥44 weeks gestation and lasting >10 seconds
- ALTE (apparent life threatening event): episode frightening to observer characterized by a combination of apnea, color change (cyanosis or pallor) marked change in muscle tone, choking or gagging.

Natural history of Apnea and Sudden infant Death Syndrome
“Extreme apnea” is most common in preterm infants <37 weeks gestation, but occurs in 2.3% of healthy term infants. Almost all extreme apnea is resolved by 43 weeks postmenstrual age. There is no evidence that apnea (either of infancy or of prematurity) is associated with SIDS. There is no evidence that home monitoring prevents SIDS.

Recommendations for Home Monitoring
- Preterm infants who continue to have episodes of extreme apnea at 37 weeks gestation or greater. Monitoring may be discontinued after 43 weeks or cessation of episodes, whichever happens later.
- Infants who are technology dependent (tracheostomy, CPAP), have unstable airways, have conditions affecting regulation of breathing or have symptomatic chronic lung disease (Home oxygen)
- All home monitors should be equipped with event recorders and follow up analysis of those recorders arranged prior to discharge.

Reference: Committee on Fetus and Newborn, Apnea, Sudden Infant Death Syndrome, and Home Monitoring, Peds111: 914, 2003 (www.aap.org)
**Hearing Screens**

All infants cared for at CPMC have a hearing screen prior to discharge. Parents of infants in the ICN may refuse the screen only on religious grounds. Parents of infants not in the ICN may refuse the hearing screen for any reason.

Infants who are readmitted to the ICN and were screened prior to discharge from the regular nursery need to have a second screen if they receive ototoxic antibiotics or are admitted for hyperbilirubinemia.

The following infants are at the highest risk for hearing impairment:

- Family history of congenital or delayed onset childhood sensorineural impairment
- Congenital infections known or suspected to be associated with sensorineural hearing impairment such as toxoplasmosis, syphilis, rubella, cytomegalovirus and herpes.
- Craniofacial anomalies including morphological abnormalities of the pinna and ear canal, absent philtrum, low hairline, cleft lip or cleft palate et cetera.
- Birth weight less than 1500 grams.
- Hyperbilirubinemia at a level exceeding indication for exchange transfusion.
- Ototoxic medications including but not limited to aminoglycosides used for more than 5 days and loop diuretics (furosemide etc.) used in combination with aminoglycosides.
- Bacterial meningitis
- Severe depression at birth, which may include infants with 5 minute Apgar scores of 0-3 or those who fail to initiate spontaneous respiration by 10 minutes or those with hypotonia persisting to 2 hours of age.
- Prolonged mechanical ventilation for a duration ≥ 10 days.
- Stigmata or other findings associated with a syndrome known to include sensorineural hearing loss (e.g. Wardenburg or Usher’s syndrome)
- Diaphragmatic hernias

All infants are tested with a brain stem auditory evoked response. The test should be done as close to discharge as possible in most infants. Overall, the refer rate of the ABR at CPMC is about 2%. Infants tested at ≤34 weeks gestational age have higher rates of false positives because of immaturity. All infants who refer on the ABR from the ICN must be retested in one month with a full diagnostic evaluation at a state approved hearing center. The appointment for follow up testing is made prior to discharge of the infant from the ICN. The hearing screeners will make the necessary appointments but we need to make sure these are documented in the record.

Results of the ABR are recorded on the “Hearing Screen Result” form and entered into the Daily Baby.

If baby is transported out before hearing test is done the discharge summary must specifically state the hearing test was not done.

The hearing screening policy for CPMC
Management of Neonatal Abstinence Syndrome (Drug Withdrawal)

General
- 5-15% of all pregnant women have substance abuse problems during pregnancy
- The infants are usually not ill but withdrawal symptoms can mimic other metabolic, infectious or CNS disease e.g. hyperthyroidism, intracranial hemorrhage, perinatal anoxia, hypocalcemia, hypoglycemia, hyperviscosity.
- Incidence of withdrawal symptoms varies with drug and pattern of usage. The incidence and timing of onset is best known for narcotic abstinence syndrome and most of the “withdrawal scores” are based on narcotic withdrawal
- 40-90% of exposed infants show some signs of withdrawal. Higher incidences are seen in methadone exposed (over 75%). Less initial or obvious withdrawal is seen in infants exposed to stimulants (cocaine, amphetamines.)
- Onset and severity depend on
  - Maternal drug dose
  - Last use of drug
  - Frequency of use during pregnancy
- ~60% of infants exposed to drugs need pharmacologic treatment. Maternal methadone is the best studied drug in terms of dose/withdrawal effects.

Maternal methadose dose and symptoms:

<table>
<thead>
<tr>
<th>Maternal dose</th>
<th>% infants requiring pharmacologic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 mg/day</td>
<td>12%</td>
</tr>
<tr>
<td>20-39 mg/day</td>
<td>44%</td>
</tr>
<tr>
<td>&gt;40 mg/day</td>
<td>90%</td>
</tr>
</tbody>
</table>

Delivery Room
Resuscitate as per NRP. Do not use narcan for resuscitation if mom used narcotics during pregnancy as this can result in seizures.

Nursery Care:
- Admit to the regular nursery if birth weight is over 2000 gm and gestational age >35 weeks. Admit to ICN if birth weight <2000 gm, gestational age <35 weeks or if infant is ill
- Laboratory orders
  - Urine for “Complete Drug Screen” (10 ml collected in plain urine bag). This will include the usual drugs of abuse other than PCP. Screen for PCP must be ordered separately (may be obtained on same urine specimen as other screen just needs a specific order.) Drug screens are generally obtained on both the mother and infant unless the family refuses. Family must be made aware that drug screen is being done.
  - Meconium can also be tested and may be more reliable since drug use as early as second trimester can be detected in the meconium. Drugs can also be detected by hair analysis in mom or baby and some experts are recommending testing umbilical tissue for drugs, however, urine screening is the most commonly used method.
- Results of urine toxicology screen depend on when drug was last used by mother. In general, half life of drugs is prolonged in infants due to hepatic and renal immaturity; half life of various drugs is as follows:
  - Cocaine-24-48 hours in an adult, 72-96 hours in an infant
  - Marijuana – 7 days-1 month in an adult, longer in an infant
  - Heroin-24 hours in adults, 24-48 hours in infant
  - Methadone – In newborn 10 days.
- Check prenatal records for Hepatitis B and C status, maternal RPR and HIV. Push for getting HIV test on mother if maternal status unknown. Suspected drug use or a positive urine toxicology screen is an indication for a social service referral.
- Mother must be informed that a drug screen will be obtained. A separate consent form is not required, but the mother has the option of refusing.

Symptoms of withdrawal
See scoring scale below – severe signs include:
- Seizures
- Diarrhea (≥ 6 stools/day)
- Severe emesis (vomiting >10% of intake)
- Increased FiO2 requirements
- Tachycardia (HR >20 bpm over baseline)
- Systolic BP >90 mmHg
- Continuous inconsolable crying despite nursing interventions

Management of withdrawal
- Scoring: Begin assessment for withdrawal at birth using the modified Finnegan scoring system. Score every 4 hours, more frequently if score is >8. Score is best validated for narcotic withdrawal.
- Supportive Treatment- 40% of infants can be managed with symptomatic treatment. Use of pharmacologic treatment prolongs hospitalization.
- Decrease sensory stimulation – swaddling, quiet dark room, holding quietly, sucrose nipple
- Use higher caloric feedings if necessary for weight gain (may need 150-250 cal/kg/day for growth)
- Consider IV fluids for infants with severe GI symptoms
- Drug treatment
  - Choice of treatment should be tailored to prenatal drug exposure. Remember that many drug users are polydrug users and the infant may need more than one medication.
  - All infants who seize should receive anticonvulsant medications
- For infants with severe withdrawal symptoms and marked irritability, the addition of Phenobarbital (loading dose 20 mg/kg, maintenance 5 mg/kg/day) has been shown to decrease symptoms and shorten hospital stay in one study. (Coyle M et al, J pediat 140:561, 2002)

Pharmacological intervention should be used for abstinence scores >8. *Dosing range varies and needs to be guided by abstinence scores.*

**Morphine (concentration 2mg/ml)**
- **Indication:** first-line medication used for prenatal opiate exposure weaning
- **Dose:** 0.05-0.15 mg/kg/dose, every 4 hours using oral morphine sulfate
- Scores of >10 for 2 consecutive scores = consideration of increasing the dose
- Start taper for prenatal exposure using a dose of Score every 2 hours until scores are <8 for 4 consecutive scores.
- Scores of <8 for 2 consecutive scores = consideration of decreasing the weaning dose.
- Taper the dose by approximately 10% no more often than every 24 hours
- Keep dosing interval at every 4 hours for the entire weaning process
- Lower dose late on the night shift so the effect of the wean can be observed during morning rounds

**Methadone (concentration 1mg/ml)**
- **Indication:** used in neonates who have received 5 or more days of continuous or frequent fentanyl. Begin methadone taper when opiates are no longer needed to treat pain and abstinence scores deem necessary.
- **Dose:** Start 0.05-0.2 mg/kg/dose with feeds every 6 to 8 hours
- Increase as needed by 0.05 mg/kg/dose until scores <8
- Wean/taper at 72hrs or after scores are stable and <8
- Taper by increasing interval time
- Proceed to daily dosage of 0.05 mg/kg/day for 3days, then discontinue
- Medication duration is about 22-48 hours and contains 8% alcohol

**Phenobarbital**
- **Indication:** to treat seizures
- **Dose:** Loading dose: 20 mg/kg/dose
  Maintenance dose: 5 mg/kg/day (may be divided BID)
Clonidine
- **Indication**: use in when morphine / methadone not controlling symptoms or in difficult to wean patients. Helps reduce adrenergic symptoms associated with NAS
- **Dose**: 1 microgram/kg/dose every 6-12 hours
  - May advance to 10 microgram/kg/day (maximum dose)

**Neonatal abstinence policy at CPMC**

<table>
<thead>
<tr>
<th>Abstinence Scoring Sheet</th>
<th>Date: __________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signs and Symptoms</strong></td>
<td><strong>TIME</strong></td>
</tr>
<tr>
<td>Excessive high pitched cry</td>
<td>2</td>
</tr>
<tr>
<td>Continuous high pitched cry</td>
<td>3</td>
</tr>
<tr>
<td>Sleeps &lt; 1 hour after feeding</td>
<td>3</td>
</tr>
<tr>
<td>Sleeps &lt; 2 hours after feeding</td>
<td>2</td>
</tr>
<tr>
<td>Sleeps &lt; 3 hours after feeding</td>
<td>1</td>
</tr>
<tr>
<td>Hyperactive Moro</td>
<td>2</td>
</tr>
<tr>
<td>Markedly hyperactive Moro</td>
<td>3</td>
</tr>
<tr>
<td>Mild Tremors Disturbed</td>
<td>1</td>
</tr>
<tr>
<td>Moderate-Severe Tremors Disturbed</td>
<td>2</td>
</tr>
<tr>
<td>Mild Tremors Undisturbed</td>
<td>3</td>
</tr>
<tr>
<td>Moderate-Severe Tremors Undisturbed</td>
<td>4</td>
</tr>
<tr>
<td>Increased Muscle Tone</td>
<td>2</td>
</tr>
<tr>
<td>Excoriations</td>
<td>1</td>
</tr>
<tr>
<td>Myoclonic Jerks</td>
<td>3</td>
</tr>
<tr>
<td>Generalized Convulsions*</td>
<td>5</td>
</tr>
<tr>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td>Fever &lt;38°</td>
<td>1</td>
</tr>
<tr>
<td>Fever &gt;38°</td>
<td>2</td>
</tr>
<tr>
<td>Frequent Yawning (&gt;3 times/interval)</td>
<td>1</td>
</tr>
<tr>
<td>Mottling</td>
<td>1</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>2</td>
</tr>
<tr>
<td>Sneezing (&gt;4 times/interval)</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory Rate &gt;60 breaths/minute</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory Rate &gt;60/min with retractions</td>
<td>2</td>
</tr>
<tr>
<td>Excessive Sucking</td>
<td>1</td>
</tr>
<tr>
<td>Poor Feeding</td>
<td>2</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>1</td>
</tr>
<tr>
<td>Projectile Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Loose stools</td>
<td>2</td>
</tr>
<tr>
<td>Watery stools</td>
<td>3</td>
</tr>
</tbody>
</table>

*Always need treatment

**Scoring Intervals:**
- Begin 2 hours after admission
- Repeat score q 4 hours
- For Scores>8, repeat in 2 hour intervals
- Consider pharmacotherapy if scores:
  - 8 for 3 consecutive periods
  - 3 periods average >8

Scored by ____________________________

*Adapted from Finnegan*
Developmental Dysplasia of the Hip (DDH)

**Definition:** A condition in which the femoral head has an abnormal relationship to the acetabulum. May include dislocation, subluxation, instability of femoral head.

**Incidence:**
- 1-10 cases/1000 live births
- ↑ Incidence in girls (OR 4.6)
- ↑ Breech presentation (OR 7)
- ↑ Family history (OR 1.7)
  - Left hip 3X more commonly involved than right hip

**Screening by Physical exam**
- All infants will be screened for DDH at the initial newborn exam. Examine for asymmetry, limited abduction and/or adduction. Ortolani (Abduction) and Barlow (adduction) tests are performed for dislocation and stability respectively. A positive sign with either test is a “clunk” which is felt as the hip is reduced (Ortolani) or dislocated (Barlow). Hip clicks as opposed to the “clunk” are generally not significant and need only follow up exams.
- **Positive Ortolani or Barlow sign:** refer to orthopedist. Most positive findings will resolve by two weeks of age, so patient should be seen by 2 weeks generally.
- **Equivocal exam or soft click:** follow up exam by pediatrician at two weeks, then serial exam as below

**Screening by Risk Factors**
- **Breech presentation** (risk for boys 26/1000, for girls 120/1000)
  - Follow up exams: if positive, refer to orthopedist
  - Consider ultrasound at 6 weeks of age or radiograph at 4 months for girls even with negative exam
- **Positive Family history** (risk for boys 9.4/1000, girls 44/1000)
  - Boys: refer if positive exam, continue periodic exams if negative
  - Girls: refer if positive exam, consider ultrasound at 6 weeks or X-ray at 4 months even with negative exam.

**Treatment**
- No triple diapers, even with positive exam. As many exams normalize by 2 weeks of age, instituting treatment too early results in over treating infants.
- Arrange for follow up with orthopedist by 2 weeks of age in infants with positive exam. Orthopedist will institute treatment at that time.
- Recheck hips in two weeks in infants with equivocal exams or at high risk
- Continue periodic hip exams as recommended (2-4 days, 2 months, 4 months, 6, 9 and 12 months) in infants with negative exams
- Consider hip ultrasound at 6 weeks of age or radiograph at 4 months of age in high risk groups

Reference: AAP Clinical Practice Guideline, 2000
http://aappolicy.aappublications.org/cgi/content/full/pediatrics;105/4/896
Dorsal Midline Cutaneous Findings

Cutaneous findings on the back around the spine may be portals of entry into the spinal-cerebral space or indicators of underlying spinal cord abnormalities. Open defects need immediate neurosurgical referral. It is assumed that the neurologic exam is normal and there are no lower limb abnormalities. Plain X-rays are rarely indicated. If MRI is indicated, make sure the Pediatrician knows to check with the neurosurgeons prior to scheduling the test to insure that the imaging center used can do newborn spine MRIs of adequate quality. MRI’s that must be done under anesthesia should be scheduled for after 50 weeks gestational age.

Finding:
- **True Isolated Hairy Tuft:** This finding is associated with tethered cord. Spine MRI at three months of age.
- **Paraspinal true hemangioma:** MRI at three months of age.
- **Dorsal Midline Pits:**
  - Pits found below the intergluteal fold (as many as 5% of newborns) are all blind sacrococygeal dimples and do not have any potential connection to intraspinal structures. Do not probe. There is potential for local irritation and infection. Parents should be instructed on how to keep these areas clean (irrigate as needed with bulb syringe—do not use Q-tips).
  - Midline dorsal pits above the intergluteal fold (incidence ~1/1500 live births) have a 60+% chance of intraspinal connections. Most are in the lumbo-sacral region (90%). Do not probe a potential sinus as there may be teratomas, cysts, blood vessels and/or neural tissue associated with the sinus. Infectious agents can also be introduced. There can also be other spinal cord abnormalities. Sinuses often ascend prior to connecting to the dura. If a sinus is present, simple traction caudally will deepen the pit (it’s attached toward the head and will pull in). If the connection is pilonidal (to the gut) traction rostrally will deepen the pit. All pits suspected to connect to the spine should be studied by MRI at three months of age. Pilonidal pits can be cared for by just keeping them clean.
- **Skin covered mass:** These may be underlying teratomas, dermoids, lipomyelomeningoceles or other neuroglial masses. These are all surgical in nature, so transfer to a tertiary center is warranted prior to imaging studies (usually MRI) being pursued.
- **Dimples:** Isolated sacral dimples can be evaluated with the traction test (see above). Dimples that are clearly in the lumbar area or above, regardless of the absence or presence of a sinus need to be evaluated by MRI. Babies with sacral dimples associated with other findings (hairy tuft, clubfoot or other lower limb deformities) should be evaluated by MRI.

Questions? Don't hesitate to call Pediatric Neurosurgery-
Management of the Newborn with Prenatal Diagnosis of Hydronephrosis

Please note that this is an area of controversy in terms of work-up and treatment that is continually evolving. These guidelines were current at the time of their writing in 2008, but may have changed since then. Consultation with a Pediatric Urologist is always recommended for the most current approach to this issue.

Fetal Hydronephrosis/Pylectasis
- Most commonly diagnosed fetal abnormality
- Found 1% of prenatal ultrasounds
- For pylectasis diagnosed by early (18-23 weeks) ultrasound, severity of dilatation of renal pelvis (RPD) predicts resolution:
  o Mild (<7 mm) 88% resolve completely
  o Moderate (7-10) 44% resolve
  o Severe (>10) 10% resolved
- If early (18-23 week) US shows pylectasis, a repeat ultrasound is recommended in 3rd trimester. If repeat RPD measurements are normal, no postnatal follow up is needed
- Normal values depend on fetal age; post-natal follow-up and imaging is dependent on in utero measurements. In general, we use classifications based on a 3rd trimester US
  o Severe: ≥15 mm
  o Moderate: 10 to 15 mm
  o Mild: >7 but ≤10 (3rd trimester)
- In a series that followed 213 infants for two years after in utero diagnosis of mild/moderate hydro, 39% had significant nephrouropathies on 2 year follow up. 10% of those had UTI’s diagnosed in first 2 years of life. Surgery was necessary in 7% of patients. (Ismaili et al, JPeds 2004;144:759)

Recommendations for the follow-up for prenatally diagnosed kidney dilatation.

Normal Dilatation: 3rd trimester Ultrasound (US) AP diameter (APD) less than 7 mm
If prenatal ultrasound in the third trimester shows a fetal kidney pelvis that has an AP measurement of less than 7 mm and no other abnormal findings (caliectasis, cortical thinning, ureteroceles, dilated ureters, echogenicity in the kidneys or bladder abnormalities (thickened, key hole sign, inadequate emptying)) no further workup is indicated as long as the is baby clinically well.

Mild Dilatation: 3rd trimester ultrasound AP diameter (APD) of 7-10 mm
If the ultrasound in the third trimester shows a unilateral dilated kidney pelvis (also referred to as hydronephrosis, pelviectasis or pyelectasis) that is “mild” or has an APD of 7-10 mm, but no other abnormal findings (see above underlined):

This is most likely a variation of normal.
- Follow-up ultrasound should be done in the 1st three months after birth to confirm that the hydronephrosis is indeed mild.
- No Prophylactic antibiotics.
- If follow-up ultrasound shows an APD less than 7 mm and the baby is clinically well, no additional follow-up is needed.
- If follow-up ultrasound shows APD 7-10 mm repeat renal US at 1 year of age. If that US shows APD 7-10 mm, repeat US at 2 years of age.
- If any follow-up ultrasound shows APD greater than 10 mm do a VCUG to rule-out reflux. Give 25 mg/kg oral amoxicillin one hour prior to the VCUG. Consult Pediatric Urology to treat reflux if the VCUG is positive or evaluate for possible lasix renogram.
Moderate Dilatation: 3\textsuperscript{rd} trimester APD greater than 10, but less than 15 mm

- If ultrasound shows a unilateral dilated kidney pelvis that is more than “mild” or if APD is greater than 10 mm, but less than 15 mm and no other abnormal findings (see above underlined):
  - Follow up ultrasound should be done prior to 5 weeks after birth. The ultrasound does not need to be done prior to discharge. Ultrasound is preferably done at least 48 hours after birth to allow for the kidneys to adjust to extrauterine life. During the first 24-48 hours any dilatation may be underestimated due to the relatively “dehydrated” state of the kidney.
  - No prophylactic antibiotics are needed.
  - If the follow-up ultrasound shows an APD of less than 10mm follow guidelines above.
  - If the follow-up ultrasound shows an APD that is between 10-15 mm perform a VCUG. If the VCUG is positive refer to Pediatric Urology: if VCUG is negative do a follow-up ultrasound at 1 year.
  - If the follow-up ultrasound shows increased an APD of 15 mm or greater, start prophylactic amoxicillin and do a VCUG to rule out reflux. If reflux is present consult with Pediatric Urology. If VCUG is normal, do refer to Pediatric Urology for assessment of the need for a lasix renogram.

Severe Dilatation: 3\textsuperscript{rd} trimester APD greater than or equal to 15 mm

- Start prophylactic antibiotics (once daily dose of 25 mg/kg amoxicillin orally).
- Patients should be referred to Pediatric Urology soon after birth to determine evaluation needs.

Other Findings are present

- If prenatal ultrasound shows any abnormality in the urinary system such as bilateral kidney pelvic APD greater than 7 mm, caliectasis, cortical thinning, ureterocele, dilated ureters, echogenicity in the kidneys, or an enlarged bladder:
  - Start prophylactic antibiotics (once daily dose of 25 mg/kg amoxicillin orally).
  - Obtain a renal ultrasound prior to discharge from the hospital.
  - Discuss the patient with Urology to determine timing and type of follow-up appointments and testing needed.

Do not hesitate to confer with Dr. Baskin if you have any questions. He can be contacted at 415-353-2065 or 415-353-2200 email: lbaskin@urology.ucsf.edu.
Approach to the Infant with a Single Umbilical Artery

Background: the incidence of single umbilical artery (SUA) is about 3/1000. In a retrospective review of a large population (Leung and Robson, AJDC, 1989) 159 cases were found among 56,919 infants. Of the 159 infants with SUA, 45% had other malformations. It is 3-4 x more common in twin pregnancies. There is no syndrome in which SUA is clearly associated.

The vast majority of significant anomalies found in this survey of infants could be detected by physical exam or determined by tests commonly done on symptomatic infants (e.g. chest x-ray or glucose level). Most “silent” lesions were either inconsequential or could be determined at the time when symptoms presented without significant compromise to the infant’s health (i.e. vertebral body anomalies, spina bifida occulta) The only exception to this was the renal system. In this study there were 27/159 patients with SUA who had no symptoms or renal findings on exam. Five of the 27 asymptomatic patients had abnormalities on renal ultrasound or IVP. A meta-analysis of 37 published studies over a 40 year period also found that approximately 16% of infants with SUA had renal abnormalities detected by renal studies; however over half of those were self-limiting or minor. The most common significant abnormality was vesicoureteral reflux. (Thummala MR, Raju T, Langenberg P, J Pediatr. Surg 33:580,1998.)

Recommendations:

- Careful physical exam for associated anomalies
- If significant findings on cardiac exam, do an echocardiogram
- Determine if an in-utero ultrasound was done; if a study was done after 22 weeks gestation showing normal kidneys, no further evaluation needed.
- If no in utero ultrasound or abnormal ultrasound, follow up renal ultrasound at 7-14 days of life
Routine Measurements in the ICN

Assessment of Gestational Age & Growth

Assessing Gestational Age
- Gestational age is assessed in all infants admitted to the NICU. The EDC based on early ultrasound and/or early pregnancy testing is the most reliable assessment of gestational age. This is especially true in infants less than 28 weeks. If prenatal care is obtained late and maternal dates uncertain, the assessment of GA based on physical and/or neurologic criteria may be more reliable. For infants for whom maternal dates are uncertain, a Ballard assessment of gestational age should be done during the first 24 hours of life and then repeated at 48 hours (for more accurate neuro assessment).

Intrauterine Growth and Birth Weight Charts
- Appropriate for gestational age infants: 10th and 90th percentiles.
- Small for gestational age or intrauterine growth retardation (IUGR) infants: less than the 10th percentile.
- Large for gestational age infants: greater than the 90th percentile.

Postnatal Growth
- After birth, infants are measured weekly and their growth plotted on a postnatal growth chart (page ). The Babson growth chart combines both birth weight and postnatal weights and is not well validated for infants <28 weeks. The NICHD combines data from multiple centers and is stratified by level of illness as well as by birth weight/gestational age. (Ehrenkranz et al, Ped 104:280-289,1999)

Intrauterine Growth by Ultrasound

![Graph of Intrauterine Growth by Ultrasound]
California Birth Weight Curves

Males

Females
### Ballard Exam

#### Neuroromuscular maturity

<table>
<thead>
<tr>
<th>New Ballard Score†</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td><strong>Posture</strong></td>
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<td><strong>Square window (wrist)</strong></td>
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<td><strong>Heel to ear</strong></td>
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</table>

The New Ballard Score is used to estimate gestational age from neuroromuscular and physical features. The scores of each feature are added to calculate a maturity rating which correlates with gestational age (See Figure 1).† Adapted from Ballard, J.L., et al. J Pediatr 1991; 119:417.

#### Physical maturity

<table>
<thead>
<tr>
<th>New Ballard Score†</th>
<th>-1</th>
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<th>1</th>
<th>2</th>
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The New Ballard Score is used to estimate gestational age from neuroromuscular and physical features. The scores of each feature are added to calculate a maturity rating which correlates with gestational age (See figure 1a).† Adapted from Ballard, J.L., et al. J Pediatr 1991; 119:417.
Postnatal Growth

Data from NICHD neonatal network. Includes growth rates of survivors >7 days.
Ehranranz R et al, PEDIATRICS Vol. 104 No. 2 August 1999, pp. 280-289

See full article for difference in growth between SGA and AGA preterms
Babson & Benda Postnatal Growth Curve

Plot growth in terms of completed weeks of gestation.


Citation: Fenton TR. BMC Pediatr. 2003 Dec 16; 3(1): 13
Physiologic Monitoring
Arterial Blood Pressure

- Blood pressure may be monitored invasively through an umbilical or peripheral arterial catheter or noninvasively with an automated blood pressure cuff monitor. Infants requiring >40% oxygen for more than 8 hours or mechanical ventilation usually have an arterial catheter at least initially for blood gas sampling and pressure monitoring.

- Blood pressure increases over the first month of life in very low birth weight infants, so “normal values” must be related to postnatal as well as gestational age.

- Normal values are not well established for the extremely low birth weight infant. The following tables include some of the better studies from the literature.

Estimating MAP: This formula slightly overestimates the 95% CI on day one for ELBW babies.

\[-2SD\ MAP = GA\ (wks) - 2\]

Blood Pressure standards for very low birth weight infants during the first day of life

http://fn.bmjournals.com/
Lowest acceptable MAP for ELBW babies
Data from 61 very low birth weight infants, day one of life (no IVH, inotropes, or sepsis)

Lower 95% CI for MAP vs. birth weight

<table>
<thead>
<tr>
<th>BW</th>
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Lower 95% CI for MAP vs. GA

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Serial changes in mean arterial blood pressure in VLBW infants
Modified from Watkins AM et al, Early Human Development, 1989:103

MAP by BW and Time
Systolic blood pressure in the first year of life
Umbilical Arterial Catheters

Placement
In general, we use “low catheters”, between the 4th and 5th lumbar vertebrae at the aortic bifurcation. If catheter is “high” (above the diaphragm) it should be between T6 and T10.

The position of the major aortic branches is as follows:
- Celiac: T11 - T12
- Superior Mesenteric: T12 - L1
- Renal: L1 - L2
- Inferior Mesenteric: L3 - L4

Estimates of insertion depth for low lying UAC:

2 x umbilical to inguinal ligament length + length of umbilical stump

Birthweight in kg + 7 (add in more if the cord stump length is long)

- Management of Vasospasm related to catheter
  - Warm contralateral limb (never warm the affected area as this will increase metabolic needs to an already compromised area)
  - For persistent or severe vasospasm, use nitroglycerine paste applied to involved toes or foot
  - For severe vasospasm involving entire limb, remove catheter immediately
**Peripheral Arterial Catheters (Radial or Posterior Tibial)**

- Indications for use are the same as umbilical catheters. Generally, radial or posterior tibial arteries used.
- Infuse only normal saline or 0.45 normal saline. Heparinize all fluids infused (1 unit/ml).
- For dampened tracing from vasospasm, consider an infusion containing lidocaine 4 mg/100 ml (0.04 mg/ml) if line is critical (discuss with neonatologist first)
- No blood products should be infused through catheter.
- Papaverine (30 mg/250 ml solution) infused with heparin (1 unit) in peripheral arterial lines has been shown to prolong catheter patency (Griffin and Siadaty, J Pediat 146: 62, 2005)

**Venous Catheters and Central Venous Pressure**

- Placement: Use graph to estimate distance. Catheter must be above the diaphragm, preferably in IVC.
- Venous catheters do not need to be routinely on a transducer – transducer is needed only if wish to measure CVP.
- Double lumen umbilical catheters are useful for very tiny infants – to avoid placing PIV for medications, blood and pressors and very very ill infants (like cooling babies) where pressors may be needed
- Dual ports means dual portal of risk, such as air bubbles and infection

Before flushing any port blood must be pulled back into the syringe to insure there are no air bubbles. Air bubbles in the venous system of infants with transitional circulation (patent foramen or R to L ductal shunting) could result in air emboli to brain or other important structures.

![Estimated Insertion length for Umbilical Venous Catheter](image-url)
Environmental Control Ambient Temperature

Delivery Room
- Term Infants
  - Dry immediately and wrap in warm blankets or place skin to skin on mother
  - Temperature check within first 1 hour of life
- Very low birth weight infants (<1500 gram estimated or <32 weeks GA):
  - Increase ambient temp of delivery room prior to delivery (up to 72 F)
  - Assign one member of resuscitation team to temperature control
  - Prewarm open table – in ELBW’s consider use of chemically activated gel mattress (available in the PYXIS machine) – using caution not to place in direct contact with infant’s skin as burns can occur and monitor infant temperature as infants can overheat on these mattresses (mattresses can heat to 41 C)
  - Wrap infant immediately in plastic wrap (do not dry) and keep infant in plastic until ready to weigh the infant on the giraffe bed
  - Use double hats
  - Transfer from DR/OR in warmed transport incubator
- Low Birth Weight Infants
  - All of above, but may not need plastic wrap.
  - Dry immediately and transport via warm transport incubator

Post Delivery
- For infants < 1000 grams or < 26 weeks gestation, use Giraffe incubators with humidification set to 70%. Incubator temperatures may need to be increased with the humidification.
  - Begin weaning infants from incubator to crib when >7 days and >1700 grams; in general the incubator temp required by the infant should be ≤31 °C before weaning is attempted.
  - Infants who require excessive number of blankets to maintain a normal temperature should be returned to the incubator.
  - Temperature instability may be masked by fluctuations in isolette temperatures (especially if the infant is on servo-control.)

The graph below demonstrates the advantage of clothing on ambient temp requirements. It may be beneficial to clothe the infants once stable.
Analgesia and Sedation

**General principles of pain management in the ICN**
- Newborns, both term and preterm do feel pain (pain perception develops around 18-20 weeks of gestation.) It is often unrecognized.
- If a procedure is painful in adults, it is painful in newborns (term and preterm) since they have increased sensitivity to pain.
- Adequate treatment of pain may be associated with decreased clinical complications and decreased mortality.
- The appropriate use of environmental, behavioral and pharmacological interventions can prevent, reduce or eliminate neonatal pain in many clinical situations.
- As with adults, prevention of pain or early treatment of pain is more effective than limiting analgesia
- Sedation does not provide pain relief and may mask the neonate’s response to pain

**Goals of Therapy:**
- Prevent pain: Avoid unnecessary procedures. Use appropriate analgesic when possible before any painful procedure including elective intubation
- Decrease pain: use swaddling, containment, sucrose nipple. Consider continuous narcotic infusion if baby seems agitated with ventilation
- Decrease anxiety, agitation
- Decrease oxygen consumption
- Decrease protein catabolism
- Prevent extubation, improve ventilation
- Prevent wound separation post-operatively – should always be used when muscle relaxants being used

**Monitoring effectiveness of therapy**
- Pain is assessed routinely using the neonatal pain score every 4 to 6 hours and recorded with vital signs
- Pain score should be reassessed after each potentially painful intervention
- Treatment should be adjusted based on the pain score
- Whenever possible, analgesia should be provided before a potentially painful procedure is performed (e.g. line placement, intubation, chest tube placement)

**Treatment**
- Nonpharmacological maneuvers are often very effective in infants
  - Decrease stimulation
  - Decrease light, noise, handling and cluster activities
  - Swaddle, use pacifier
  - “Sucrose” pacifier – dipped pacifier may be used in most infants who are NPO
  - Change position
  - Touch, music, soothing voice
  - Holding, rocking, rubbing, skin to skin care, breast feeding
- Pharmacologic Treatment
  - The use of routine analgesia (continuous drip narcotics) has been recommended by some for infants requiring mechanical ventilation. However, the safety of long term exposure to analgesic and/or sedatives has not been established and infants who received prolonged narcotic drips had more days of ventilation with no improvement in neurodevelopmental outcome. Narcotic drip infusions may cause hypotension in ELBW infants during the first several days of life. Do not give routine narcotic drips to extremely low birthweight infants who are hypotensive.
Recommended Approach to Procedural Pain in Neonates

- **Heel lance**: Consider venipuncture, sucrose with pacifier, swaddling, containment, skin-to-skin contact with mother, always use lancet (Tenderfoot)

- **Venipuncture**: Sucrose with pacifier, swaddling, containment, facilitated tucking, EMLA/ELAMAX topical lidocaine cream at the site (when not urgent and infant > 36 weeks corrected GA)

- **Venous or arterial puncture**: Sucrose with pacifier, swaddling, containment, facilitated tucking, topical lidocaine cream at the site, consider subcutaneous lidocaine locally

- **Lumbar puncture**: Sucrose with pacifier, EMLA cream at the site, consider subcutaneous lidocaine locally, opioid analgesics

- **Intubation**: Combination of opioid analgesics, sedatives

- **Chest tube**: Sucrose with pacifier (if appropriate), subcutaneous lidocaine, consider opioid analgesics or short-acting anesthetic agents

- **Umbilical catheter**: Sucrose with pacifier (if appropriate), swaddling, containment, facilitated tucking, avoid sutures or hemostat clamps on the skin around the umbilicus

- **Central line**: Sucrose with pacifier, swaddling, containment, facilitated tucking, topical lidocaine cream to the site, subcutaneous lidocaine if will not obscure site, opioid analgesics

- **Nasogastric tube**: Sucrose with pacifier, swaddling, containment, facilitated tucking, gentle technique, apply lubrication

- **Circumcision**: Sucrose with pacifier, EMLA / ELAMAX cream to the site, dorsal nerve block or penile ring block using lidocaine, consider acetaminophen for postoperative pain

- **Eye examination**: Sucrose with pacifier, local anesthetic eye drops if prolonged exam or procedure associated

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http://aappolicy.aappublications.org/
http://neoreviews.aappublications.org/cgi/reprint/neoreviews;6/2/e76.pdf

CPMC NICU policy on Pain Management

### Analgesics and Sedatives/Hypnotics

<table>
<thead>
<tr>
<th>Analgesic Agents</th>
<th>Intermittent Dose</th>
<th>Infusion Dose</th>
<th>Local/topical</th>
<th>Comments/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.05-0.2 mg/kg IV q 4-6 h</td>
<td>Load: 0.1 mg/kg. Infuse: 0.01-0.03 mg/kg/hr</td>
<td></td>
<td>Adjust interval for gestational age as it may accumulate in very preterm infants Run drip on smart pump <strong>Reversal with Narcan</strong></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Analgesia: 1-4 microgram/kg IV q 2 to 4 h Anesthesia: 10-20 microgram/kg/dose</td>
<td>Bolus dose then Infuse: 0.5-4 microgram/kg/hr</td>
<td></td>
<td>May cause chest wall rigidity if given as rapid bolus. Because of short half-life, continuous infusion preferred. Tolerance develops rapidly <strong>Reversal with Narcan</strong></td>
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<tr>
<td>Methadone</td>
<td>0.05-0.2 mg/kg Oral q 12-24 hours</td>
<td></td>
<td></td>
<td>Possible oral alternative for pain control. No data available for routine use in preterms. <strong>See drug withdrawal</strong></td>
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<tr>
<td>Analgesic Agents</td>
<td>Intermittent Dose</td>
<td>Infusion Dose</td>
<td>Local/topical</td>
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<tr>
<td><strong>Acetaminophen</strong></td>
<td>10-15 mg/kg po or 20-30 mg/kg rectal q 6 h</td>
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</table>

**Anesthetic Agents**

| **Lidocaine** | | 2-5 mg/kg/ subcutaneously 0.5-1 mg endotracheally | | |
| **EMLA / ELAMAX** | | 0.5-2 gm under occlusive dressing one hour before procedure | | No safety data for recurrent use in preterm infants |
| **Propofol** | | 2-4 mg/kg/hour IV (may begin with 2-4 mg/kg induction dose, then begin infusion) | | For moderate to deep sedation |

**Anxiolytics/Sedatives:** There is no safety data for long term sedation in preterms. Sedatives and anxiolytics should not be substituted for pain medication, but used for agitation. Both lorazepam and midazolam have been associated with myoclonic seizures

| **Midazolam (Versed)** | 0.05 - 0.1 mg/kg q 2-4 hours | 0.01-0.06 mg/kg/hour infusion | | Short acting benzodiazepam but very long half life in infants <32 wks. If used concurrently with narcotic, decrease dose by 25%. My cause myoclonic seizure like activity Reverse with flumazenil (5-10 microgram/kg IV) |
| **Lorazepam (Ativan)** | IV:0.05-0.1 mg/kg/dose q 8-12 h in infants <2000 gm, q 6-8 h in infants ≥ 2000 gms. Oral: 0.25-0.7 mg/kg/dose po | <33 weeks: 60 microgram/kg/hr x 24 h (loading), then 30 microgram/kg/hr. Do not give loading dose to infants <28 weeks gestation. ≥33 weeks: 60 microgram/kg/hr. | | Relatively long acting. Contains 2% benzyl alcohol. Levels accumulate with prolonged use. Phlebitis May cause rhythmic myoclonic jerks in preterm infants Reverse with flumazenil (5-10 microgram/kg IV) |
| **Chloral hydrate** | 25-75 mg/kg per dose oral or rectal | | Single use for procedural sedation. Gastric irritation |
| **Pentobarbitol (for MRI sedation in select cases)** | 1-1.5 mg/kg IV and may repeat x1 1-3 mg/kg IM | | Short acting with low rate of apnea unless given by rapid IV push. Use with caution in babies with hypotension, bradycardia or arrhythmias. |
Special Considerations in the Care of the Extremely Low Birth Weight Baby

Survival

Although the extremely low birth weight babies represent only a small fraction of the infants admitted to the intensive care nursery, they consume a disproportionate amount of the nursery resources in terms of nursing and medical care. The increased survival of these tiny babies is due less to any major technological innovations than to the concerted efforts of prenatal care providers and neonatal care providers to give them the best possible chance to survive. The data is based on survival of infants delivered at CPMC where infant was resuscitated in DR. GA is based on completed weeks of gestation.

<table>
<thead>
<tr>
<th>CPMC 2005-7</th>
<th>Gestational Age at Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N (excluding no resuscitation)</th>
<th>Survived to discharge (%)</th>
<th>CLD (at 36 wks) (%)</th>
<th>Severe IVH/PVL (% Grade 3 &amp; 4)</th>
<th>Severe ROP (% Grade 3 &amp; 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
<td>23</td>
<td>33</td>
<td>76</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>57</td>
<td>41</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>24</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An estimate of outcome in extreme prematurity can also be obtained from the NICHD network via their outcome calculator. Use caution with this calculation as many of sites involved in this data set are not comparable to our population (different racial and socio-economic mix, less access to prenatal care.)

Outcome

Long term neurologic and developmental outcome in the ELBW infants is variable from study to study. Adverse outcomes are more common as gestational age and birth weight decrease, with severe intraventricular hemorrhage (≥grade 3), with chronic lung disease, with exposure to postnatal dexamethasone and with decrease maternal education.

The following data includes outcome from a number of multicenter trials as well as some population specific and center specific trials.
### CPMC Outcomes


<table>
<thead>
<tr>
<th>GA</th>
<th>#Birth</th>
<th>Survive</th>
<th># FU</th>
<th>CP</th>
<th>Low MDI</th>
<th>Blind</th>
<th>Deaf</th>
<th>Normal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>13</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3(50)</td>
</tr>
<tr>
<td>24</td>
<td>28</td>
<td>12</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>5(75)</td>
</tr>
<tr>
<td>25</td>
<td>22</td>
<td>17</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6(75)</td>
</tr>
<tr>
<td><strong>ALL</strong></td>
<td><strong>63</strong></td>
<td><strong>35</strong></td>
<td><strong>22</strong></td>
<td><strong>4 (18)</strong></td>
<td><strong>8 (36)</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>14 (66)</strong></td>
</tr>
</tbody>
</table>

*percent based on number followed, not survival. ‡: severe CP=10%

The **NICHD trial** prospectively enrolled infants born from 1993 through 1998 with BW <1000 gm at multiple centers. Follow up was at 18 months. The data from the cohort born in 1997-1998 is presented below:

<table>
<thead>
<tr>
<th>CP</th>
<th>22-26 wks [1102 (61%) survived to discharge, 84% followed.] mean BW 697</th>
<th>27-32 wks [633 (86%) survived to discharged, 82% followed] mean BW 851</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>18.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Moderate-severe CP</td>
<td>10.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Baley MDI&lt;70</td>
<td>37.2</td>
<td>22.8</td>
</tr>
<tr>
<td>PDI&lt;70</td>
<td>26.0</td>
<td>16.9</td>
</tr>
<tr>
<td>Blind (bilateral)</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Neurodevelopmentally impaired</td>
<td>44.6</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Vohr et al, Neurodevelopmental Outcome of ELBW Infants, Pediatrics 105: 1216, 2000

### Population Based Studies

<table>
<thead>
<tr>
<th>Study Population</th>
<th>GA</th>
<th># followed</th>
<th>CP</th>
<th>MDI&lt;70</th>
<th>Blind</th>
<th>Deaf</th>
<th>Severely Disabled</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.C</td>
<td>23</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>UK/Ireland</td>
<td>26</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>4</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>B.C</td>
<td>24</td>
<td>43</td>
<td>14</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>16 (37%)</td>
</tr>
<tr>
<td>UK/Ireland</td>
<td>90</td>
<td>11</td>
<td>17</td>
<td>10</td>
<td>2</td>
<td>24</td>
<td>24 (27%)</td>
</tr>
<tr>
<td>B.C</td>
<td>25</td>
<td>77</td>
<td>17</td>
<td>10</td>
<td>13</td>
<td>2</td>
<td>25 (32%)</td>
</tr>
<tr>
<td>UK/Ireland</td>
<td>167</td>
<td>15</td>
<td>29</td>
<td>12</td>
<td>25</td>
<td>24</td>
<td>40 (24%)</td>
</tr>
<tr>
<td>Combined</td>
<td>412</td>
<td>67(16%)</td>
<td>68(17%)</td>
<td>26 (6%)</td>
<td>9 (2%)</td>
<td>120</td>
<td>29%</td>
</tr>
</tbody>
</table>


### Preparation

See check lists on line for preparation steps for Tiny Baby Birth

### Delivery Room Management

- **Thermal regulation**
  - Increase temperature in delivery room to at least 72° F
  - Assign 1 member of the resuscitation team to thermal control
  - Preheat bed with radiant warmer before delivery and consider use of a chemically activated gel mattress (available in PYXIS) using caution not to put in direct contact with infant’s skin
  - Use double hats
  - Have warm blankets available to cover infant and place in incubator
  - Wrap infant immediately in clear plastic wrap without drying. Transport to the NICU in a warm transport incubator. Do not remove infant from bag until ready to weigh infant on the giraffe bed scale.
- Use pulse oximeter to monitor heart rate/saturation in DR
- Begin ventilation in <40% oxygen and allow saturation to increase slowly as long as heart rate is increasing
- **<750 gms (or ≤25 weeks):**
  - Intubate immediately. Begin ventilation in 21-40% oxygen and allow saturation to increase slowly as long as heart rate is increasing. Give surfactant once the heart rate is >120 and ventilation is established. Wean oxygen based on saturations.

- **>750 gms (≥26 weeks):**
  - Some of these babies may not require immediate intubation in the delivery room. If they are crying vigorously and not retracting consider beginning with early nasal CPAP. If there is any distress, intubate and give surfactant if the infant is <28 weeks gestation.
  - Secure the tube carefully and effectively as removing the tape can damage the skin.

**ET placement guideline**
500-600 gm = 6 cm  
600-800 gm = 6.5-7 cm  
800-1000 gm = 7 cm

**Immediate Management in the NBICU**

**Thermal Regulation:**
- Place in giraffe bed. After procedures are completed, close top and, when temperature is stable, begin humidification at 70%

**Respiratory management**
- Early surfactant (3 doses) continue to give doses if infant remaining on ventilator even if weans to room air. Aggressive weaning and early extubation to CPAP should be considered.
- Use minimal ventilation to maintain pCO2 between 45 and 60 and saturation
- Consider high frequency ventilation modality if lungs are particularly stiff and high pressures (>22 after 1st hour) needed to ventilate

**Lines and monitoring**
- Place umbilical arterial catheter and double lumen venous catheter. Do not place peripheral IV if avoidable. Use 1 port of the UVC for TPN and drip medications and the other with plain D5W for the Indocin, blood transfusions and medications not compatible with the TPN. Make sure to draw back blood to clear air bubbles on both lumens of the dual lumen catheters before flushing to avoid air emboli (which may go to arterial circulation through patent ductus and foramen).

**Treatment of hypotension**
- See Blood pressure graphs for normal values in ELBW infants. Mean arterial pressure is often low on day one, possibly secondary to open PDA. In general, if infant is not acidic and has no other sign of inadequate organ perfusion, do not use fluid boluses. Treat hypotension only if MAP is below the 10% for GA and day of life.
- Fluid bolus: use with caution in ELBW infant
- Use blood or FFP if anemic or blood loss at delivery
- Use normal saline if hypovolemic and not anemic
- Pharmacologic treatment: begin only if mean arterial blood pressure is consistently <2 SD below mean for GA and age of life.
- Dopamine
- Hydrocortisone 1 mg/kg q 8 h if serum cortisol low or hypotension is refractory to vasopressors.

**Fluid and Electrolyte Management** *(see additional information in fluid section)*

- **<750 grams:**
  - Begin with D-5-W starter TPN at 80 ml/kg/day on day one. Monitor sodium frequently (q8 hours for first 3 days of life) and increase infusion as needed to maintain sodium <150. Use electrolyte measurements from the iSTAT point of care blood gas machine to minimize blood sampling. Urine output is usually low on Day 1 and increases by 12-24 hours at which time total fluid requirements will increase to 100-180 ml/kg/day depending on immaturity of skin and insensible water loss. The goal is to keep fluids in early days as low as possible and still push up calories and keep Na levels <150.
  - Humidify isolette to 70%. Increase humidity to 90% if fluid requirements are >160/kg/day.
If sodium >150 and IV fluid is >180 or the baby is hyperglycemic on 5% glucose, begin oral sterile water at 0.5 to 1 ml/hour continuous drip gavage
Follow total urine output relative to total fluid intake and weight to estimate needed change in fluid requirements. Expected weight loss is approximately 1-2% per day for first 5-7 days of life.

750-1000 grams
Follow guidelines above but total fluid intake requirement is generally lower
Begin D-10-W starter TPN
Monitor electrolytes q 12 hours
Adjust Fluid therapy every 8-12 hours based on weight, urine output and electrolytes. Give the minimal amount of fluid to prevent hypernatremia and decrease fluid intake once the initial (~3-5 days) period of high insensible water loss is past

Nutrition
Begin glucose infusion of 4-6 mg/kg/min (6-9 gm/kg/day) on day 1. Advance cautiously as glucose intolerance frequently appears on day 3-4.
Begin protein immediately with starter TPN and increase to 2.5 gm/kg/day protein on day 2 when write first complete TPN. Increase to total of 3.5 gm/kg/day of protein over the next few days (unless BUN rising).
Begin lipids by day 2-3 of life. Start with 0.5 gm/kg/day 20% lipid solution and increase by 0.5 g/kg/day as tolerated. Monitor triglyceride levels.
Make sure mom is pumping and using tiny tubes if volume of milk is low
Start enteral feedings of 1 ml q 6 h as soon as indomethacin/neoprofen dosing is complete unless very distended or large PDA with retrograde flow is present, or infant is requiring pressors to maintain blood pressure. Decrease interval first then begin slow advance on feeds.
Begin probiotics per protocol

Patent Ductus Arteriosus
Begin prophylactic indomethacin at birth if <28 weeks (up to 27 6/7 weeks)
Monitor with echocardiogram after 3rd dose is given. If PDA still present, continue indocin or consider treating with ibuprofen. (link to PDA section)

Infection
Begin Ampicillin and Gentamicin. Length of treatment determined by risk factors.
Avoid skin breakdown: Follow skin protocol carefully. No peripheral IV’s if possible. Avoid any tape on skin. Use cotton balls to collect urine prevent contact with skin. If skin is cracking use aquafor q day or bid.
Avoid use of CHG (chlorhexidine gluconate) as may cause skin burn and wash off all povidone from skin (for first 2 weeks)

Renal Function
Glomerular filtration rate is extremely low in these infants and tubular function relatively immature. The babies have a very limited ability to concentrate or dilute their urine. Expect significantly delayed clearance of drugs and a decreased ability to regulate fluid and electrolytes.
If baby has received chronic furosemide, monitor for renal stones at 6-8 weeks of life.

Neurological function
This group of infants is at highest risk of intraventricular hemorrhage, with incidences of 40-60% reported in infants <1000 gms. IVH usually presents in first 72 hours of life. In the ELBW infants, an early ultrasound (<72 hours) is indicated with a repeat at 7-14 days of life. Late ultrasound is indicated (looking for PVL.)
Sedation, pain control
See Sedation and analgesia regarding agents and doses. Consider using short term sedation in infants with agitation. Always use pain medications prior to painful invasive procedure such as chest tube placement. Do not begin continuous infusion of narcotics if infant is hypotensive.
Skin Care

- The epidermis is only 1 cell layer thick on these infants so the skin surface is extremely permeable and prone to damage. Avoid tape, alcohol or caustic substances (such as urine) on skin. Humidify incubator to decrease transepidermal water loss for first 5 days of life (70%), then decrease humidification to 50% until 30 weeks corrected gestational age.

Special Considerations in the Late Preterm Infant

- Infants born at 34 0/7 – 36 6/7 weeks gestational age often look like term infants but are notorious for having characteristics of preterms. This group was previously called near term infants – the name change is to remove any illusions that these are term infants.
- They represent 25% of infants who developed kernicterus during early 1990’s when early discharge was being pushed
- This is the largest growing segment of preterm births - accounting for 8.5% of all birth, ¾ of all preterm infants and at least 1/3 of NICU admissions
- An infant born at 34 weeks is 4.6 times more likely to die than a term infant
- All complications of prematurity are seen in late preterm with lower attack rates
- Delayed discharge is typically due to jaundice, poor feeding and apnea
- Late preterms are twice as likely to be readmitted to the hospital
- Care needs to be exercised when considering these infants for discharge

AAP statement on the late preterm infant: [http://aappolicy.aappublications.org/cgi/reprint/pediatrics;120/6/1390](http://aappolicy.aappublications.org/cgi/reprint/pediatrics;120/6/1390)

AAP minimum discharge criteria for late-preterm infants (selected elements)

- Timing of discharge is individualized and based on feeding competency, thermoregulation, and absence of medical illness and social risk factors. Late-preterm infants usually are not expected to meet the necessary competencies for discharge before 48 hours of birth.
- A physician-directed source for continued medical care with a follow-up visit arranged for 24 to 48 hours after hospital discharge.
- Vital signs should be documented as being stable for the 12 hours preceding discharge, including a respiratory rate of less than 60 breaths per minute, a heart rate of 100 to 160 beats per minute, and axillary temperature of 36.5 to 37.4°C (97.7–99.3°F) measured in an open crib with appropriate clothing.
- At least 1 stool has been passed spontaneously.
- Twenty-four hours of successful feeding, either at the breast or with a bottle, and the ability to coordinate sucking, swallowing, and breathing while feeding has been demonstrated. Any infant with a weight loss of more than 2% to 3% of birth weight per day or a maximum of 7% of birth weight during the birth hospitalization should be assessed for evidence of dehydration before discharge.
- A formal evaluation of breastfeeding, including observation of position, latch, and milk transfer, has been undertaken and documented in the chart by trained caregivers at least twice daily after birth.
- A feeding plan has been developed and is understood by the family.
- A risk assessment for the development of severe hyperbilirubinemia has been performed and appropriate follow-up has been arranged.
- Maternal and infant test results are available and have been reviewed, including blood test results for maternal syphilis and hepatitis B surface-antigen status; cord or infant blood type and direct Coombs test results.
- A car safety seat study completed by a trained professional to observe for apnea, bradycardia, or oxygen desaturation has been passed.
- Family, environmental, and social risk factors have been assessed. When risk factors are identified, the discharge should be delayed until they are resolved or a plan to safeguard the infant is in place.

[CPQCC Toolkit on Late Preterm Infant](http://aappolicy.aappublications.org/cgi/reprint/pediatrics;120/6/1390)
Fluid and Electrolytes

Careful fluid and electrolyte management is essential for the well being of the sick neonate. Inadequate administration of fluids can result in hypovolemia, hypervolemia, metabolic abnormalities and renal failure.

- In the near term and term neonate excess fluid administration results in generalized edema and abnormalities of pulmonary function.
- Excess fluid administration in the very low birth weight infant is associated with patent ductus arteriosus and congestive heart failure, intraventricular hemorrhage, necrotizing enterocolitis and bronchopulmonary dysplasia.

Body Composition and Surface Area

- The body composition of the fetus changes during gestation with a smaller proportion of body weight composed of water as gestation progresses.
- The preterm neonate is in a state of relative total body water and extracellular fluid excess. After birth this excess water must be mobilized and excreted.
- A proportion of the diuresis observed in both term and preterm infants during the first days of life should be regarded as physiologic.
- The surface area of the newborn is relatively large and increases with decreasing size. Therefore, insensible water losses will be greatest with small size and decreased gestational age.

Hormonal Effects

- The renin-angiotensin system is very active in the first week of neonatal life resulting in increased vascular tone and elevated levels of aldosterone.
- Increased aldosterone levels enhance distal tubular reabsorption of sodium resulting in an impaired ability to excrete a large, or acute, sodium load.
- Arginine vasopressin (AVP, ADH) levels rise after birth. AVP secretion is increased in response to stress, such as birth, asphyxia, RDS, positive pressure ventilation, pneumothorax and intracranial hemorrhage.

Renal Hemodynamics

- After birth, renal blood flow increases in response to increased blood pressure (renin-angiotensin) with a secondary increase in glomerular filtration rate.
- The neonatal kidney is less efficient at excreting an acute sodium or water load than the kidney of an infant or child.

Sodium Homeostasis

- Sodium is required for fetal growth with an accretion rate of 1.2 mEq/kg/day between 31-38 weeks.
- Sodium retention is aided by increased aldosterone levels in newborns.
- In preterm infants <34 weeks sodium reabsorption is decreased, the fractional excretion of Na may exceed 5%. However, the preterm infant is unable to rapidly increase sodium excretion in response to high sodium levels or a large sodium load.

Water Handling

- Both term and preterm infants are able to excrete dilute urine. Conversely, preterm infants are able to concentrate urine to ~ 600 mOsm/L and the term infant to ~ 700 mOsm/L. (Adults can concentrate to ~ 1300 mOsm/L.) Therefore, both preterm and term neonates generally have the capacity to regulate their intravascular volume within a range of fluid intakes.

**Maintenance Water Requirement =**

**Insensible Water (skin + respiratory) + Urine + Stool + New tissue mass (in growing infants)**
Insensible water loss changes markedly with gestational and postnatal age. Very low birth weight infants have greater skin water loss than do more mature infants. Skin water losses decrease with postnatal age.

Healthy term and preterm infants may have a physiologic diuresis (>4 ml/kg/hr U.O.) between 24-48 hours. Fluids should not be increased during diuresis unless sodium is high or clinical dehydration is present.

Renal water loss is initially less in preterm infants because of lower glomerular filtration rates. However, the ELBW infants have high urine output even in the face of hypernatremia and dehydration because of poor concentrating ability.

A “negative” water balance in the first 7-10 days of life allows for the normal contraction of extracellular fluid. A weight loss of 3-10% of birth weight over the first 5 days of life is appropriate. Very low birth weight infants may lose up to 15% of birth weight.

In critically ill infants, fluid orders should be reviewed at least every 8 hours and adjusted as necessary to maintain normal electrolytes.

Specific gravity is not a reliable indicator of hydration in the VLBW infant because of limited concentrating and diluting capacity of the kidney.

Infants <1000 grams may have high urine outputs in spite of dehydration.

**Estimated Water Requirements**

Remember other elements may impact these “needs” – for example humidified incubators, respiratory circuits (see below for estimates of increased or decreased water needs). Use frequent Na measurements and increase fluids as needed to maintain Na below 150. iSTAT point of care gas with lytes = EG7 cartridge is best way to monitor frequently.

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>Dextrose</th>
<th>Fluid Requirements (ml/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;750</td>
<td>5%</td>
<td>&lt;24 hr+ 80-120 24-48 hr 100-150 &gt;48 h 100-150</td>
</tr>
<tr>
<td>750-1000</td>
<td>5-10%</td>
<td>80-120 100-150 100-150</td>
</tr>
<tr>
<td>1000-1500</td>
<td>10%</td>
<td>80 100-120 120-130</td>
</tr>
<tr>
<td>&gt;1500</td>
<td>10%</td>
<td>60 80-120 120-140</td>
</tr>
</tbody>
</table>

*use lower figure if urine output poor, higher if good urine output
†use lower figure if humidified to >60%, higher figure if diuresing well

**Based on the above principles:**

- One should expect a 10-15% weight loss over the first 5-7 days of life (up to 20% in infants <750 g).
- During 1st 3-5 days of life, infants >1000 grams should lose 1 to 3% of body weight/day.
- Failure to lose weight initially, or in infants receiving <60 cal/kg suggests fluid retention.
- Infants which experience significant intrapartum stress will be slow to void and will therefore require less fluid over the first 24-48 hours.
- The small or extremely immature infant <1000 g will experience increased insensible water losses (IWL). IWL = (I-O) ± Δwt.
- As the preterm and term infant is able to regulate urine output in response to hypovolemia, urine output will reflect intravascular volume. In other words, the infant will generally not maintain inappropriately high urine output in the face of intravascular volume depletion.

**Recommendations for fluid management**

- Initiate fluid therapy at 60-80 ml/kg/d with D10W (see special considerations on tiny baby fluids)
- Infants < 30 weeks should be in humidified giraffe (70% for first 2 weeks then 50% until corrected 30 weeks gestational age)
- Infants <1000 g should have electrolytes done every 6-8 hours and weights recorded more often that once a day if sodium very high. Electrolytes in infants 1000-1500 grams in first days may need lytes done every 12 hours. Consider doing the electrolytes as part of the iSTAT system when gases are done to minimize blood volumes needed.
- For serum Na+ >145 mEq/L, increase infusate by ~10 mL/kg/d without Na+ in the infusate.
• Increase fluids for urine output <0.5 mL/kg/hr by ~10 mL/kg or, in infant ≤ 26 weeks, calculate IWL and change fluids accordingly.
• Increase fluid administration gradually over the first week of life to 120-130 ml/kg/d by day 7, allowing for expected physiologic weight loss.
• When calculating I.V. fluid rates for 24-hour period take into consideration added fluid given with catheter flushes and medication and blood products (other than packed red cells). In the VLBW infant this can provide as much as 20-30 ml/kg /day
• Adjust fluids based on insensible losses
• Increase fluids if:
  • Radiant heat (open table or heat lamp) 50-100%
  • Phototherapy 10%
  • Newer blue light technology generates less heat and losses from these lights may be negligible
  • Body temperature 30% for each degree over 37˚ of sustained fever
  • Activity and feeding variable
  • Increased respiratory rate variable
• Decrease fluids if:
  • Endotracheal intubation 10%
  • Decreased activity (e.g. Pavulon) 10-20%
  • Humidification of incubator ≥60% 20-30%
  • Decreased heat loss (dressed or blankets) 25%
  • Low urine output 30%

Special Cases

• **ELBW infants**
• Postoperative abdominal surgery
  • Fluid requirements may be twice or three times that noted above.
  • The more extensive the procedure the greater the needs.
  • Infants may require 125-150 ml/kg/day immediately postoperative with subsequent increases as determined by blood pressure measurements and urine output.
  • Isotonic saline also may be required because of third spacing of fluid into tissues and other spaces, e.g., the bowel lumen.
  • Gastric drainage is replaced q8-12h, depending on volume, with solution containing Na and K.
  • Colloid also may be needed because of rapid fluid shifts, decreases in arterial pressure, protein leaks (esp. if drain in place or losses at wound) or coagulopathy
• Asphyxiated infants
  • These infants may have increased secretion of arginine vasopressin (which is likened to SIADH) and are thought to be at increased risk for cerebral edema.
  • Fluid intake should be kept on the low side for 48-72 h, i.e., ≤ 60 ml/kg/day, or until seizures are no longer considered a problem.
  • These infants require close monitoring of serum sodium and weight. Treatment of SIADH is by restriction of fluids, not increased sodium intake.
• Infants of diabetic mothers
  • These infants receive IV glucose because of increased danger of hypoglycemia
  • They frequently do not receive sodium and have been found to develop rather substantial hyponatremia at 24 h if this is not added at or before this time. This danger is greater the greater rate of glucose needed to maintain blood glucose. Addition of sodium should be considered at 16-18 h.

**Recommendations for electrolyte management**

**Sodium**
- No routine sodium is needed in first 48 hours of life.
- Add 2-3 meq/kg/day after 48 hours in infants ≥26 weeks gestation. Determine sodium requirement in infants <26 weeks based on serum sodium, weight loss etc. Consider "inadvertent" sodium administration that baby is receiving via catheter flushes and medications. In the ELBW infant
maintenance sodium is usually not required until the 4th-5th day of life (but may be needed to balance other needed components of TPN such as phos or acetate)

- Infants <28 weeks gestation may need higher sodium intake after 1 week
- Growing VLBW infants may need higher sodium intakes, as much as 6-8 meq/kg/day
- Sodium losses are increased in infants on diuretic therapy

**Potassium**

- No potassium during 1st 48° of life unless K+ is low (< 3.5)
- Maintenance potassium = 1-3 meq/kg/day.
- No potassium if serum K+ > 6.
- Decrease or remove potassium if anuric

**Chloride**

- Maintenance = 1-3 mEq/kg/day
- Many ELBW infants are hyperchloremic. Use acetate as anion in these infants

**Calcium**

- Consider parenteral calcium immediately in the following babies
  - ELBW (<1000 gm) infants
  - Asphyxiated term infant.
  - Severe growth retarded infants
  - Infants with symptomatic hypermagnesemia (hypotonia, hypotension)
  - Infants of diabetic mothers needing IV therapy
- Treatment doses
  - Dose is 200-300 mg/kg/day for maintenance
  - Ideally give via central line (UVC). May give in UAC if perfusion is good and no other access (central administration should be over 30 minutes)
  - Intermittent calcium gluconate bolus dose is 100 mg/kg/dose every 6-8 hours
  - For infants with persistent hypocalcemia needing high concentrations, administer calcium as intermittent bolus infusions rather than high concentrations in the intravenous fluid. Do not mix with sodium bicarbonate as this may precipitate.

Do not give calcium in line with TPN containing calcium and phosphorus as these solutions are carefully balanced to avoid precipitation (remember Ca+Phos = bone.) If no other access and need to give additional calcium or phosphorus the TPN needs to be stopped and saline flush given before and after the additional dose is given.
Electrolyte Disturbances and Corrections

General Principles
- Other than acid base measurements, the electrolytes immediately after birth reflect the maternal status
- Always consider “lab error” or “sampling error” when unexpectedly abnormal value is found
- Consider repeating lab test before treating
- iSTAT values are whole blood not serum so some differences may be expected in simultaneous specimens – these differences are not always predictable (generally Na is lower on iSTAT)

Hyponatremia
- Definition: Sodium <130

Etiology
- Dilutional: characterized by excessive weight gain
  - Excess free water administration
  - Congestive Failure
  - Renal failure with excessive fluid intake
  - Inappropriate ADH (rare in preterm infants)
- Excess Loss
  - Immature kidneys
  - Diuretic Therapy
  - Hypoadrenalism: CAH, Hypoaldosteronism, sepsis, shock, adrenal hemorrhage
  - Vomiting
  - Excess stool output (especially ileostomy, jejunostomy)
  - High output from gastric suction tube
  - Large loss of serous fluid (chest tube, wounds, repeated CSF taps)
- Inadequate Intake

Treatment
- Dilutional: Restrict water

\[
\text{Total water surplus (ml)} = (\text{Ideal-Actual Na}) \times 0.6 \times \text{(wt in gms)}
\]

\[
\text{Ideal Na}
\]

- Sodium Depletion: Replace salt deficit over 24-48 hours
- If symptomatic, consider using 3% saline = 0.513 meq/ml (osmolarity=1026 mOsm/L)

\[
\text{Total sodium deficit (meq)} = (\text{Ideal Na-Actual Na}) \times 0.6 \times \text{(wt in kg)}
\]

Hypernatremia
- Definition: Sodium >146

Etiology
- Dehydration
  - Excess water loss: transdermal, urine, stool
  - Inadequate free water intake
- Excess sodium intake

CPMC NICU Manual v7
Inappropriate fluid therapy
- Repeated buffer administration (sodium bicarbonate or THAM)
- Inadequate sodium excretion

**Treatment**
- Dehydration: Increase free water (correct slowly – over 24-48 hrs)

**Hypokalemia**
- Definition: $K^+ <3$ mEq/L
- Low potassium is rarely life threatening and can be corrected gradually (without potassium bolus) except in the following conditions:
  - Infant is receiving digoxin
  - Potassium is <2.0 mEq/L

**Etiology**
- Alkalosis
- An increase of 0.1 units pH causes a 0.6 meq fall in serum K
- Inadequate intake
- Excessive loss
- Diuretic therapy
- Hyperadrenalism or steroid therapy
- Bartters syndrome, Gitelman’s syndrome, congenital alkalosis of GI origin
- GI losses
- Amphotericin therapy – may be exacerbated by hypomagnesemia
- N.B. true hypokalemia may be missed if hemolysis occurs during sampling. Capillary specimens are usually hemolyzed to a greater or lesser degree.

**Treatment**
- Correct alkalosis, if present
- Discontinue diuretics if present
- Usually may be corrected slowly by increasing potassium in IV fluid by 2-3 meq/kg/day
- If necessary to do more rapid correction (ordered at CPMC through the PICU pathway):

<table>
<thead>
<tr>
<th>Potassium (as chloride or acetate)</th>
<th>DOSE: 0.5-1 meq/kg</th>
<th>Infuse over 1-2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Maximum 0.5 meq/kg/h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximal concentrations (in NS or D5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIV: 0.04 meq/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CVL 0.2 meq/ml</td>
</tr>
</tbody>
</table>

**Hyperkalemia**
- Definition: $K>6.0$ mEq/L
- Symptoms rarely appear in preterm infants until $K>7.0$

**Common causes**
- Hemolyzed specimen
- Acidosis
- Very preterm ($\leq 25$ wks gestation) in first 48 hours
- Severe bruising, tissue damage, excess K release
- Shock, sepsis
- Renal failure and oliguria
- Excessive potassium administration
- Hypoadrenalism
- Congenital adrenal hyperplasia
- Adrenal insufficiency of prematurity

**Treatment**
- Monitor with ECG: peaked T waves → QRS widening → SVT or ventricular tachycardia.
- Remove all potassium from IV solutions
- Correct acidosis with bicarbonate and/or ventilation
- Check calcium and correct if abnormal
- Increase potassium excretion
- Lasix if renal function good
- Kayexelate enema: 1 gm/kg mixed in normal saline with concentration of 0.5 gm/ml. Give via feeding tube inserted 1-3 cm into rectum, retained for 30 minutes.

**Cardiac arrhythmias or K>8:**
- Glucose/insulin infusion – bolus of 0.05 unit/kg of insulin with 2 ml/kg of d-10 W. Infuse 0.25 –0.5 units/gram of glucose at normal glucose infusion rate. Alternatively give 1 unit insulin/kg/hour with 2-4 ml/kg/hour of 10% glucose.
- Calcium gluconate 10%: 1-2 ml/kg over 30 minute (100 mg/kg/dose)

**Hypochloremia**
- Definition: Chloride <95 mEq/L

**Etiology**
- Secondary to metabolic alkalosis or compensated chronic respiratory acidosis
- Excessive chloride loss
- Diuretic therapy
- GI (vomiting or congenital alkalosis of GI origin)
- CSF loss through repeated taps

**Treatment**
- Correct underlying cause
- Give KCL po or IV
- Discontinue diuretics if possible
- Replace chronic sodium chloride losses
- Ammonium chloride IV for acute severe hypochloremia
- meq of chloride (as ammonium) = chloride deficit (meq/L) x 0.2 x wt (kg).
- Give 1/2 dose and recheck lytes

**Hyperchloremia**
- Definition: Chloride >115 mEq/L

**Etiology**
- High chlorides are very common during first week of life in infants <1000 g. May reflect dehydration or renal loss of bicarb
- Metabolic acidosis
- Dehydration
- Respiratory alkalosis

**Treatment**
- Decrease CI intake: Substitute acetate as anion
- Correct acid/base status
**Metabolic Acidosis**

- **Definition:** Excess Acid or loss of buffer; serum bicarb < 18 or base deficit < -6

<table>
<thead>
<tr>
<th>Increased Anion Gap (&gt;16)</th>
<th>Normal anion gap (&lt;16)</th>
<th>Low anion gap (&lt;8) with acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis: shock, hypoxia</td>
<td>Renal bicarbonate loss: renal tubular acidosis, acetazolamide</td>
<td>Low albumin</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>GI losses: Diarrhea, ileostomy losses, cholestyramine</td>
<td>Retained non-sodium cations, hypercalcemia, hypermagnesemia)</td>
</tr>
<tr>
<td>Late metabolic acidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzyl alcohol toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylate toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

- Acute treatment of metabolic acidosis is controversial. No human studies substantiate its safety or effectiveness. The concern is that bicarbonate may change the extracellular pH but may make the intracellular pH lower. See article on topic by Ascher et al: *Sodium bicarbonate: Basically Useless Therapy*: All efforts should be made to first correct the underlying cause of the acidosis such as:
  - hypoxia
  - hypotension
  - poor perfusion
  - patent ductus arteriosus
  - sepsis

- If acidosis persists consider addition of buffer to TPN (as acetate) or use slow correction (bicarbonate drip – calculate the deficit and aim for correction over 12-24 hours)
- THAM can be used as alternative buffer but little data exists on use in infancy. THAM has a higher sodium load and larger volume of administration. Dose 1-2 mmol kg/dose (3.3 – 6.6 ml/kg/dose)
- Sodium bicarbonate should be diluted before administration 1:1 with sterile water. Do not dilute with 10% dextrose as
  - increases osmolality and risk of IVH
  - disturbs glucose homeostasis

  **if acute treatment for acidosis is deemed necessary:**

  \[0.25 \times \text{base deficit} \times \text{wt(kg)} = \text{mEq of bicarbonate}\]

  Use 8.4% NaHCO$_3$, diluted 1:1 with H$_2$O, given slowly over 60 minutes

  \[1 \text{ ml 8.4% NaHCO}_3 \text{ contains 1 mmol bicarbonate}\]

- If chronic acidosis, consider renal tubular cause and check urine pH at time of acidosis (if acidotic, should be <=5)
  - Give oral bicarbonate: 0.6 x base deficit x wt (kg). Give over 24 hours
  - Add acetate to TPN

**Hypocalcemia**

Definition: Total Calcium < 7.0 mg% or ionized Ca < 4.0 mg/dl or < 1 mmol/L (iSTAT units) or borderline calcium and symptomatic

- Cord blood calcium is high (10-11 mg/dL), falls to nadir (7.5-8.5) at 24-48 hours of life. More exaggerated fall in preterm infants, SGA infants and infants of diabetics
Early onset
• 50% of infants <2000 gm, nearly 100% of infants <1500 gm: nadir at about 12-24 hours
• Infants of diabetic mothers: More frequent in poorly controlled diabetics
• Asphyxia, birth depression

Late onset: usually at >6 days of life
• Hypoparathyroidism (idiopathic, transient, congenital, maternal hyperparathyroidism)
• Magnesium deficiency
• Vitamin D deficiency (renal failure, liver failure, malabsorption, inadequate intake)
• Excess phosphate intake, alkalosis and bicarbonate therapy
• “Hungry bone syndrome” – SGA infants or infants treated with high dose Vitamin D after rickets or hypoparathyroidism

Symptoms of hypocalcemia suggesting need for treatment
• hypotension requiring inotropic support
• persistent pulmonary hypertension of the newborn (PPHN)
• unexplained jitteriness
• seizures

Treatment
Symptomatic infants:
• Calcium gluconate 10%: 100-200 mg/kg (1-2 ml/kg) by infusion over 30 minutes in secure IV line or by bolus over at least 30 minutes. May give via UVC if position of catheter known to be in IVC. Give by UAC only if perfusion and blood pressure are normal. Check compatibility in fluids in line before giving bolus.
• Monitor ECG for bradycardia during "pushes" of calcium.
• Calcium extravasation can cause severe skin sloughs. If refractory hypocalcemia exists, check phosphorus, albumin and magnesium levels.
• In larger, healthy infants oral supplementation of calcium can be given. 75 mg/kg/day of elemental calcium given as 10% calcium gluconate (use IV preparation - it is well absorbed and has a lower osmolality than oral preparations but this is a large oral volume and longer term oral treatment should be accomplished using calcium glubionate oral liquid).
• Calcium conversions:
  o 1 mEq Ca++ = 20 mg Ca++
  o 1 ml 10% calcium gluconate = 9 mg Ca++
  o 1 ml 10% calcium chloride = 27 mg Ca++
  o 1 ml Neocalglucon = 23.6 mg Ca++
  o 1 mL of 10% calcium gluconate contains 0.2 mmol calcium

Asymptomatic infants:
• Hypocalcemia in preterm infants who are well and asymptomatic will generally resolve by Day 3 with no treatment.
• In VLBW infants at high risk of hypocalcemia who will not be fed enterally, begin calcium infusion of 200-300 mg/kg/day by addition to TPN
• Consider hypomagnesemia if recalcitrant hypocalcemia

Hypercalcemia
Definition: Total Calcium >11.0 mg%, ionized Ca > 5.0 mg/dl
• Symptoms may include poor feeding, vomiting, hypotonia, polyuria, encephalopathy. Symptoms are most often related to severe (>14 mg/dl) levels and symptomatic hypercalcemia is usually secondary to hyperparathyroidism.

Etiology
• Increased bone resorption: hyperparathyroidism, hyperthyroidism, phosphate depletion, hypophosphatasia
• Increased absorption: Hypervitaminosis D,
• Other: Massive subcutaneous fat necrosis, acute adrenal insufficiency, excessive thiazide

Treatment
• Severe: volume expansion with normal saline (20/kg) then 2 x maintenance IV fluids
Furosemide to increase excretion
Glucocorticoids if secondary to fat necrosis or hypervitaminosis A or D
Discontinue IV or po phosphate supplements unless phosphate is low.

**Hypomagnesemia**

- **Definition:** Mg++ <1.5 mg% (<.75 mmol/L)
- May occur in conjunction with severe or refractory hypocalcemia or with GI losses.

**Etiology**

- Renal losses: Diuretics or Bartter’s syndrome, occasionally with amphotericin therapy
- Symptoms: neuromuscular irritability, coma, apnea, flaccidity, seizures, ectopic beats, labile rate and rhythm.

**Treatment**

- Replace Magnesium as magnesium sulfate (use caution as multiple commercially available solutions are available: 100 mg/ml (0.8 mEq/ml); 125 mg/ml (1 mEq/ml); 250 mg/ml (2 mEq/ml); and 500mg/ml (4 mEq/ml)
- Give maintenance magnesium - 0.5 mEq/kg/day
- For severe hypomagnesemia (< 1.2 mg/dl) give IV MgSO4 25-50 mg/kg/dose.
- Monitor heart rate during infusion as may be arrhythmogenic.
- 1 ml of 50% magnesium sulphate contains 2 mmol magnesium
- May cause hypotension if given too quickly
- At CPMC ordered through the PICU pathway

| Magnesium Sulfate | Dose: 0.2-0.4 meq/kg (25-50 mg/kg) | Infuse IV over 2-4 hours (max 1 meq/h) Diluted in normal saline or D5W |

**Hypermagnesemia**

- **Definition:** Mg++ > 2.5 mg% (1.15 mmol/L)
- Usually asymptomatic unless serum Mg++>5, but serum level may not reflect tissue level after prolonged administration. With severe Magnesium toxicity may see respiratory depression, hypotonia and ileus
- Usually secondary to maternal magnesium administration or iatrogenic
- Also seen with adrenal insufficiency

**Treatment**

- Calcium gluconate: 100-200 mg/kg/dose IV
- Fluid bolus

**Other Reading**

Modi N. Sodium intake and preterm babies. Arch Dis Child 1993;69:87-91
Nutrition

Feeding of Preterm Infants

Proper nutrition in infancy is essential for:

- Normal growth
- Resistance to infection
- Long term health
- Optimal neurologic and cognitive development

Providing adequate nutrition to preterm infants is challenging because of several problems:

- Immaturity of bowel function
- Inability to suck and swallow
- High risk of necrotizing enterocolitis (NEC)
- Illnesses that may interfere with adequate enteral feeding (e.g., RDS, patent ductus arteriosus)
- Medical interventions that preclude feeding (e.g., exchange transfusion, indomethacin therapy).

Feeding the Gut (Trophic Feedings)

The provision of small amounts of feedings starting soon after birth aims at preventing atrophy of the gut. A number of studies in recent years have demonstrated the general feasibility of this approach as well as beneficial clinical effects, with no recognizable increase in the risk of necrotizing enterocolitis. Although we have no formal protocol for the use of trophic feedings, such feedings are being used increasingly and their use is encouraged. Colostrum/human milk should be used whenever available. Otherwise, preemie formula should be used. The use of dilute formula, although practiced widely, has no rational basis and no demonstrated benefits, except that the larger volume may improve gastric emptying. **Trophic feedings should be initiated at a volume not to exceed 15 ml/kg/d. These feedings are traditionally given in small boluses of 1 - 3 ml/kg per feeding.** Trophic feedings should continue until the infant’s respiratory and cardiac status has stabilized. Older preterm infants (i.e. > 27 weeks) and infants with minimal respiratory compromise may bypass trophic feeds and begin feedings using a nutritive feeding regimen.

Feeding the Baby (Nutritive Feedings)

The rate of increase should not exceed 20 ml/kg/day except in situations where feedings were held and are being restarted. Feeding volume is increased first by reducing the interval between feeds to q 3 hrs or q 4 hrs and subsequently by increasing the bolus volume. Infants less than 1200 g may tolerate larger volumes with continuous slow infusion of feedings than rapid bolus feedings (over 30-60 minutes.)

Intestinal motility is often impaired in the infant in the in sick infants due to immaturity, sedation, or critical illness and thus feeding aspirates are common. Aspirates should be checked but, as a rule, should be refed, except when they are clearly bilious or when there are other clear signs of bowel obstruction. Aspirates greater than half the prior feed, especially if they contain mostly milk or formula rather than gastric juice, should prompt a physical examination of the infant, and subsequent aspirates as well as the infant's medical condition should be monitored closely.

Highlights of Physiology and Pathophysiology

- 10 weeks of gestation - the gut has formed and has completed its rotation back into the abdominal cavity
- 16 weeks of gestation - weeks the fetus can swallow amniotic fluid
- 24 weeks of gestation - GI motor activity is present but organized peristalsis is not established until 29-30 weeks. This improved peristalsis is facilitated by antenatal corticosteroid treatment.
- 32-34 weeks of gestation - coordinated sucking and swallowing develops
- At term - the fetus swallows about 150 ml/kg/day of amniotic fluid, which has 275 mOsm/L, contains carbohydrates, protein, fat, electrolytes, immunoglobulins and growth factors, and plays an important role in development of GI function.
Preterm birth interrupts this development.

- Even if nutrients are provided parenterally, lack of enteric intake leads to:
  - Decreased circulating gut peptides
  - Slower enterocyte turnover and nutrient transport
  - Decreased bile acid secretion
  - Increased susceptibility to infection due to impaired barrier function by intestinal epithelium
  - Lack of colonization by normal commensal flora and colonization by pathogenic organisms
  - This is worsened by use of broad spectrum antibiotics

- For fat digestion, the newborn depends on lingual lipase, which is stimulated by sucking and swallowing and by nutrients in the stomach but not the small bowel.
- Institution of feedings in the preterm infants may be complicated by the following factors:
  - Immature suck and swallow
  - Small gastric capacity
  - Immature gastro-esophageal sphincter
  - Decreased gut motility
  - Decreased enzyme production
  - Decreased bile salt production and absorption

Contra-Indications for Feeding

There are relatively few absolute contra-indications for enteral feeds. These include:

- Ongoing treatment with indomethacin or ibuprofen, or received it within the last 12hrs. This practice is controversial
- Hemodynamically significant patent ductus arteriosus (esp. if reverse flow in aorta during diastolic run off through a large ductus)
- Severe polycythemia
- Significant metabolic acidosis until shock is ruled out as the etiology
- Severe respiratory instability or there is impending endotracheal intubation
- Hemodynamic instability as evidenced by clinical signs of sepsis, hypotension or is needing dopamine (at a dose >5 microgram/kg/min) or other vasopressor drugs
- Received an exchange transfusion within the past 24 h.
- Has abdominal distension or other signs of GI dysfunction (including postoperative GI surgery)
- Post episode of severe asphyxia (perinatal or post-natal) – unclear how long feeds should be held

Guidelines for Feeding

Initiation of feedings, their volume and the rate of advance of feedings are related to birth weight, gestational age and how the infant has tolerated feeds to date. General guidelines include:

- Initial volume is 2 ml/kg per feeding with a minimal absolute volume of 1-2 ml
- Do not advance feedings faster than 20 ml/kg/day
- Do not advance feedings if there are any signs that the baby is not tolerating feeds.
- Aggressive advances of feedings may increase the risk of NEC (studies vary on this point)
- A small volume, even if not advanced, is much better than nothing at all. Even very small volumes stimulate maturation of gut motility and production of enteric peptides (trophic feeds.)
- Bolus feedings are preferable to continuous feedings

The goals for "full feedings" are

- Volume: 150-180 ml/kg/d
- Calories: 110-130 kcal/kg/d
- Protein: 3.5-4 gm/kg/day

- Some infants will require a higher caloric intake to achieve consistent weight gain (including some SGA infants, postoperative infants and infants with high energy needs such as those with chronic lung disease)
- Do not wait for infant to stop growing to advance feedings – volume adjustments may be needed every 2-3 days

Method of feeding

- Because infants usually have not yet developed coordinated sucking and swallowing they must be fed by gavage – beyond this fact there is little national consistency in feeding methods and most techniques are standardized within a particular nursery (often with very strong feels toward the local preference – many of which have only limited research data to support them.)
Orogastric tubes / Nasogastric tubes
- Orogastric tubes are often chosen because infants are obligate nose breathers and feeling it is best not to occlude the nares with a tube.
- Orogastric tubes often cause gagging in older infants and may be in the way for bottle/breast attempts – once infant is demonstrating feeding readiness (about 33 weeks) consider moving the indwelling tube to the nose.
- Repeated insertion of a nasal gastric tube can cause inflammation of the nose with subsequent obstruction.
- Duodenal or jejunal tubes should be avoided if possible. They have far higher rates of complication and feedings are less well tolerated and do not stimulate secretion of lingual lipase. Residuals are no longer useful in assessing tolerance of feedings.
- Polyurethane or silastic tubes should be used for indwelling tubes as polyvinyl tubes will harden in gastric environment and have been associated with gastric irritation and perforation.
- If possible indwelling tubes should be changed once a week as they can become colonized.

Nipple feedings can be considered as the infant matures. The best judge of when to start nipple feedings is an experienced Nurse. Infants typically start to develop suck and swallow coordination about 33 weeks.

Content of feeding
- Milk provided by the infant's mother is the feeding of choice.
- Fresh milk that has not been frozen is preferred when available. Freezing entails some loss of nutrients, but, with the exception of live neutrophils and lymphocytes, all the protective components of breast milk remain essentially intact.
- Expressed, stored milk should always be fed in the order in which it was obtained. In this way, the infant receives the colostrum first, which is most protective, followed by transitional and mature milk.
- Encourage the use of “tiny tubes” for first days of pumping (captures even drops of colostrum and “rewards” pumping efforts.
- Routine cultures of maternal breast milk are not indicated. For infants < 1000 grams if there is concern about contamination, send a freshly pumped sample for culture. If milk contains pathogens (pathogenic gram negative organisms or beta streptococcus or staphylococcus aureus), discard milk. Instruct mother on proper pumping techniques and check that the collection device is cleaned properly.
- Donor milk
  - Available from the Mother's Milk Bank of San Jose
  - Donor milk is generally mature human milk and likely contains less protein and sodium than mother's preterm milk but still confers most of the immunological and nutritional benefits of human milk.
  - Donated by volunteers. If donor mother delivered prematurely, the milk bank reserves her milk for preterm infants and it is not pooled milk. Most donors are > 1 month postpartum. Mature milk is pooled (a bottle is not from a single donor).
  - Donors are screened for HIV, hepatitis and TB but not for CMV. Average caloric density is probably about 0.6 cal/ml
  - Milk is heat treated to 56˚ C. This is adequate to destroy HIV and probably most (though not 100%) CMV.
  - Informed consent should be obtained from parents before using banked breast milk.
  - Donated milk form non licensed banks is not allowed due to Tissue Banking Restrictions of human milk – each bottle must be carefully tracked under tissue banking regulations
- Mother’s choosing to breast feed should begin pumping as soon after birth as feasible – initiation of pumping within hours of birth is associated with better milk production.
- Because human milk does not contain protein and minerals in amounts needed by the growing preterm infant, fortification is necessary. Below are the estimated nutrient requirements (“Advisable Intakes”) of preterm infants and contrasts these with the composition of unfortified and fortified human milk.
- Begin with either:
  - Breast milk (preterm breast milk is 290 mOsm/L) or
  - Formula for preterm infants (e.g., Premature Enfamil™ or Similac Special Care™, 260 mOsm/L or 20 cal/oz concentration).
- There is no evidence that diluted milks should be used for first feedings. In fact, hypo-osmolar solutions may slow gastric emptying, leading to increased incidence of residuals and feeding intolerance.
- Remember that fetuses swallow amniotic fluid, which is 275 mOsm/L, and this swallowing begins at 16 weeks gestation.

**Fortification of Human Milk**
- Provides additional calories
- Improved intake of calcium, phosphorus and protein.
- Fortify feedings (breast milk and formula) as follows:
  - When infant is tolerating 100 ml/kg/d, feedings may be fortified to 22 cal/oz
  - When infant has been tolerating 150 ml/kg/d feedings may be fortified to 24 cal/oz

**Fortification modalities:**
- **HMF (human milk fortifier)**
  - Mixture of MCT oil and carbohydrate. Also contains additional mineral, protein and vitamins. Cow milk protein based.
  - HMF is a sterilized product (compared to cans of formula powder which are not terminally sterilized)
  - 1 packet of HMF per 50 ml of human milk makes 22 calories/oz
  - 1 packet of HMF per 25 ml of human milk makes 24 calories/oz
  - Fortification above 24 calories / oz should not be done with HMF alone due to overloading of some nutrients (speak with nutritionist)
- **Mixing MBM half and half with 24 cal/oz preterm formula should be considered if maternal milk volume low (tolerance is better if at least some human milk is fed in each feed)**
- **Adding powdered infant formula to MBM**
  - Keep in mind cans of powdered formula are not terminally sterilized and can contain some bacteria
  - This should be restricted to infants who are close to going home (to document tolerance and teach family how to mix)
  - Must be used in instances where infant requires fortification with a special formula product (e.g. pregestimil)
- **MCT oil (7.7 cal/ml) – 0.25-1 ml 4-12 x day**
  - Watch for oily stools
  - Avoid giving >50% of total calories as fat
- **Polycose (4 cal/gm) - 1 teaspoon /ounce 20 cal milk = 30 cal/oz**
  - Will increase osmolarity and can cause loose stools
  - Do not add if <14 days old

---

### Table of Modalities to Fortify Human Milk

<table>
<thead>
<tr>
<th>Human Milk fortifier</th>
<th>Caloric count / oz</th>
<th>Amount to add</th>
<th>Volume of MBM</th>
<th>Adjustments for home use</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMF</td>
<td>21</td>
<td>1 packet</td>
<td>100 ml</td>
<td>N/A</td>
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<tr>
<td></td>
<td>22</td>
<td>1 packet</td>
<td>50 ml</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>1 packet</td>
<td>25 ml</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>26+</td>
<td>-----</td>
<td>-----</td>
<td>Will give too high mineral concentration consult with nutritionist to fortify to this level</td>
</tr>
</tbody>
</table>

### Neosure powder

<table>
<thead>
<tr>
<th>Human Milk fortifier</th>
<th>Caloric count / oz</th>
<th>Amount to add</th>
<th>Volume of MBM</th>
<th>Adjustments for home use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neosure powder</td>
<td>22</td>
<td>1 level teaspoon</td>
<td>130 ml</td>
<td>For home use per 120 ml (4 oz) for ease of measurement</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>1 level teaspoon</td>
<td>70 ml</td>
<td>For home use per 60 ml (2 oz) for ease of measurement</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>1 level teaspoon</td>
<td>40 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>1 level teaspoon</td>
<td>30 ml</td>
<td></td>
</tr>
</tbody>
</table>
EnfaCare Powder

<table>
<thead>
<tr>
<th>Caloric count / oz</th>
<th>Amount to add</th>
<th>Volume of MBM</th>
<th>Adjustments for home use</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>1 level teaspoon</td>
<td>180 ml</td>
<td>per 8 oz MBM</td>
</tr>
<tr>
<td>24</td>
<td>1 level teaspoon</td>
<td>80 ml</td>
<td>per 3 oz MBM</td>
</tr>
<tr>
<td>27</td>
<td>1 level teaspoon</td>
<td>45 ml</td>
<td>per 1.5 oz MBM</td>
</tr>
<tr>
<td>30</td>
<td>1 ¼ level teaspoon</td>
<td>40 ml</td>
<td></td>
</tr>
</tbody>
</table>

Term Infant Formula Powder

<table>
<thead>
<tr>
<th>Caloric count / oz</th>
<th>Amount to add</th>
<th>Volume of MBM</th>
<th>Adjustments for home use</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>½ level teaspoon</td>
<td>100 ml</td>
<td>¾ teaspoon per 5 oz MBM</td>
</tr>
<tr>
<td>24</td>
<td>1 level teaspoon</td>
<td>100 ml</td>
<td>1½ teaspoon per 5 oz MBM</td>
</tr>
<tr>
<td>27</td>
<td>1 level teaspoon</td>
<td>55 ml</td>
<td>1½ teaspoon per 3 oz MBM</td>
</tr>
<tr>
<td>30</td>
<td>1 level teaspoon</td>
<td>40 ml</td>
<td>1 scoop per 4.5 oz MBM</td>
</tr>
</tbody>
</table>

Alternative Formulas
  - Indication: Cow milk protein allergy (50% overlap between soy and cow’s milk protein), lactose intolerance and galactosemia.
  - Problems: Iron absorption is less efficient with soy formulas and manganese absorption is increased. In preterms, the risk for osteopenia is greater with these formulas. Also higher calorie/kg may be needed for growth because of difference in protein.
- "Elemental" and predigested formulas
  Available types:
  - Neocate: free amino acids, contains some MCT. Most "elemental" of formulas. Very low vitamin E.
  - Elecare: amino acid based, contains MCT.
  - Alimentum: hydrolyzed casein as protein source. 33% of fat as MCT.
  - Pregestimil: Hydrolyzed casein as protein source. 55% of fat as MCT.
  - Nutramigen: Hydrolyzed casein as protein. 0 MCT oil. Lowest osmolality of all the formulas (260 mOsm/L).
  - Indication:
    Malabsorptive states (i.e., short gut, post severe gastroenteritis, cystic fibrosis).
    Allergic states – controversy exists whether feeding of these special formula results in less allergies in infants.
  - Some literature supports using these formulas in all formula fed infants until a clear family history of allergies can be determined.

Preparing Formulas of Higher Caloric Density
Whenever possible liquid preparations of formula should be used in the NICU as they are terminally sterilized. Powdered formulas are not.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Concentration kcal/oz</th>
<th>Level Scoops of Powder</th>
<th>Amount of Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powdered regular or soy term infant formulas, Nutramigen, Pregestimil</td>
<td>20</td>
<td>1</td>
<td>2 oz = 60 ml</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>3</td>
<td>5.5 oz = 165 ml</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>3</td>
<td>5 oz = 150 ml</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>3</td>
<td>4.25 oz = 130 ml</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>4</td>
<td>5 oz = 150 ml</td>
</tr>
</tbody>
</table>
### Feeding Intolerance

- Common among very small preterm infants
- Most tiny infants have episodes that require either temporary discontinuation of feedings or a delay in advancing feedings.
- Most episodes resolve spontaneously and without sequelae, any signs of feeding intolerance should be regarded as potentially serious because of the increased risk of NEC among these infants.
- Signs that indicate possible intolerance of feeding include:
  - Gastric residuals or emesis
  - Abdominal distension
  - Blood in the stool (gross or occult)
  - "Loose stools" or diarrhea
  - Metabolic acidosis
  - Temperature instability
  - Onset of apneic episodes
  - Hyperglycemia

  - Management of intolerance should be related to the type and severity of the presenting signs
    - Non bilious Gastric residuals
      - If these are smaller than ½ the volume of a feeding and are not increasing in volume, and if the infant otherwise appears well, feeding can continue but the infant should be observed carefully for other signs of feeding intolerance.
      - If the infant has any other worrisome findings, hold the feedings, consider obtaining an abdominal radiograph and observe the infant.
      - If the residuals are greater than the volume of a feeding or are progressively increasing in volume, hold the feedings and observe closely
    - Bilious residuals are a more serious sign
      - Hold feedings, evaluate infant closely, and consider further workup including abdominal radiograph, CBC and platelets.
    - Abdominal distension is a serious sign.
      - Discontinue feedings, obtain abdominal radiograph, and consider further evaluation and treatment.
    - Blood in stool
      - If soon after birth consider swallowed maternal blood as the source – send Apt test
      - If infant has no other symptoms look for signs of fissure.
      - If no fissure or if any other signs of intolerance discontinue feedings, consider obtaining clotting studies and abdominal radiograph.
    - Metabolic acidosis in conjunction with feeding intolerance must be considered NEC until proven otherwise. Persistent metabolic acidosis in NEC is a grave prognostic sign
    - Loose stools, temperature instability, apnea, hyperglycemia. Hold feedings and evaluate infant carefully.

### Table: Feeding Intolerance Formulas

<table>
<thead>
<tr>
<th>Formula</th>
<th>Concentration kcal/oz</th>
<th>Level Scoops of Powder</th>
<th>Amount of Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neosure Powder</td>
<td>24</td>
<td>3</td>
<td>160 ml (5 oz for going home)</td>
</tr>
<tr>
<td>(liquid is 22 cal/oz)</td>
<td>27</td>
<td>2</td>
<td>95 ml (3 oz for going home)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>2</td>
<td>85 ml</td>
</tr>
<tr>
<td>Neocate</td>
<td>20</td>
<td>1</td>
<td>30 ml</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>3</td>
<td>70 ml</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6</td>
<td>125 ml</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>5</td>
<td>90 ml</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>5</td>
<td>80 ml</td>
</tr>
</tbody>
</table>
- If feedings have to be stopped for any of these reasons, notify the Neonatologist. If there is any doubt about how well an infant is tolerating feedings, it is best to hold feedings, evaluate the infant and discuss the case with the other members of the team.

- Experienced ICN Nurses are experts at feeding small preterm infants and are valuable resources for advice on feeding problems.

<table>
<thead>
<tr>
<th>Born at &lt;32 weeks OR birthweight &lt;1800g</th>
<th>Transition to Oral Feed</th>
<th>Stable Growing</th>
<th>Preparation for Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed</td>
<td>Parenteral nutrition including &quot;starter TPN&quot; IV then, Breast milk or preterm formula</td>
<td>When full feeds reached add Breast Milk Fortifier 1 packet per 50ml breast milk (22 cal) &amp; then 1/25 ml (24 cal) or advance caloric density of Preterm Formula</td>
<td>Move fortification from HMF to powdered infant formula or move to transitional preterm formula (Neosure or Enfacare)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Transition to Oral Feed</th>
<th>Stable Growing</th>
<th>Preparation for Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begin at 1ml/kg q 2 hourly or as tolerated (in ELBW may start every 4 hours and decrease toward 2 hour intervals)</td>
<td>Up to 3 hourly feeds as tolerated (when over 1250 g)</td>
<td>Work with lactation to make sure infant going to breast at least once each day</td>
<td>Move to ad lib schedule (on demand)</td>
</tr>
<tr>
<td>Usually increase feed volume by 1ml, every 12 to 24 hours depending on tolerance Increase more rapidly once tolerated.</td>
<td>Increase volume as needed for adequate calories for growth</td>
<td>Usual volume is 160-180 ml/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feed Volume</th>
<th>Transition to Oral Feed</th>
<th>Stable Growing</th>
<th>Preparation for Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase to 150-170 ml/kg/day</td>
<td>Increase volume as needed for adequate calories for growth</td>
<td>Usual volume is 160-180 ml/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplements</th>
<th>Transition to Oral Feed</th>
<th>Stable Growing</th>
<th>Preparation for Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamins and Iron as needed for erythropoietin</td>
<td>Multi-vitamins (with Iron if not on Epo protocol) once over 2 weeks old and tolerating full feeds</td>
<td>If breast milk fed: Multivitamins 1 ml / day (to meet recommended 400 IU Vitamin D)</td>
<td>Iron at 3-6 mg/kg/day</td>
</tr>
<tr>
<td>Born at 32-35 weeks AND birthweight 1800+g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Feed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk or preterm formula</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk fortified to 22 cal/oz or preterm formula</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast milk fortified to 22 cal until fully feeding at breast or formula (consider an interim formula such as Neosure or Enfacare)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 hourly unless risk of hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 hourly feeds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 hourly feeds or on demand</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the baby is going to be breast fed, then the first feeds offered should be breast feeds.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Feed Volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1-2 60-90 ml/kg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3-5 90-120 ml/kg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 days 120-150 ml/kg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 180 ml/kg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 ml/kg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase to 200 ml/kg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase to 200 ml/kg/day or more if poor growth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase to 200 ml/kg/day if poor growth or on demand</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supplements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D 400 units if exclusively breast fed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Vitamin and Iron Supplementation**

- Vitamins and iron are typically added once on full feeds, tolerating feeds well and generally when infant is over 2 weeks of age (exceptions in special needs like severe anemia, on erythropoietin.)
- Vitamin preparations are quite hyperosmolar

Infants ≥ 35 weeks (at birth)

<table>
<thead>
<tr>
<th>Milk</th>
<th>Vitamin</th>
<th>Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Milk</td>
<td>Vitamin D 400 units/day</td>
<td>1 mg/kg/day by 4-6 months (may be in cereal/meats)</td>
</tr>
<tr>
<td>Formula</td>
<td>Vitamin D 400 units/day</td>
<td>None unless depleted blood supply due to hemorrhage or lots of blood sampling</td>
</tr>
</tbody>
</table>

Infants <35 weeks

<table>
<thead>
<tr>
<th>Milk</th>
<th>Vitamins</th>
<th>Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human milk (unfortified)</td>
<td>1 ml Multivitamin with iron</td>
<td>2-4 mg/kg/day iron (in multivit prep)</td>
</tr>
<tr>
<td>Human milk with HMF</td>
<td>22 cal fortification needs added Vitamin D:</td>
<td>2-4 mg/kg/day by day 30 until 12 mo</td>
</tr>
<tr>
<td></td>
<td>200 units if &gt;2.5 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 units if &lt;2.5 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 cal fortification will meet 400 IU of D when infant taking over 350 ml/day (a 2.5 kg infant on full feeds) – before that at least 200 units of Vitamin D are needed</td>
<td></td>
</tr>
<tr>
<td>Human milk enriched with formula</td>
<td>Need 400 units Vitamin D (1 ml MVI)</td>
<td>1-3 mg/kg/day (contained in multivitamins with iron)</td>
</tr>
<tr>
<td>Similac Special Care 24 cal and Premature Enfamil (24 cal)</td>
<td>Need additional 200 units of Vitamin D (0.5 ml of MVI)</td>
<td>Contains 2 mg/kg in 120 cal/kg &lt;1000 gm: add 2 mg/kg/day 1000-1500: add 1 mg/kg/day &gt;1500: none needed</td>
</tr>
<tr>
<td>Similac Special Care 20 cal and Premature Enfamil 20 Cal</td>
<td>Need additional 200 units of Vitamin D (0.5 ml of MVI)</td>
<td>Contains 2 mg/kg at 120 cal/kg &lt;1000 gm: add 2 mg/kg/day 1000-1500: add 1 mg/kg/day &gt;1500: none</td>
</tr>
<tr>
<td>Neosure Enfacare</td>
<td>Need additional 400 units of Vitamin D (1 ml of MVI)</td>
<td>Contains 2 mg/kg at 120 cal/kg Discharge home with 1-2 mg/kg/day = 3-4 mg/kg/day</td>
</tr>
</tbody>
</table>

**Special Circumstances**

<table>
<thead>
<tr>
<th>Vitamins</th>
<th>Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants on Epogen</strong></td>
<td>Add Vitamin E 15 units/day</td>
</tr>
<tr>
<td><strong>Cholestatic Jaundice</strong></td>
<td>ADEK 1 ml q d</td>
</tr>
<tr>
<td><strong>Post-hemolytic anemia</strong></td>
<td>Folate 50 microgram/day – should be met by feedings – not in multivitamin preparations and not readily available in liquid form</td>
</tr>
</tbody>
</table>
Oral Vitamin Preparations:

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Infant multivitamin per 1 ml</th>
<th>Infant multivitamin with iron per 1 ml</th>
<th>AquADEXK per 1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (units)</td>
<td>1350-1500</td>
<td>1350-1500</td>
<td>5750</td>
</tr>
<tr>
<td>D (units)</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>C (mg)</td>
<td>32-35</td>
<td>32-35</td>
<td>45</td>
</tr>
<tr>
<td>E (units)</td>
<td>5</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Thiamine B1 (mg)</td>
<td>0.4-0.5</td>
<td>0.4-0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Riboflavin B2 (mg)</td>
<td>0.5-0.6</td>
<td>0.5-0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>7-8</td>
<td>7-8</td>
<td>6</td>
</tr>
<tr>
<td>B6 (microgram)</td>
<td>0.4</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>B12 (microgram)</td>
<td>1.4-2</td>
<td></td>
<td>400</td>
</tr>
<tr>
<td>K (microgram)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>9-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Selenium (microgram)</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Biotin (microgram)</td>
<td></td>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

Probiotics

At birth GI tract is sterile. Normal term infants colonize their guts with gram positive micro-organisms (primarily Streptococci and Bifidobacterium species) compared to the NICU flora seen in preterm infants. This altered microflora may be partially due to delayed feeds and broad spectrum antibiotics. Normal intestinal flora may serve beneficial functions:
- Protect against pathogenic infections by competing with micronutrients and receptor sites
- Maintaining low pH
- Providing a physical barrier to prevent invasion of bacteria across the gut wall

Administration of probiotics to preterm infants may
- Prevent or decrease the severity of NEC
- Improve weight gain
- Improve feeding tolerance

Treatment
- Infants <1500 g birthweight
- ABC dophilus is combination of S. thermophilus, B. infantis, B. bifidum
- <1000 g = ¼ teaspoon once a day dissolved in milk
- 1000-1500 g = ½ teaspoon once a day dissolved in milk
- Continue until discharge or 36 weeks (whichever is sooner)

[CPMC policy on Probiotics](#)
Feeding of Late Preterm Infants (35+ weeks) and Term Infants

- If the infant is to be breast fed, do not supplement with formula unless there is a medical indication
- Put to breast as often as possible in the first several days
- On average, a term breast fed infant takes about 30-50 ml/kg/day in the first 24 hours of life when breast feeding exclusively
- Feed by 3-4 hours after birth in stable infants. If not breast feeding, begin with 60 ml/kg/day or ad lib – overfeeding in the first days by formula may cause intolerance and loose stools
- Advance feedings by 5 ml/feeding or every other feeding as tolerated
- Human milk is the best choice for infants. Cow's milk based formula is the second choice. Soy formulas should be reserved for specific indications
- Withhold feedings in the following instances:
  - Infants with marked tachypnea and respiratory distress on day 1. Begin feeding po when improving, or consider gavage feeding if still too tachypneic to nipple on day 2.
  - Severely asphyxiated infants (Apgar <3 at 5 minute and/or cord pH<6.9 and evidence of multisystem involvement) until 3 to 5 days of age because of the possibility of gut ischemia. If the infant is to be NPO for >24 hours, begin parenteral nutrition. If infant only has low Apgar and recovers quickly, there is no evidence for withholding feedings.
  - Discontinue feeding and evaluate any infant with bilious vomiting or abdominal distension.

References


Newborn Services Clinical Guidelines February 2006 Auckland NZ District Health Board University of Iowa Neonatology Handbook
Parenteral Nutrition

General
- First IV solution for <1500 g infants should be starter TPN
  - 5% and 10% dextrose bags are kept in NICU medication refrigerator
  - Solution contains 2.5% protein (at typical daily fluids this gives about 2 gm/kg of protein)
- Infants expected to be NPO over 2 days should be started on TPN
- May use UVC or UAC for initial TPN
- Place central line if not expected to reach adequate enteral nutritional intake by day 7
- Adequate growth may occur on 80-90 kcal/kg/day of non-protein energy intake of parenteral nutrition. If parenteral nutrition is the sole source of nutrition, caloric intake should be limited to 100/kcal/kg (exception: when growth is documented as inadequate on this amount)
- For peripheral IV, limit glucose to 12.5% solution

Guidelines
To achieve fetal weight gain, the following protein and energy intakes are estimated to be needed postnatally:

<table>
<thead>
<tr>
<th>Body wt (gm)</th>
<th>500-700</th>
<th>700-900</th>
<th>900-1200</th>
<th>1200-1500</th>
<th>1500-1800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal wt gain (g/day)</td>
<td>13 g/kg/d</td>
<td>16 g/kg/d</td>
<td>20 g/kg/d</td>
<td>24 g/kg/d</td>
<td>26 g/kg/d</td>
</tr>
<tr>
<td>Protein intake</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Parenteral</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Enteral</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>3.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Energy intake</td>
<td>89 kcal/kg/d</td>
<td>92 kcal/kg/d</td>
<td>101 kcal/kg/d</td>
<td>108 kcal/kg/d</td>
<td>109 kcal/kg/d</td>
</tr>
<tr>
<td>Parenteral</td>
<td>89 kcal/kg/d</td>
<td>92 kcal/kg/d</td>
<td>101 kcal/kg/d</td>
<td>108 kcal/kg/d</td>
<td>109 kcal/kg/d</td>
</tr>
<tr>
<td>Enteral</td>
<td>105 kcal/kg/d</td>
<td>108 kcal/kg/d</td>
<td>119 kcal/kg/d</td>
<td>127 kcal/kg/d</td>
<td>128 kcal/kg/d</td>
</tr>
</tbody>
</table>


Volume
- Use guidelines for maintenance water requirements to determine total volume.
- For infants with lung disease or extremely low birth weight infants, limit total volume of <140 ml/kg/day once sodium is stable

Glucose (3.4 kcal/gm)
- Maximum 12.5 % by peripheral vein, 30% by central vein.
- If the infant is less than 1000 grams, begin with 5% glucose and give 5-6 g/kg/day. Increase by 0.5-1 gm/kg/day as tolerated. Most infants can meet caloric needs at 18 gm/kg/day of glucose, some infants may require 20 gm/kg/day for adequate growth
- In infants over 1000 grams, start with 10% glucose and give 10-12 g glucose/kg/day as tolerated
  - Increase glucose by 1 to 2 g/kg/day as tolerated.
  - Give a maximum glucose of 18-20 g/kg/day as tolerated.
- Consider insulin drip in infants <1000 g if they remain glucose intolerant on severely limited calories after 3-5 days of life.
- Glucose tolerance may be improved by early addition of adequate amino acids
- Glucose tolerance may improve by addition of trophic feeds (possibly promotes insulin release)

Protein (4.0 kcal/gm)
- Use only pediatric formulations of amino acids. Add cysteine 40 mg/gm of amino acids
- Begin amino acids early (<24 hours) with 2 gm/kg/day and advance by 1 gm/kg/day to 3.5 gm/kg/day
- Starter TPN should be started at birth in <1500 gm infants
- If BUN>50, limit protein to 3 gm/kg/day

Lipids (Use only 20% fat emulsion = 2 kcal/ml)
- Start with 0.5 g/kg/day and increase by 0.5 g/kg/day to maximum of 3.0 g/kg/day. To prevent fatty acid deficiency 0.5 g/kg/day of lipid is needed.
- If given through a U.A. catheter it may interfere with arterial pressure readings.
Lipids may safely supply 40-60% of the calories in infants. Avoid fat loading (60% or more of calories) when glucose is not being tolerated. Remember to taper lipids when weaning off parenteral nutrition.

Monitor serum triglycerides: Measure after starting and while increasing dose and then every week when dose is stable. Keep serum triglyceride <180 mg%. Check levels if serum is lipemic on spun hematocrit. Levels can be drawn while lipids are infusing.

Contraindications
- Limit use in infants with pulmonary hypertension or indirect bilirubin near exchange level to free fatty acid levels of 0.5-1 gm/kg/day
- Relative contraindications
  - Marked thrombocytopenia (less than 30,000 platelet count)
  - Severe lung disease requiring high inspired O2
  - Acute stage of sepsis
  - Coagulopathy

Electrolytes
- Sodium: 2-4 mEq/kg/day after the first 48-72 hours of life. Very low birth weight infants may require more sodium
- Potassium: 2-3 mEq/kg/day
- Chloride: 2-3 mEq/kg/day
- If infant is acidotic or if chloride is high, use acetate as the anion. Prolonged substitution of acetate for Cl may cause CO2 retention.

Calcium and Phosphorus
- Calcium: 200-600 mg/kg/day (usual dose is 300 mg/kg/day)
- 200 mg calcium gluconate = 1 mEq Ca
- Do not use over 300 mg/dl in peripheral line or over 1000 mg/dl in central venous lines.
- Phosphorus: 1-2 mmol/kg/day (usually limited by Cation concentration) Not giving phosphorus will result in bone demineralization. Protein solutions contain a minimal amount of phosphorus.
- Approximately 1.5 meq of Na or K must be given for each 1mmol of phosphorus given.
- It is ideal to keep the mEq ratio of Ca++/PO4 = at 1-2/1

Magnesium: 0.5 mEq/kg/day as MgSO4
- Do not add initially to TPN if mother’s received magnesium either for tocolysis or for pre-eclampsia

Trace Minerals
- Neotrace solution at a dose of 0.2 ml/kg/day
- Zinc 300 microgram
- Copper 20 microgram
- Manganese 5 microgram
- Chromium 0.17 microgram
- If the infant has hepatic cholestasis with direct bilirubin > 3 mg/d consider decreasing trace element solution to 0.1 ml/kg/day and give zinc (300 microgram/kg/day).
- Add selenium if the infant is on parenteral nutrition for > 1 week (1-2microgram/kg/day)
- Iron is not routinely given in parenteral nutrition. The bioavailability and safety of IV iron in newborns is disputed. Studies have shown erratic levels after IV iron. Iron should only be considered after 2 months of exclusive parenteral nutrition in an infant who is no longer receiving blood transfusions.

Vitamins
- Pediatric MVI is used on following dosage schedule:
- <1 kg: 2.5 ml  1-3 kg: 3.3 ml  >3 kg: 5 ml
- Each 5 ml vial of Pediatric MVI contains: Vit A (2330 IU or 700 microgram), Vit D (400 IU), Vit E (7 IU), Vit C (80 mg), Niacin (17 mg), Thiamin (B1: 1.2 mg), Riboflavin (B2: 1.4 mg), Pyridoxine (B6: 1 mg), Vit B12 (1 microgram), Pantothenic (5 mg), Biotin (20 microgram), Folic Acid (140 mg) and Vit K (0.2 mg).
Medications
- Heparin: 1 unit/ml
- Famotidine: 1 mg/kg: Do not use routinely as it may contribute to bacterial overgrowth in the neonate’s stomach/intestines. Consider adding if infant is receiving steroids.
- Many commonly used medications are “compatible” with parenteral nutrition. Consult compatibility chart (in med room) or pharmacist regarding compatibility. Use extreme caution if meds are given in line with parenteral nutrition - any break in sterile technique raises risks of line infection as the PN solution is an excellent nutrient source for babies and bacteria. The medication line must be set up in line with the TPN and lipids when they are set up and port should only be accessed via a scrubable port.
- Certain drip medications may be stable in parenteral solutions including dopamine, aminophyline, insulin, fentanyl. Amphotericin and acyclovir are incompatible.

Monitoring for Effectiveness & Toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Daily</td>
</tr>
<tr>
<td>Length &amp; Head</td>
<td>Weekly</td>
</tr>
<tr>
<td>Circumference</td>
<td>Weekly</td>
</tr>
<tr>
<td>Blood chemistries</td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Daily until stable</td>
</tr>
<tr>
<td>Glucometer</td>
<td>Q shift</td>
</tr>
<tr>
<td>Metabolic panel</td>
<td>2 x/week</td>
</tr>
<tr>
<td>LFT</td>
<td>At onset</td>
</tr>
</tbody>
</table>

Complications of parenteral nutrition
- Metabolic/Growth
  - Hyperglycemia
  - Hypoglycemia (sudden cessation of infusion)
  - Hyperammonemia: uncommon with current amino acid solutions
    - Symptoms: Lethargy, failure to thrive, vomiting, seizures, coma
  - Hyperlipidemia
  - Cholestatic jaundice: seen most commonly after 3 weeks PN.
    - Cholestasis may appear while PN is being tapered or after it is discontinued. Ultrasound evidence of gallbladder sludge and gallstones may be seen. Etiology is unclear. Potential treatments are:
      - Start feedings
      - Limit ratio of non-protein calories per g protein to 25-40:1
      - Limit Copper, Manganese (done by cutting trace element dose to 0.1 ml/kg/day and increasing the zinc to 300 microgram/kg/day)
      - Discuss with GI needing to limit the glucose load (18 gm/kg/day)
      - Begin oral Actigal (ursodiol) 10-15 mg/kg/dose, every q 8-12 h
      - Add ADEK once tolerating feeds
  - Electrolyte imbalances
  - Osteopenia
  - Trace element deficiencies

- Catheter Related Complications
  - Sepsis: usually catheter related rather than solution related.
    - Unexpected glucosuria or hyperglycemia is early sign
    - Culture from line and from peripheral vein
    - Further sepsis work up as indicated
Insulin Infusion in Glucose Intolerant Infants < 1000 gm

Background
Very low birthweight infants (<1000 gms) are frequently glucose intolerant. This limits the caloric intake by parenteral nutrition for prolonged periods of time. Several studies have shown that glucose tolerance can be improved and better weight gain achieved with the use of insulin to improve glucose tolerance.

Consider Insulin Infusion in the following patients:
- B.W. <1000 gm
- Age >4 days
- Serum glucose >180 gm
- Non protein caloric intake <80 kcal/kg
- Exclusions:
  - Infants of mothers with gestational diabetes or insulin dependent diabetes
  - Infants with renal failure (creatinine >2)

Methods
- Detailed CPMC protocol on Insulin Administration:
- 2 syringes are sent from pharmacy – 1 to flush the tubing (insulin adheres to the tubing wall) and a second smaller syringe to use to infuse on the smart pump
- Titrating Infusion: Begin infusion with 0.04 units/kg/hr = 0.04 ml/kg/hr
  - For glucose >240, check serum glucose, glucose infusion rate and increase insulin infusion by 0.01 ml/hr. For glucose >180, increase insulin infusion by 0.01 ml/hr
  - When glucose normalizes (<180), wean the insulin by 0.01 units=0.01 ml until stable glucose <180 is reached.
  - For glucose <80, stop insulin infusion and check glucose in 1 hour
    - Average range of insulin infusion: 0.04 unit/kg/hr to 1 unit/kg/hr. If infant is requiring >1 unit/kg/hour consider other causes of glucose intolerance such as sepsis.
- Increasing glucose concentration:
  - Increase glucose in TPN by 1-2 gm/kg/day to maximum of 20 gm/kg/day
  - Increase insulin as necessary to maintain glucose between 70 and 180 mg%.
- Weaning off insulin:
  - When the infant has stable glucose tolerance and is receiving adequate calories, begin to wean the insulin by 0.01 unit/kg/day
  - Monitoring
    - Do glucometer testing every hour for four hours or until stable x 2
      - after initiating insulin therapy
      - after glucose infusion is increased
      - after change in insulin infusion rate
    - Monitor glucometer q four hours after stable infusion rates of glucose and insulin have been reached.
    - Increase frequency of glucose monitoring to every hour if infant is septic (or suspicious for sepsis), in congestive heart failure and when lipids are increased.
Metabolic Problems

Glucose Control & Hypoglycemia

Background and Pathophysiology
Glucose is the major energy source for fetus and neonate. The newborn brain depends upon glucose almost exclusively. Up to 90% of total glucose used is consumed by the brain. Alternate fuels (e.g., ketones, lactate) are produced in very low quantities. The usual rate of glucose utilization is 4-8mg/kg/min. Glucose regulatory mechanisms are sluggish at birth. Thus, the infant is susceptible to hypoglycemia when glucose demands are increased or when exogenous or endogenous glucose supply is limited. Severe or prolonged hypoglycemia may result in long term neurologic damage.

Definition
There is no consensus on what defines "hypoglycemia" in the neonate. For treatment purposes, we define hypoglycemia as: Serum glucose <45 mg/dL

Incidence: The definition of neonatal hypoglycemia has been based on statistical criteria. The incidence of this condition in term AGA infants is approximately 2%.

Infants at Risk for hypoglycemia: Any prenatal or postnatal event which results in decreased glycogen and/or fat stores, increased insulin secretion or increased glucose utilization can produce hypoglycemia in the newborn

- Infants of diabetic mothers - usually within first hours of life – esp. if control poor
- Small for gestational age infants (< 2500 gm at 40 weeks) or <10% for any gestational age – usually within first 24-48 hours
- Large for gestational age infants (> 4250 gm at 40 weeks)
- Prematurity (<37 weeks gestation)
- Perinatal asphyxia (5 minute Apgar < 5 and/or cord pH < 7.1)
- Polycythemia (Hct >65%)
- Infants receiving high glucose concentrations in whom the infusion has been stopped or infants whose mother’s are receiving high glucose infusion rates
- Cold stressed infants
- Beckwith Wiedemann
- Severe Rh disease or other immune hemolytic diseases
- Transposition of great vessel
- Long term exposure (over 2 weeks) to maternal betamimetics within 1 week of birth

Signs: Non-specific, including tremulousness, twitching, jitteriness, irritability, exaggerated Moro reflex, high pitched cry, seizures, apnea, limpness, poor feeding, cyanosis, temperature instability, and coma. Many infants are asymptomatic.

Diagnosis: When initial Glucometer screening test is abnormal a plasma glucose measurement must be sent to the lab for confirmation. For diagnostic purposes it is imperative that plasma glucose be measured by quantitative chemical analysis and NOT only by a Glucometer. This is because of their inaccuracy and imprecision relative to accepted laboratory determined glucose values. Treatment decisions in infants without signs ("asymptomatic") of hypoglycemia should not be based only on Glucometer.

Treatment
Treatment is dependent on infant’s level of illness and the degree of hypoglycemia. In term infants or late preterm infants who are otherwise well (regular nursery) a protocol and algorithm are in place.
The full policy is available at: [http://insidecpmc.org/departments/nursing/protocols/np-g7.pdf](http://insidecpmc.org/departments/nursing/protocols/np-g7.pdf)

For preterm infants and infants who are ill (in the NICU)

**Asymptomatic Infants:**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Plasma Glucose</th>
<th>Treatment Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>20-45 mg/dL</td>
<td>Oral: If developmentally capable of feeding orally, and if clinical condition permits (i.e., no significant respiratory distress, etc.), immediately offer ad infant formula, or allow breast-feeding. Consider gavage feeding. If enteral feeding is not possible, treat parenterally.</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;20 mg/dL</td>
<td>Parenteral: Treat with IV. Initial bolus of D10 of 2 ml/kg then 4-8 mg glucose/kg/min using D10W</td>
</tr>
</tbody>
</table>

**Symptomatic Infants:**

- **Immediate Bolus:** 2 ml/kg of IV 10% glucose, given over 1-2 minutes. (Do not use D25W or D50W.)
- **Continuous Infusion:** 6-8 mg glucose/kg/min using D10W; this is equivalent to 90-120 ml/kg-day as 10% dextrose in water (see Figure at end of section)
Guidelines for Monitoring Plasma Glucose in Hypoglycemic Infants

In hypoglycemic infants, glucose values should be repeated 1-2 hours after initiation of treatment if the infant remains asymptomatic, or every 20-30 minutes if symptomatic. If signs of hypoglycemia persist or recur, or if plasma glucose concentration as determined by the neonatal or hospital laboratory remains below 40 mg/dL, increase glucose infusion rate to 10 to 12 mg/kg/min. If further hypoglycemia persists, IMMEDIATELY notify neonatologist for consideration of further treatment and diagnosis.

Infants unresponsive to I.V. glucose or needing prolonged glucose infusions

- Obtain CRITICAL blood sample
  - This needs to be done when hypoglycemic (ideally <45 mg/dL)
  - Serum glucose sent on ice STAT to lab
  - Serum cortisol level – 1 red microtainer (can be same 1 as glucose so send on ice)
  - Serum insulin level – 2 red microtainers
  - Serum growth hormone – 2 red microtainers
  - Alternatively can send larger red top instead of 4 microtainers for the insulin and growth hormone

- Obtain endocrine consult. Consider other causes of refractory hypoglycemia such as hypopituitarism or congenital adrenal hyperplasia or hyperinsulin states.
- Increase infusion rate and glucose concentration to provide 12-15 gm/kg/day. May need central line (including umbilical line) if unable to provide adequate glucose in 12.5% solution.
- Hydrocortisone 25-50 mg/meter²/day IV or oral (q 6-8 h) for prolonged refractory hypoglycemia which is not adequately controlled high dose glucose. Wean slowly over 5-7 days after glucose is stable.
- Glucagon 0.03 to 0.3 mg/kg/dose (maximum dose=1 mg) IV or IM for emergency treatment. Infusion of 0.5 mg/kg/day has been used in SGA infants.
This graph may be used in management of neonates as an aid for determining:

- the IV rate needed to achieve a desired glucose infusion rate, i.e., in mg/kg/min as is needed for writing orders; or
- determining the glucose infusion rate of an existing IV to determine an infant’s caloric intake.

As an example, a 2.5 kg infant whom you would like to have receive 6 mg/kg/min of glucose should be receiving 9.5 ml/hr of D10W (equivalent to 90 ml/kg of IV fluid).

References:


University of Iowa Children’s Hospital Management of Hypoglycemia, Hyperglycemia, and Normoglycemia in Preterm and Term Neonates 2007
**Hyperglycemia**

**Definition**
- Unknown and controversial, many suggest a definition of plasma glucose as >180 mg/dL
- Hyperglycemia almost always occurs in the first hours to days of life.
- Incidence is unknown and is often iatrogenic

**Infants at Risk**
- Infants with birth weights > 1 kg receiving intravenous fluids at high dextrose infusion rates (>8mg/kg/min)
- VLBW infants < 1 kg at moderate glucose infusion rates (4-8 mg/kg/min)
- Infants with congenital diabetes mellitus (rare)
- Infants whose mothers received selected drugs, e.g. diazoxide
- Acute onset can be a sign of sepsis, NEC or other acute illness
- Rarely, neonatal diabetes

**Signs**
- Generally asymptomatic and found on screening
- Polyuria due to glycosuria (rare if blood glucose < 250 mg/dL)
- Intracranial hemorrhage if hyperglycemia occurs rapidly as a result of an abrupt increase in plasma glucose concentration, e.g., following an IV D25W or D50W glucose bolus

**Treatment:** If plasma glucose > 200 mg/dL.
- Reduce glucose infusion rate.
- IV insulin administration (0.04-0.1 unit/kg/hr) if reducing the rate of glucose infusion is not effective, or is not possible. This treatment should not be undertaken without first consulting the neonatologist.
- Avoid hypo-osmolar solutions (i.e. less than 5 % dextrose)

**Guidelines for Monitoring Plasma Glucose in Hyperglycemic infants:**
Plasma glucose measurements should be determined every 1 to 4 hours depending on the degree of hyperglycemia, with therapy adjusted according to plasma glucose results. Glucose determinations should be done on capillary blood from an extremity, or from a non-glucose-containing indwelling catheter.

**Complications:**
- Glycosuria: Some infants, especially those <1,000g, may not be able to fully utilize high glucose infusion rates, and will spill glucose in their urine. Although glucose-induced osmotic diuresis is rare in neonates, it should be looked for once glycosuria is present. The presence of glycosuria is an indication to perform a chemical determination of plasma glucose for the purpose of defining an individual infant's renal glucose threshold. If glycosuria is present and the plasma glucose is <200 mg/dL, it is NOT necessary to decrease the glucose infusion rate.
- Hyperosmolality: Each 90 mg/dl of glucose contributes 5 mOsm/liter
- Factitious hyponatremia
Metabolic Bone Disease: Rickets/Osteopenia

Poor bone mineralization is common among very immature infants (birthweight <1000 gm). It is usually asymptomatic but may first be manifest by fractures, particularly of ribs and extremities. It is usually seen after 6 weeks of age, especially in infants with chronic lung disease on diuretics or infants who have required prolonged parenteral nutrition.

Etiology

- Inadequate calcium and phosphorus intake – Most common:
  - Growing preterms have high calcium and phosphorus requirements and relatively inefficient absorption which may not be supplied by breast milk, regular formula or parenteral nutrition.
- Vitamin D deficiency – Less common:
  - Human milk has inadequate Vitamin D for preterms. If unsupplemented, they may become deficient.
  - Infants with hepatobiliary disease may be unable to absorb adequate Vitamin D.
  - Chronic renal failure: Unable to convert to 1,25 OHD.
- Calcium loss
  - Malabsorption
  - Excessive urinary loss from diuretics (Lasix)
- Copper deficiency: Can present as osteopenia, often indistinguishable from scurvy by x-ray.
- Renal and parathyroid disorders

Diagnosis

- X-ray
  - Often seen as poorly mineralized bones on chest x-ray: digital films may not give same estimate of calcification as traditional films.
  - Flaring of ribs
  - Subperiosteal new bone formation
  - Wrist and/or knee films show cupping, fraying of metaphyses
  - Long bones and ribs may show fractures
- Biochemical
  - Vitamin D, Ca\textsuperscript{++} or PO\textsubscript{4}\textsuperscript{++} deficiency:
    - Ca usually normal or borderline
    - PO\textsubscript{4} low to normal
    - Alkaline phosphatase high
    - 25 (OH) D\textsubscript{3} levels low to normal or elevated in Ca deficient states (usually < 7 gm/l in severe D deficiency)
  - Copper deficiency
    - low serum copper
    - low ceruloplasmin

Therapy

- Osteopenia
  - Increase calcium intake to 220-250 mg/kg/day
  - Increase phosphorus to 100 mg/kg/day
  - Insure Vitamin D intake minimum 400-800 units/day
  - Furosemide induced urinary calcium losses may be decreased by adding a thiazide (Diuril) to the regimen.
- Rickets: as above
  - Maximize mineral status
  - Consider checking Vitamin D and copper status
Newborn Screening and Inborn Errors of Metabolism

The newborn screen does NOT detect disorders of the urea cycle (ornithine transcarbamylase deficiency), glutaric acidemia type 1, lysosomal storage disease, peroxisomal disorders, and most mitochondrial disorders.

Disorders Detectable by NBS as of July 16, 2007:

- **Cystic Fibrosis**
  - High IRT (Immunoreactive Trypsinogen elevated with injury to pancreas or GI obstruction such as meconium ileus) and two cystic Fibrosis mutations (CRTR mutation panel used to identify positive result).

- **Endocrine**
  - Primary congenital Hypothyroidism and variant hypothyroidism
    - Primary congenital Hypothyroidism – primary screen is looking for elevated TSH levels (newborn screening will miss hypothyroidism that is due to brain anomalies)
    - In California prevalence: Primary congenital hypothyroidism is 1 in 2,000 births
  - Congenital adrenal hyperplasia – Salt wasting and simple virilizing 21-hydroxylase deficiency.
    - Primary screen is 17-OH progesterone. Cut off values vary with birth weight. Secondary screen of cortisol and 17-OH are done if first tier screening is abnormal.

- **Hemoglobin**
  - Sickle cell disease and other hemoglobinopathies
    - SS, SC, SD, SE, CC, DD and S/beta thalassemia
  - Thalassemias
    - Alpha thalassemia major
    - Hemoglobin H disease
    - Hemoglobin H/constant spring
    - Beta thalassemia major
    - Hemoglobin E/beta thalassemia
    - Hemoglobin E/delta beta thalassemia
  - Other hemoglobinopathies (Hb variants)

- **Amino Acid Disorders (tandem mass spectrometry)**
  - Phenylketonuria (PKU) – classic and variant
    - Reported as phenylalanine/tyrosine ratios as well as actual phenylalanine and tyrosine levels
    - Cut off: phenylalanine: 0-140 µmole/L; tyrosine 0-700µmole/L;
      phenylalanine/tyrosine ratio 0-2.3
  - Biopterin deficiency (GTPCH and PTPS and DHPR and PCD)
  - Arginine/arginase deficiency
  - Argininosuccinic acid lyase deficiency (ASAL)
  - Citrullinemia Type I and Type II
  - Gyrate atrophy of the choroid and retina
  - Homocitrullinuria, hyperornithinemia, hyperammonemia (HHH disease)
  - Homocystinuria/cystathionine beta-synthase deficiency (CBS deficiency)
  - Methionine adenosyltransferase deficiency (MAT deficiency)
  - Maple syrup urine disease (MSUD)
  - Prolinemia
  - Tyrosinemia

- **Organic Acid Disorders**
  - 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency
  - 2-methylbutyryl-CoA deficiency
  - 3-hydroxy-3methylglutaryl-CoA lyase deficiency
  - 3 methylcrotonyl-CoA carboxylase deficiency
  - 3-methylglutaconic aciduria Type I
  - Beta-ketothiolase deficiency
  - Ethylmalonic encephalopathy
  - Glutaric acidemia type -1
  - Isobutyryl-CoA dehydrogenase deficiency
- Isovaleric academia
- Malonic aciduria
- Methylmalonic acidemia
  - Mut –
  - Mut 0
  - Cbl a, B
  - Cbl c, D
- Multiple carboxylase deficiency
- Propionic academia

- Fatty Acid Oxidation Disorders
  - Disorders of carnitine
  - Long chain hydroxyl CoA (LCHAD) dehydrogenase deficiency
  - Medium chain hydroxyl CoA (MCAD) dehydrogenase deficiency
  - Multiple acyl-CoA dehydrogenase deficiency (MAD)
  - Glutaric academia type-2
  - Medium/short chain L-3-hydroxy acyl-CoA dehydrogenase deficiency
  - Short chain acyl-CoA dehydrogenase deficiency (SCAD)
  - Trifunctional protein deficiency
  - Very long chain acyl-CA dehydrogenase deficiency (VLCAD)

- Carbohydrate and other metabolic disorders
  - Galactosemia (>50 enzyme units)
  - Biotinidase deficiency

**Timing of collection:**
- Specimens must be collected after 12 hours of age, in NICU screening is recommended by 24 hours of age and no later than 6 days
- Screens before 12 hours are accurate for hemoglobinopathies and galactosemia (the 2 tests invalidated by transfusion)
- All specimens should be collected prior to transfusion regardless of age of the newborn. If collected prior to 12 hours a second specimen will be required.
- If an infant has been transfused prior to the newborn screen the galactosemia and hemoglobinopathy results are inaccurate
  - In infants with severe anemia the filter paper spot testing often can’t be done. If anemia is severe hold 2 purple tops for testing for galactosemia and hemoglobinopathy if newborn screen is QNS
  - A whole blood specimen for DNA analysis of hemoglobin should be sent to the NBS Hemoglobin Reference Laboratory at CHO. This can be done any time after the transfusion
  - The galactosemia screen can be repeated 3 months after the transfusion if symptoms warrant the repeat.
- Infants transferred in before 6 days of age must have a newborn screen done even if it was performed before transfer

For information about specific symptoms and diagnosis of the disorders, go to the [newborn screening website](http://www.cdph.ca.gov/programs/nbs/Documents/NBS-DisordersDetectable092206.pdf)

Treatment guidelines for these disorders are available for download at State Newborn Screening site:


Please go to state screening website for full information on screening and recommended follow up and parent information materials.

**AAP fact sheets for Newborn Screening**

**STAR-G has extensive FAQ on these metabolic disorders**
Metabolic Disorders (Inborn Errors of Metabolism)

Pathophysiology
Inborn Errors of Metabolism are a group of disorders created from one gene defect that is passed either by autosomal recessive or X-linked fashion and causes a clinically significant block in a metabolic pathway. Pathogenesis is usually due to the accumulation of a substrate behind the block or the deficiency of a product. The IEMs can be thought of by category: organic acidemias, aminoacidopathies, urea cycle defects, disorders of carbohydrate metabolism, fatty acid oxidation defects, primary lactic acidosis, lysosomal storage disorders, peroxisomal disorders, disordered steriodogenesis and disorders of metal transport.

Organic Acidemias
- Methylmalonic or propionic academia, multiple carboxylase deficiency
- Caused by abnormal metabolism of proteins, fats or carbohydrates
- Characterized by marked metabolic acidosis with ketosis
- Elevated lactate and mild to moderate hyperammonemia
- Vomiting or signs of encephalopathy common
- Neutropenia and thrombocytopenia

Fatty Acid Oxidation Defects
- Short, medium and long chain acyl-CoA dehydrogenase deficiencies
- Organic acid disorder with hypoketotic hypoglycemia and hyperammonemia
- Cardiomyopathy common
- Presents with Reyes syndrome clinical picture
- MCAD (medium chain acyl CoA dehydrogenase deficiency) is most common of all inborn errors of metabolism and accounts for 5% of SIDS

Primary Lactic Acidosis
- Pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency and Cytochrome oxidase deficiency
- Metabolic lactic acidosis

Aminoacidopathies
- Clinical presentation similar to organic acidemias but more heterogeneous
- Hereditary tyrosinemia presents as bleeding diathesis due to liver disease or Fanconi syndrome
- Non-ketotic hyperglycemia includes seizures, hiccups and hypotonia
- MSUD presents at end of the first week of life with feeding difficulties, lethargy, coma, seizures and the characteristic odor.
- Phenylketonuria and homocystinuria

Urea cycle Defects
- Citrullinemia, ornithine transcarbamylase deficiency, arginosuccinic aciduria
- Inability to detoxify nitrogen
- Severe hyperammonemia and respiratory alkalosis after 24 hours of age

Disorders of Carbohydrate Metabolism
- Heterogeneous group: Galactosemia, hereditary fructose intolerance, fructose 1,6-diphosphate deficiency and glycogen storage diseases
- Inability to metabolize specific sugars, aberrant glycogen synthesis or disorders of gluconeogenesis.
- Manifests with hypoglycemia, hepatosplenomegaly, lactic acidosis or ketosis

Lysosomal storage disorders
- Mucopolysaccharidosis, Tay-Sachs, Niemann-Pick and Gaucher disease
- Accumulation of various glycosaminoglycans, glycoproteins or glycolipids within lysosomes of various tissues
Peroxisomal Disorders
- Zellweger syndrome presents with large fontanel, organomegaly, Down’s like facies, seizures and bony abnormally chondrodysplasia punctata.
- Neonatal adrenoleukodystrophy
- Failure of peroxisomal enzymes, presents like lysosomal storage disorders

Other Categories:
- Disordered steroidogenesis (Smith-Lemli-Opitz and CAH)
- Disorders of metal metabolism (Menkes syndrome, hemochromatosis)
- Transient Hyperammonemia of the newborn

Clinical findings
History: Family history of consanguinity, mental retardation, SIDS, symptom of onset with formula changes or institution of feeding, history of growth disturbances, lethargy, recurrent emesis, poor feeding, rashes, seizures, hiccups, apnea, tachypnea.

Physical: Tachypnea apnea, lethargy, hypertonicity/hypotonicity, jaundice, hepatosplenomegaly, ambiguous genitalia, dysmorphic or coarse facial features, rashes, patchy hypopigmentation, ocular findings such as cataracts, lens dislocation or pigmentary retinopathy, intracranial hemorrhage, unusual odors.

Laboratory: Metabolic acidosis with increased anion gap, primary respiratory alkalosis, hyperammonemia, hypoglycemia, ketosis or ketonuria, low BUN, hyperbilirubinemia, lactic acidosis, high lactate/pyruvate ratio, non-glucose reducing substances in urine, elevated liver function tests including PTT and PT, neutropenia and thrombocytopenia.

Initial Approach
- Rule out non-metabolic causes of symptoms such as infection or asphyxia
- Labs: send at time of symptoms, prior to giving any potential therapy
  - Blood:
    - Basic: Neonatal newborn screen (state filter paper), CBC with diff, Blood gas, glucose, electrolytes for anion gap, LFTs, total and direct bilirubin, PT, PTT, uric acid, ammonia.
    - Lactate, pyruvate, plasma amino acids, acylcarnitine profile and very-long-chain fatty acids as on algorithm.
    - Blood ammonia, lactate and pyruvate should be collected without tourniquet, kept on ice and analyzed immediately.
  - Urine:
    - Basic: Color, odor, pH, glucose, ketones, reducing substances (+ in Galactosemia, fructose intolerance, tyrosinemia)
    - Ferric chloride (MSUD, PKU), and DNPH reaction (Screen for alpha-keto acids).
    - Amino and organic acids per algorithm.
    - Urine orotic acid must be ordered separate from urine organic acids.
  - CSF: Glycine, lactate, pyruvate if appropriate.
- Algorithms —remember not all inborn errors of metabolism present with acidosis, hyperammonemia or hypoglycemia. See Algorithm at end of section.

Management
- Consult metabolic specialist
- Manage considering the potential disease category
- Hydration/nutrition/Acid-Base management
  - Rehydrate infant.
  - Stop all oral intake to eliminate protein, galactose or fructose and withhold protein for 48-72 hours during acute illness or until aminoacidopathy, organic aciduria or urea cycle defect excluded.
  - Establish positive caloric balance with IV glucose at minimum 8-10 mg/Kg/min, even if insulin is required to keep the blood glucose level normal
Very few conditions will not benefit from glucose (pyruvate dehydrogenase deficiency improve with lipids but lipids should only be given to improve calories if fatty acid oxidation defects ruled out).

- Treat significant acidosis with continuous infusion of bicarbonate

**Elimination of Toxic metabolites**

- Ammonia reduction is urgent (Degree of neurologic injury in urea cycle defects depends upon the duration of hyperammonemic coma) Frequent measurements (can rise by 100s of uM in hours) critical. Patients with plasma levels greater than 10-times normal should be hemodialyzed and transfer to UCSF or Stanford should be arranged.

- Sodium Benzoatoe + sodium phenylacetate (Ammonul®) may help. Loading dose of Ammonul® is 250 mg/Kg (250 mg each drug) in 25 ml 10% dextrose over 90 minutes, followed by continuous infusion of 250 mg/Kg/day. Discuss with metabolic specialist. Ammomul is a non-formulary medication and will need to be ordered 24hrs in advance if needed. In acute disease transfer to metabolic center with dialysis capability is indicated.

- Arginine HCl (Load 600 mg/Kg in 25 ml of 10% dextrose over 90 minutes, followed by 200-600 mg/Kg/day infusion) may stimulate waste nitrogen excretion by stimulation ornithine transcarboxylase in urea cycle defects (except arginase deficiency).

- Minimize situations that will lead to catabolism and production of ammonia such as blood transfusions or inadequate IV glucose/dehydration.

- Hemodialysis is indicated if ammonia level is rising quickly, exceeds > 300 uM or if intractable anion gap metabolic acidosis.

- Eradicate gut flora with short course of oral or intravenous metronidazole if organic acidemia suspected. Gut flora can increase organic acid synthesis.

- L-Carnitine can be low in organic acidemias. Give carnitine load (50-200 mg/Kg IV infusion over 2-3mins, followed by 50-300mg/kg/day continuous infusion. Dilute in NS to a concentration of 4-8mg/ml for continuous infusion route).

**Treatment of coexisting/precipitating infections**

- Neutropenias and thrombocytopenias with organic acidemias
- E. Coli sepsis with galactosemia

**Cofactor replacement**

- Proprionic academia, beta-methylcrotonyl deficiency, holocarboxylase synthetase deficiency and biotinidase deficiency can be treated with Biotin 5-20 mg (1mg capsule oral formulation only).

- Methymalonic acidaemia is treated with Vitamin B12 (cyanocobalamine) 1-2mg IM daily.

- Maple syrup urine disease is treated with Vitamin B1 (thiamine) 50-150 mg/day orally or can give by IV infusion. Dilute in NS to a concentration of 50 mg/ml for IV infusion.

- Vitamin B6 (pyridoxine) 50-100 mg IV administered over 15-30 minutes for seizures unresponsive to usual anticonvulsants. Note this is not a per kg dose.

---

**If Patient is Dying**

If autopsy not permitted, ask for pre-mortem or immediately post-mortem specimens (consent must be obtained for any specimens obtained after infant’s death)

- Blood should be centrifuged and the plasma frozen (minimum 5ml)
- Urine and spinal fluid should be refrigerated (minimum 5 ml)
- Dried blood spot on a newborn screening filter paper
- A sterile skin biopsy (used for fibroblast culture) can be performed when child is alive or 1-2 hours after death. Alcohol should be used to clean the skin but BETADINE SHOULD BE AVOIDED as it will inhibit cell growth. The sample should be kept in sterile saline at room temperature and sent to the cytogenetics lab for culture and processing or call up to pathology and get a vial of tissue transport media

- Other tissue samples such as liver, skeletal muscle, cardiac muscle and brain and kidney can be useful in some disorders. (Stored unfixed, immediately frozen below -20 degrees). If there are dysmorphic features a full skeletal radiologic series can be helpful to evaluate for dysostosis multiplex, chondrodysplasia punctata or other bony abnormalities.
Lab Samples

**Plasma Amino Acids** (Quantitative) sent to Quest Diagnostics—Green Top 2ml (min 0.5 ml of plasma) shipped frozen on Dry Ice overnight express.

**Urine Organic Acids**: 2ml Random Urine specimen

**Urine Acylglycine Profile**: 5 ml random Urine sent on dry ice

**Plasma Acylcarnitine profile**: 0.5ml plasma or 0.2ml minimum, heparinized green top preferred, but can use plasma spotted x 4 on PKU filter paper

**Lysosomal disease Screen**: 10 ml in green top tube, send Mon-Thurs only to Dr. David Wenger, Lysosomal Diseases Testing Laboratory, Jefferson Alumni Hall, Rm 394, 1020 Locust St. Philadelphia, PA 19107.
Renal Function

Characteristics of the Newborn Kidney

- Low renal blood flow due to increased RVR and decreased renal arterial perfusion pressure.
- Decreased glomerular filtration rate
  - Adult: $120 \text{ ml/min/m}^2$
  - Term infant: approximately $20 \text{ ml/min/m}^2$
  - Preterm <34 week: approximately $11\text{ ml/min/m}^2$
    - GFR increases postnatally in both term and preterm infants after 24-48 hrs, doubles by 2 weeks of age but remains relatively low until 18 months of age. Adult levels are attained by the second year of life. Preterm infants do not increase GFR significantly until 34 weeks gestation.
- Decreased ability to excrete fluid load
- Altered tubular function (newborn kidney is optimized to retain essential dietary solutes for growth)
  - Decreased sodium excretion with salt load
  - Decreased proximal tubular reabsorption of sodium especially in preterm
    - <34 weeks FeNa is high (up to 15% in sick, very preterm infants)
  - Decreased distal tubular response to Aldosterone
  - Decreased tubular maximum for glucose, phosphate, bicarbonate and amino acids
  - Decreased ability to acidify urine (lowest pH usually 5.5)
  - Reduced concentrating ability due to tubular insensitivity to vasopressin, low serum urea, short Loop of Henle; maximum osmolarity 500-800 mOsm/L; reaches adult value of 12-1400 mOsm/L by 6-12 months of age.
- Decreased excretion of drugs
  - The half-life of most drugs excreted via the kidney is prolonged. The lower the gestation, the longer the half-life.
Renal Failure

In neonates it is generally acute renal failure. To become chronic, by definition, the GFR has to be 25% of normal for at least 3 months.

Incidence is reported to be between 6-24% of newborns admitted to NICU. Extremely preterm infants are most vulnerable. Several studies suggest that there may be a genetic predisposition to developing ARF in some infants.

**Definition:** Markedly decreased GFR resulting in increased serum creatinine (> 1.5 mg/dL), BUN and disturbances in fluid and electrolyte balance. Infant can be oliguric (urine output < 1 ml/kg/hr) or nonoliguric.

**Etiology of Acute Renal Failure**

- **Prenatal Injury** such as maternal use of Angiotensin-converting enzyme inhibitors, angiotension II receptor antagonists, Nonsteroidal anti-inflammatory drugs
- **Congenital Renal Diseases**
  - Renal agenesis
  - Renal dysplasia/hypoplasia
  - Autosomal recessive/dominant polycystic kidney disease
  - Finnish-type congenital nephrologic syndrome
- **Pre-renal (functional) – most common**
  - Decreased effective perfusion (low volume or increased resistance)
    - Decreased true intravascular volume
    - Hypoxia / asphyxia
    - Hemorrhage
    - Dehydration
    - Third space losses (sepsis, traumatized tissue, necrotizing enterocolitis)
    - Gastrointestinal losses
    - Hypoalbuminemia and associated decreased effective intravascular volume
    - Congestive heart failure
    - Pericarditis, cardiac tamponade
    - Indocin
    - Vasoconstricting drugs
- **Intrinsic Renal**
  - Acute tubular necrosis
  - Perinatal asphyxia
  - Ischemic/hypoxic insults
  - Drug-induced
  - Aminoglycosides
  - Intravenous contrast media
  - Nonsteroidal anti-inflammatory drugs (indomethacin)
  - Angiotensin-converting enzyme inhibitors (captopril, enalapril)
  - Amphotericin B
  - Interstitial nephritis
- **Vascular lesions**
  - Renal artery thrombosis
  - Renal vein thrombosis
- **Postrenal / Obstructive**
  - Obstruction in a solitary kidney
  - Bilateral ureteral obstruction
  - Bilateral fungal bezoar
Urethral obstruction
- Posterior urethral valves
- Extrinsic tumors
- Neurogenic bladder due to myelomeningocele

**Diagnosis**

Labs: Urinalysis and urine electrolytes, serum chemistries, CBC, coagulation panel

Renal ultrasound

**Differentiation of prerenal from intrinsic renal disease:**

<table>
<thead>
<tr>
<th></th>
<th>Prerenal</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Na (mEq/L)</td>
<td>&lt;20 (10-50)</td>
<td>&gt;40 (30-90)</td>
</tr>
<tr>
<td>Urine/plasma osmolarity</td>
<td>&gt;2</td>
<td>&lt;1.1</td>
</tr>
<tr>
<td>Urine/plasma creatinine</td>
<td>&gt;20</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Urine/plasma urea</td>
<td>&gt;5</td>
<td>&lt;10</td>
</tr>
<tr>
<td>FeNa (%) [urine Na]/(serum creatinine) x 100</td>
<td>&lt;2</td>
<td>&gt;3*</td>
</tr>
<tr>
<td>Urine osmolarity</td>
<td>&gt;400</td>
<td>&lt;400</td>
</tr>
<tr>
<td>Renal Failure Index(urine Na/urine Cr) x100</td>
<td>&lt;3</td>
<td>&gt;3</td>
</tr>
</tbody>
</table>

*Use >20% if <7 days and <32 weeks gestation.

**Treatment**

*Pre-renal*
- Correction of underlying disorder and supportive care
- Fluid challenge followed by furosemide
- Dopamine at low dose is commonly used but studies do not support that it has any sustained beneficial effect
- Theophylline (5-8 mg/kg) in the first hours of life has been shown to improve GFR and water excretion – especially in asphyxiated infants but needs further studies before routine use is recommended.

*Intrinsic renal*
- Stop nephrotoxic drugs
- Strict I & O: Restrict fluids to insensible water loss and urine output
- Dialysis as needed
- Provide nutritional support (high calorie, restricted protein, low phosphate
- Renal consult
Elevated Creatinine/Decreased Urinary Output

Renal Ultrasonography

Hydronephrosis, hydroureter, enlarged bladder

Normal or increased echogenicity

Obtain serum chemistries, urinalysis, urine osmolality, urine for sodium, creatinine

Calculate FENa and RFI

FENa >2.5%
RFI >3

Intrinsic Renal Disease:
• Discontinue any nephrotoxic agents if possible
• If oliguric/anuric, restrict fluids to insensible losses + urine output
• Provide supportive therapy with attention to electrolyte, acid-base, and calcium/phosphorus balance
• +/- Dopamine
• +/- Diuretics
• Consult nephrology

Postrenal ARF:
• Drain bladder with indwelling catheter
• Start urinary tract infection prophylaxis
• Discontinue any medications that can cause urinary retention
• Consult urology

Prerenal Renal Failure:
• Provide volume resuscitation
• Treat underlying condition

Algorithms for assessment of acute renal failure. FENa = fractional excretion of sodium. RFI = renal failure index.
Nephrocalcinosis

Renal calcifications have been reported in as many as 30% (range 25-60%) of infants <32 weeks gestation. Risk factors include conditions that cause hypercalciuria with or without hypercalcemia:
- Birth weight <1000 gm
- Gestational age <30 weeks.
- Chronic lung disease (prolonged oxygen dependence)
- Use of loop diuretics (Furosemide)
- Parenteral nutrition
- Hypophosphatemia
- Subcutaneous fat necrosis
- Renal Candidiasis

Diagnosis
- **Renal ultrasound**: areas of increased echogenicity due to calcifications in the medulla and calyces, usually appear in the fifth, sixth or seventh week of life (Mean 47 days, range 32-82). About 59% are bilateral. Most are asymptomatic and are detected on screening US.
- **Urinalysis**: sometimes present as microscopic hematuria and/or urinary crystals - secondary to renal calculi.
- Urine Calcium:Creatinine ratio > 0.21

Prevention
- Early institution of feedings to increase phosphate intake may be helpful
- Addition of thiazide when furosemide is used will decrease urinary calcium excretion.

Treatment
- Discontinue furosemide or add thiazide diuretic to decrease calciuria
- Consider using thiazide diuretic in infants with severe stone formation.

Prognosis
- Most resolve spontaneously in the first year of life
- 30 - 40% may be seen until 5 years of age
- There are some reports of long term decrease in GFR and tubular function
Cardiac

Patent Ductus Arteriosus (PDA)

Incidence of persistent PDA at 72 hours of life:
- <26 weeks gestation - 65%
- 26-30 weeks gestation - 25%
- >30 weeks gestation - 10%

Diagnosis
- Clinical signs: hyperactive precordium, continuous or systolic murmur heard best along mid to lower sternal border, wide pulse pressure with low diastolic pressure, bounding pulses
- ECHO: Visualization of duct, turbulent flow, retrograde flow in aorta (large PDA)
- CXR: Increased vascular marking, increased heart size
- In infants <28 wks GA being treated prophylactically for a ductus, therapy may be started without an echocardiogram unless there is a suspicion of congenital heart disease. For infants 28 weeks GA an echocardiogram should be done prior to therapy.
- Unless looking for congenital heart disease or concerned about a clinically problematic PDA it is best to defer echo to check for PDA until after day 2 to allow the natural closure to occur.

Treatment
Supportive treatment for congestive heart failure (fluid restriction, diuretics, digoxin) is not effective treatment—give indomethacin or ibuprofen or surgical ligation.

Indomethacin (Indocin®) Protocol
- Prophylactic
  - <28 weeks gestation: begin treatment at birth (no echo needed)
  - Confirm platelet > 100,000 prior to first dose
  - The earlier the treatment the more effective it is in producing permanent closure and preventing IVH
  - Confirm closure with echo after completion of treatment
  - Limit fluid intake to <100 ml/kg/day during prophylactic treatment (unless sodium >150)
- Therapeutic
  - 28+ weeks gestation
  - Clinical symptoms (murmur + widened pulse pressures, hyperactive precordium and/or severe respiratory distress) with confirmed PDA on echo
  - Confirm platelets > 50,000 prior to first dose
  - Generally not necessary to treat within first 24 hours of life

Dose and Schedule

<table>
<thead>
<tr>
<th>Prophylaxis: Infants &lt;28 weeks gestation</th>
<th>All doses q 12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; dose</td>
<td>0.2 mg/kg</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; dose</td>
<td>0.1 mg/kg</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; dose</td>
<td>0.1 mg/kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All Doses q 12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28 weeks</td>
<td></td>
</tr>
<tr>
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<td>3&lt;sup&gt;rd&lt;/sup&gt; dose</td>
<td>0.2 mg/kg</td>
</tr>
</tbody>
</table>

- If echocardiogram shows a significant ductus is still present, doses may be continued for total of 6 doses
- Consider ligation if very large PDA in infant <28 weeks gestation that did not respond to indomethacin
Exclusions

- Platelets <50,000 or frank bleeding
- Septic shock
- Necrotizing enterocolitis or GI bleed
- Renal failure (creatinine>2) and caution if UOP < 1 ml/kg/hour
- Ductus depending cyanotic lesion
- Active (and untreated) infection
- Ductus compromising perfusion enough to necessitate immediate closure would choose ligation

Ibuprofen (NeoProfen®)

- Has been shown in multiple clinical trials to be effective in closing the PDA in preterm infants with both symptomatic and asymptomatic PDA.
- Most trials conducted in infants <30 weeks gestation showed less oliguria (and presumably less GI hypoperfusion) than noted with indomethacin
- Has no effect on IVH prevention.
- Not recommended for prophylaxis for two reasons: no IVH protection and is much stronger displacer of bilirubin from albumin than indomethacin.

- Dose: 10 mg/kg initially, then 5 mg/kg q 24 hours x 2.

Details of administering these medications can be found in the nursing policy [http://mysutter/SHWBR/CPMC/Policies/Clinical/Nursing/Nursing%20Protocols/np-i4.pdf](http://mysutter/SHWBR/CPMC/Policies/Clinical/Nursing/Nursing%20Protocols/np-i4.pdf)

Surgical Closure of PDA should be considered if

- Persistent clinically compromising ductus after closure failure of indomethacin and/or Ibuprofen
- Hemodynamically significant PDA and presence of contraindication(s) to pharmacological closure
- Presence of PDA and NEC - Necrotizing Enterocolitis will not resolve without PDA closure.
Congenital Heart Disease

Congenital heart disease (CHD) affects ~1% of newborn infants
Many lesions are diagnosed prenatally

Most common lesions
- PDA
- Ventricular septal defect
- Atrial septal defect
- Pulmonic stenosis
- Tetralogy of Fallot

Factors that increase risk for CHD
- Associated anomalies (chromosomal problems, syndromes, congenital viral infections)
- Maternal diabetes
- Prior infant with congenital heart disease
- Teratogens in pregnancy (alcohol, anticonvulsants, lithium, retinoic acid)

Important considerations
- Not all lesions have associated murmurs at birth
- Not all lesions are obvious in newborn period – including some ductal dependent and cyanotic lesions
  (all infants in well baby nursery at CPMC have screening oximetry when newborn screen is drawn to help identify some of these infants)
- Some lesions only present as the ductus closes or pulmonary vascular resistance drops and blood flow to the lungs increases

Evaluation
- Physical examination
  - Cyanosis
  - Poor peripheral perfusion, diminished pulses, differential pulses between arms and legs
  - Single 2nd heart sound or abnormally loud 2nd heart sound
  - Murmurs, gallops, clicks
  - Hyperdynamic precordium or bounding pulses
  - Hepatosplenomegaly (uncommon from heart disease in immediate newborn period)
  - Other anomalies
- Oximetry (consider pre and post ductal)
- Blood gas – to assess for acidosis as well as see pO2
- Chest Xray
  - Heart size, shape
  - Pulmonary vascularity
  - Pulmonary causes for distress / cyanosis
- ECG – of limited value in newborn period except to assess arrhythmia
- Echocardiography
- Cardiac consultation – if highly suspect cyanotic lesion call cardiologist while echo tech en route

Possible Presentations of Congenital Lesions in Newborn Period
- Respiratory distress
  - Total anomalous venous return with obstruction may present with severe respiratory symptoms soon after birth and requires emergency intervention
  - VSD, PDA, ASD after pulmonary vascular resistance drops
  - AV canal
  - Total anomalous pulmonary venous return without obstruction
  - Truncus arteriosus esp after pulmonary vascular resistance drops
- Desaturation (cyanosis) with normal or increased pulmonary vascular markings
  - Transposition of great arteries
  - Truncus arteriosus
- Double outlet right ventricle
- Ebstein’s anomaly – large heart on CXR
- Total anomalous venous return

- Desaturation (cyanosis) with decreased pulmonary vascular markings
  - Tetralogy of Fallot (some mild forms are pink at birth)
  - Tricuspid atresia
  - Pulmonary atresia or severe stenosis with (especially with intact ventricular septum)

- Shock or acidosis
  - Coarctation of aorta or interruption of the arch (often present days after delivery when ductus closes)
  - Hypoplastic L heart and other Left sided outflow tract obstructions
  - Aortic stenosis

**Treatment**
- Varies with lesion but general considerations include:
- Use PGE in lesions when ductal mixing is needed
- Oxygen usage may worsen picture by dropping pulmonary vascular resistance or by facilitating ductal closure
- Oxygen saturations in the 75-85% range are adequate in many cyanotic or mixing cardiac lesions (even lower in some lesions) – discuss desired goals with cardiologist
- Fluid and nutritional management are important

[Comprehensive information sheets on congenital heart lesions](#) can be found on Cincinnati Children’s site
Use of Prostaglandin E1 (Alprostadil) for Maintaining Ductus Patency

**Indications:** To maintain ductus patency and improve either pulmonary or systemic flow.
- LV outflow tract obstructions (interrupted arch, coarctation, critical aortic stenosis)
- RV outflow tract obstruction (pulmonary atresia or stenosis, tricuspid atresia, needed in some tetralogy of Fallot)
- Transposition of great arteries
- Hypoplastic left heart

**Administration**
- Need good IV that will not infiltrate—consider PICC if access an issue
- Can be given via peripheral IV, UV, PICC, (UAC if no other access – should be a high line)
- Be prepared to intubate the infant as apnea is common
- May need other fluid to infuse simultaneously to keep line open
- Once started, the infusion must not be stopped for any reason as ductus may close rapidly

**Dose**
- Provided as 500 microgram/ml ampule. Mix in NS, D5W or D10W
- Initial dose: 0.05 - 0.1 microgram/kg/minute.
- Begin with 0.05 microgram/kg/minute. If no improvement in PO2 increase to 0.1 microgram/kg/minute.
- Use smart pump dilutions
- Single strength 250 microgram in 50 ml = 5 microgram/ml
- Double strength 500 microgram in 50 ml = 10 microgram/ml
- Suggested dilution: Add 1 ampule (500 microgram) to 49 ml D5W
- Concentration: 5 microgram/ml
- Once stable, may slowly titrate dose down to as little as 0.01 microgram/kg/min.

**End-Point**
- Should see improved pH in RV obstruction but not necessarily improved oxygenation
- Should see improved peripheral perfusion if LV obstruction
- Will see bright red flush of skin with cutaneous vasodilatation

**Side effects**
- Tend to occur with doses >0.05 microgram/kg (starting dose)
- Apnea (central basis), greater in infants weighing < 2kg
- Cutaneous vasodilation (flush)
- Systemic hypotension - if severe must stop infusion (consider use of dopamine with PGE infusion)
- CNS effects - idiosyncratic not dose related (jittery, seizure-like), seizures
- Fever common, rare malignant hyperthermia
- Platelet dysfunction
- Prolonged infusion may cause gastric outlet obstruction
- Diarrhea
Hypertension in the Newborn and Infant

The definition of hypertension is systolic, diastolic or mean pressures >95% for age and sex on 3 separate measurements.

- 95th percentile or systolic BP = 65 mmHg in 24 weeker and 90 mmHg for term
- By definition, 5% of all infants will have BPs above 95th percentile
- Incidence of hypertension ranges from 0.2% in normal newborns to 2.6% in infants needing intensive care
- Incidence 9% in infants with BPD, IVH, history of prolonged umbilical catheters or PDAs

Symptoms: Lethargy, irritability, apnea, tachypnea, seizures, intracranial hemorrhage, congestive heart failure or cardiogenic shock.

Diagnosis/Evaluation:

- Cuff Pressures: Check BP 1½ hours after last feeding or intervention, use appropriate cuff (2/3 the length of the limb segment and 75% of the limb circumference), wait 15 minutes for stillness, obtain 3 readings 2 minutes apart.
- Intra-arterial pressures: higher readings, up to 5 mmHg for mean and diastolic pressures
- Normal BP increases with gestational age, post-conceptual age and BW. (Tables of BP)

History: Recent and current medications, procedures (UAC)
Initial Studies: BUN, Creatinine, electrolytes, Ca, UA with micro, chest Xray, renal US with Doppler flow studies, HUS
Further work-up: Thyroid function, urinary VMA/HVA, cortisol, aldosterone, ECHO

Causes

- Renal-vascular
  - Thromboembolism
  - Renal Artery Stenosis
  - Renal Venous Thrombosis
  - Compression of Renal Artery
- Cardiac: Coarctation of the aorta
- Pulmonary: Bronchopulmonary dysplasia
- Renal Disease
  - Polycystic Kidney Disease
  - Multicystic-dysplastic kidney
  - Ureteropelvic junction obstruction
  - Acute Tubular necrosis
  - Hemolytic-uremic syndrome
  - Obstruction by tumor
- Endocrine
  - Congenital Adrenal hyperplasia
  - Pseudohypoaldosteronism type II
- Medications/Intoxications
  - Maternal: Opioids (Cocaine, heroin)
  - Infant
    - Dexamethasone
    - Theophylline/Caffeine
    - Pancuronium
    - Phenylephrine
- Neoplasm
  - Wilms Tumor
  - Mesoblastic nephroma
  - Neuroblastoma
- Neurologic
  - Pain
  - Intracranial hypertension
Seizures
- Subdural Hemorrhage

- Miscellaneous
  - Closure of abdominal wall defect
  - Adrenal hemorrhage
  - Hypercalcemia
  - ECMO
  - Birth Asphyxia

Treatment
- See table below for doses and schedules
- Treat all iatrogenic causes
- Unless hypertension is immediately life-threatening, do not automatically give an anti-hypertensive agent. Treat the etiology if possible.

- Mild-Moderate / Maintenance (Consultation recommended)
  - Captopril - Begin at low dose and double q 6-8 hr until control achieved. Monitor closely for hypotension.
  - May add Diuretic as second agent
  - Other possible agents:
    - ß -Blocker (Propranolol) - should be avoided in babies with CLD
    - Isradipine and Amlodipine - Ca channel blocker with easy suspension for outpatient use

- Severe (Obtain consultation) Continuous IV infusion most appropriate.
  - Monitor BP with intra-arterial line as some agents can cause hypotension and shock.
  - Nitroprusside (0.4 microgram/kg/min IV infusion)
  - Labetalol 0.3 mg/kg/dose q 20 minutes until pressure controlled or 0.2-1 mg/kg/hr as continuous infusion
  - Hydralazine
  - AVOID Enalapril as it can cause oligo or anuria
A range of medications are available to treat hypertension – with a broad range of dosing. The more commonly used medications and starting dosages appear in the medication section of the manual. Table below offers additional options – consultation is advised before increasing to higher range doses.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Route</th>
<th>Dose</th>
<th>Max Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Ca+ channel blocker</td>
<td>Oral</td>
<td>0.1 mg/kg/dose QD-BID</td>
<td>0.6 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>ACE Inhibitor</td>
<td>Oral</td>
<td>0.01 - 0.5 mg/kg/dose TID</td>
<td>6 mg/kg/day</td>
<td>Monitor creatinine &amp; K+</td>
</tr>
<tr>
<td>Enalapril</td>
<td>ACE Inhibitor</td>
<td>Oral</td>
<td>0.08 mg/kg per day</td>
<td>0.58 mg/kg/day</td>
<td>Same as for captopril</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Vasodilator (arteriolar)</td>
<td>IV bolus</td>
<td>0.15 - 0.6 mg/kg/dose Q4h</td>
<td>7.5 mg/kg/day</td>
<td>Tachycardia frequent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral</td>
<td>0.25-1.0 mg/kg/dose</td>
<td></td>
<td>Suspension stable x 1 wk</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Ca+ channel blocker</td>
<td>Oral</td>
<td>0.05-0.15 mg/kg/dose TID-QID</td>
<td>0.8 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>ß and ß blocker</td>
<td>IV bolus</td>
<td>0.20 to 1.0 mg/kg/dose depends on HR</td>
<td>10-12 mg/kg/day</td>
<td>Contraindicated with CLD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV infuse</td>
<td>0.25 to 3.0 mg/kg/hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral</td>
<td>1 mg/kg per dose BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Ca+ channel blocker</td>
<td>IV Infusion</td>
<td>1-3 microgram /kg/min</td>
<td></td>
<td>May cause reflex tachycardia</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Beta blocker</td>
<td>Oral</td>
<td>0.5-1.0 mg/kg/dose TID</td>
<td>8-10 mg/Kg/day</td>
<td>Bradycardia, Max dose depends on HR avoid if BPD / CLD</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Vasodilator</td>
<td>IV infusion</td>
<td>0.5-10 microgram /kg/min</td>
<td></td>
<td>Thiocyanate toxicity with &gt;72 h use or renal failure</td>
</tr>
</tbody>
</table>

Ref: NeoReviews Vol 3 No 8 August 2002
Infection

Hospital Acquired Infections (previously called nosocomial infections)

Hospital acquired infections are a significant source of morbidity and mortality in all hospitalized patients, but particularly in the relatively immunocompromised patients in the ICN. The rate of infection at >3 days of life in ~7000 infants BW <1500 grams was reported by the NICHD collaborate neonatal group. Twenty percent of all infants had positive blood cultures after day 3: 43% of infants <750 gm, 28% of infants 751-1000, 15% of infants 1001-1250 and 7% of infants 1251-1500 grams. In addition to birth weight, highly significant correlation was seen between use of central lines, delay in enteral feedings and days of ventilation. (Stoll BJ et al, Pediatrics: 225, 2002) Several quality improvement collaboratives have been formed to help reduce these infection rates with some successes being seen.

The goal is to have zero nosocomial infections – these infections once almost considered a birth right of the tiny baby must now be considered an error. In adult populations nosocomial infections are conditions on the National Do Not Pay list.

Measures to Prevent Nosocomial Infection

- Careful handwashing: 1 minute scrub to the elbows with antiseptic soap at beginning of day. Handwashing (15 seconds with antimicrobial soap) before and after touching patient or any items around a patient bed. If hands not visibly soiled may use alcohol gel instead of soap and water – a full pull of gel rubbed in until dry.
- No long sleeves (including lab coats) when in contact with babies and no jewelry below the elbows – The Right to Bare Arms
- Use appropriate infection control precautions
  - Universal (body secretion precautions): all infants
  - Contact Isolation
    - Who: Acute respiratory infections; viral; gonococcal conjunctivitis; staphylococcal furunculosis; herpes simplex; impetigo; influenza; infection with multiply resistant bacteria, e.g. gram negative bacteria resistant to aminoglycosidosis; or relatively resistant such as pseudomonos, serratia; methcillin resistant staph aureus (MRSA); pneumonia - viral, staphylococcal or streptococcal Group A; congenital rubella; scalded skin; skin, wound or burn infection.
    - How: Gowns if soiling likely, and gloves. Infant should be in an incubator. All linens, diapers and equipment considered potentially contaminated
  - Protective Isolation
    - Who: Preoperative infants with gastroschisis, omphalocele or meningocele, neutropenic infants, infants on ventilators, suspected immune deficiencies.
    - How: Isolette, gloves with all handling.
  - Strict Isolation
    - Who: Varicella, herpes zoster
    - How: Negative air flow Isolation room required.
- Strict asepsis techniques when inserting and maintaining central lines
  - Full barrier precautions when placing lines (hat, mask, gown, gloves and all in the immediate area – including Xray must where hat and mask during procedure.)
  - Remove lines as soon as no longer essential for management
  - Aseptic technique for changing lines
  - No entry into lines except via capped ports that can be adequately scrubbed (15 second hub scrub with alcohol or chlorhexidene)
• Prevention of ventilator associated pneumonia
  o Careful technique when intubating (sterile gloves and watch where you place the laryngoscope and ET) and suctioning (using only closed systems)
  o Elevate head of bed if infant will tolerate it
  o Minimize saline use with suctioning
  o Good mouth hygiene – suctioning with new device every 2-4 hours and before suctioning ET or turning infant
  o Extubate as soon as possible

Education slide set on infection reduction topic:
Educational slide set on ventilator associated pneumonia prevention:

CDC National Health Safety Network algorithms
Algorithm for Ventilator Associated Pneumonia

Patient with underlying diseases\(^{1,2}\) has 2 or more serial x-rays with one of the following:
- New or progressive and persistent infiltrate
- Consolidation
- Cavitation
- Pneumatoceles, in ≤1 y.o.

Patient without underlying diseases\(^{1,2}\) has 1 or more serial x-rays with one of the following:
- New or progressive and persistent infiltrate
- Consolidation
- Cavitation
- Pneumatoceles, in ≤1 y.o.

Infants ≤ 1 y.o.
- Worsening gas exchange (e.g., O\(_2\) desats [e.g., pulse oximetry <94%], ↑ O\(_2\) req., or ↑ ventilation demand)

and three of the following:
- Temperature instability with no other recognized cause
- Leukopenia (< 4,000 WBC/mm\(^3\)) or leukocytosis (≥ 15,000 WBC/mm\(^3\)) and left shift (≥ 10% band forms)
- New onset of purulent sputum\(^3\), or change in character of sputum\(^4\), or ↑ respiratory secretions, or ↑ suctionsing requirements
- Apnea, tachypnea\(^5\), nasal flaring with retraction of chest wall or grunting
- Wheezing, rales\(^6\), or rhonchi
- Cough
- Bradycardia (<100 beats/min.) or tachycardia (> 170 beats/min.)

Children >1 or ≤ 12 y.o.
At least three of the following:
- Fever (>38.4°C/101.1°F) or hypothermia (< 36.5°C/97.7°F) with no other recognized cause
- Leukopenia (< 4,000 WBC/mm\(^3\)) or leukocytosis (≥ 15,000 WBC/mm\(^3\))
- New onset of purulent sputum\(^3\), or change in character of sputum\(^4\), or ↑ respiratory secretions, or ↑ suctionsing requirements
- New onset or worsening cough, or dyspnea, apnea, or tachypnea\(^5\)
- Rales\(^6\) or bronchial breath sounds
- Worsening gas exchange (e.g., O\(_2\) desats [e.g., pulse oximetry < 94%], ↑ O\(_2\) req., or ↑ ventilation demand)

☐ PNU1:
Clinically defined pneumonia

CPMC NICU Manual v7
Bacterial Infections in the Newborn

Incidence
- Term Infants: 0.6-1.2/1000 live births
- Preterms:
  - <1500 gm: 13/1000
  - 1500-2500 gm: 4-8/1000

Risk factors for infections
- Obstetrical (maternal) factors associated with infection in the infant
  - Preterm labor
  - Premature rupture of membranes
  - Prolonged rupture of membranes
  - Acute chorioamnionitis
  - Fever
    - When the maternal temperature is >38˚ the rate of infection in the infant increases to approximately 20/1000 (10 fold increase). When the mother is febrile and colonized with Group B strep, the attack rate in the infant is as high as 30-80/1000.
  - Maternal colonization with Group B beta hemolytic streptococcus
  - Previous infant with Group B Strep infection
- Infant
  - Prematurity
  - Asphyxia
  - Male sex
  - Twin gestation
  - Sustained fetal tachycardia >160 bpm
  - Group B streptococcus colonization and infection

Bacteriology

Early onset (<3 days)
- Transplacental, chorioamnionitis, ascending from vagina, exposure at birth
- Usually multi-system or pneumonia
- Mortality 15-45%
  - Group B beta hemolytic streptococcus
  - E. Coli
  - Enterococcus
  - Coagulase negative Staphylococcus
  - Staphylococcus aureus

Late onset and/or nosocomial infections
- Colonizing organism, often from floral of the NICU, hospital acquired infections
- May be focal (including non-bacteremic UTI and meningitis)
- Mortality 10-20%
  - Coagulase negative staphylococcus
  - Gram negative bacilli: E. Coli, Klebsiella, Pseudomonas, Serratia, Enterobacter
  - Late Group B Strep
  - Staph aureus including MRSA (methicillin resistant staph aureus)
  - Candida

Symptoms of sepsis in the newborn
- Most infants with early onset sepsis will have signs of infection at delivery or soon thereafter. They will often have a history of fetal distress or fetal tachycardia and low Apgar scores. Many of the signs, however, are nonspecific and initial manifestation may be minimal. Late onset infections are also characterized by nonspecific signs.

Common clinical signs of infection
- Hypothermia or temperature instability
- Fever
- Poor feeding
- Respiratory distress: Hypoxia, tachypnea, grunting
- Transition that is delayed more than 4 hours
- Apnea
  - Early onset in preterm infants
  - Any after 1st hour of life in term infants
- Cyanosis
- Hypotension, poor perfusion
- Abdominal distension, vomiting, diarrhea
- Metabolic acidosis
- Skin manifestations
  - Petechiae, purpura
  - Rashes
  - Sclerema
- Jaundice
- Irritability
- Lethargy
- Hepatomegaly

**Laboratory findings**

- **CBC**
  - Abnormal findings which have been associated with sepsis include:
    - Total white count <4000 or >30,000
    - Total neutrophil count <1000
    - Immature to total neutrophil ratio (I:T) >0.2.
    - As many as 1/3 of all infants with proven sepsis had a normal white count and/or neutrophil count and I:T ratio at the time of onset of symptoms
    - White count is of use only in conjunction with other clinical, laboratory and historical findings

- **Latex agglutination tests**
  - Latex agglutination tests are available for Group B beta-hemolytic strep, E. coli and Neisseria meningitides.
  - CSF latex may be useful in the infant who has been pretreated with antibiotics, or whose mother received antibiotics prior to delivery.
  - There is no role for use of these tests in urine.
  - There is cross reactivity between the antigens for Neisseria and E. coli, so you will occasionally have a positive antigen test for both bacteria.

- **C reactive protein**
  - A non-specific acute phase reactant that is elevated in many non-infectious inflammatory states (infection, meconium aspirations syndrome, asphyxia, post-operative.)
  - Value may not be elevated at birth
  - Not affected by gestational age
  - Increased in 50-90% of patients with sepsis
  - Order the Inflammatory CRP
  - Units may vary by center
  - Values < 1-2 mg/dL are reassuring; values over 10 mg/dL are highly suggestive of inflammation
  - In overwhelming sepsis value may not initially be elevated as infant is not building immune response (takes 4-6 hours to build response)
Approach to Infants at Risk for Sepsis

Signs of neonatal sepsis?
Respiratory distress (including tachypnea, grunting, retractions in absence of O2 need), temperature instability (fever or trouble keeping warm), hypoglycemia, apnea, lethargy, low Apgar scores or need for resuscitation in the delivery room, poor perfusion with normal temperature, poor feeding, metabolic acidosis, early onset of jaundice

NO

YES

Mom GBS Status

Mom GBS -

Definite maternal chorioamnionitis?

YES

NO

Limited diagnostic evaluation: CBC and blood culture
Observe >48 hrs * If suspect sepsis or many risk factors revert to full diagnosis & treatment

Mom GBS ?

Definite maternal chorioamnionitis?

NO

YES

Preterm
Mom Temp >38.0

NO

YES

Mom GBS +

Definite maternal chorioamnionitis?

NO

YES

Gestational age <35 weeks?

YES

NO

Inadequate Maternal Antibiotics before delivery (< 4 hrs)

Full diagnostic evaluation #

NO

YES

Definite maternal chorioamnionitis?

@ OB should make dx of definite chorioamnionitis = fever >38 for >1 hr AND 2 or more signs intra-amniotic infection (e.g. foul fluid, fetal tachycardia, uterine tenderness)

* Discharge <48 hrs only if 38+ wks & early follow up is in place

* Full diagnostic evaluation: CBC, blood culture, CXR if respiratory distress
LP if: Maternal chorioamnionitis with GBS and infant has symptoms OR Mom pretreated with Abx and infant symptomatic (blood culture may be negative) OR Negative blood culture and plan to continue meds >48 hours should do tap for cell count OR Positive blood culture

# Full diagnostic evaluation: CBC, blood culture, CXR if respiratory distress

NO

Observe >48 hrs * If suspect sepsis or many risk factors revert to full diagnosis & treatment

* Discharge <48 hrs only if 38+ wks & early follow up is in place

CPMC NICU Manual v7
Assessment of Infection in the Symptomatic Infant

Most of the clinical signs and symptoms of infection are nonspecific in the newborn. Respiratory distress is a common symptom in infection but also in numerous other disorders of the newborn including meconium aspiration, respiratory distress syndrome, and transient tachypnea. Symptoms consistent with infection, however, must lead to the evaluation for sepsis. Even in the absence of any known risk factors, infants who are symptomatic should be cultured and treated pending the results of the cultures.

Maternal pretreatment will affect the decision for length of treatment in both symptomatic and asymptomatic infants. Studies suggest that treatment during labor will prevent most (but not all) cases of Group B β strep sepsis. However, infants who have signs and symptoms of early onset sepsis may have negative cultures after administration of antibiotics to the mother even though the infection has not been eradicated. Thus, the length of treatment will be a clinical decision based on the presenting symptoms in the infant (severe vs. mild or nonspecific), the maternal risk factors (e.g. colonization with Group B strep vs. colonization plus fever plus chorioamnionitis). Negative cultures at 48 to 72 hours do not necessarily guarantee that infection was not present. Ten to 15% of infants with positive post-mortem cultures and death attributed to infection had negative blood cultures just prior to death. Approximately 15% of infants with positive CNS cultures had negative blood cultures.

Sepsis Work-Ups

- Infants < 72 hours of age
  - CBC, differential and platelet count
  - Blood culture (if central line is in place you need to do 2 cultures – 1 may be from the line, draw through a capped port that can be adequately cleaned off before drawing)
  - CSF culture, gram stain, protein and glucose if infant will tolerate it (if infant will not tolerate consider increasing dose of ampicillin to meningitis levels = 100 mg/kg/dose)
  - Chest radiograph if any respiratory symptoms
  - ET aspirate, gram stain and culture if intubated

- Infants ≥ 72 hours
  - Same as <72 hours plus
  - Urine (bladder tap or urine catherization)
  - stool culture for predominant organism if any GI symptoms (e.g. early Necrotizing enterocolitis) – remember to add to the order that you want predominant organisms isolated
  - Do CSF culture unless too unstable (incidence of positive LP increases as infants are older and meningitis may not have positive blood culture once beyond 72 hours of age)
  - If deep lines are present, you must do blood culture through line and peripherally
  - For any infant with a focus of infection (e.g. abscess), culture the area in addition to blood cultures.

Length of treatment

Length of treatment is dependent on organism and site of infection. In general, infants with positive blood cultures are treated for 10 to 14 days. Most meningitis is treated for 14 days with the exception of Gram negative meningitis which may require 21 days of therapy. Infants with persistently positive cultures (blood or spinal fluid) may require longer courses of therapy. See Remington and Klein, Infectious Diseases of the Fetus and Newborn Infant for recommendations on length of treatment for specific diseases.

Infants with negative cultures but strong clinical evidence for infection usually receive a full course of therapy. If symptoms resolve quickly and all cultures and chest radiographs are negative, 5-7 days of treatment may be justified. If mother has been pretreated and infant is sick, a longer course of therapy may be desirable even with negative cultures. CRP may help guide treatment decisions although may also be non-specific.

See section on fungal infection for length of treatment for candidal sepsis.
Gentamicin, Tobramycin and Vancomycin Trough Levels

- On all infants with renal problems or with high creatinine levels
- Infants whose treatment will be ≥ 3 days (if longer course of treatment is probable or known)
- Peak gent and tobramycin levels are done when specific organism identified – vancomycin peaks are seldom needed

Resources:
MMWR statement on Preventing GBS Disease

CSF Values in High Risk Infants

- Values that are suggestive of meningitis in infancy are
  - WBC count >30 cells/mm3
  - Protein values >200 mg/dL
  - Glucose <30% of the blood value
- Bloody taps are difficult to interpret – ratios of CSF values vs. blood values are not reliable

<table>
<thead>
<tr>
<th>CSF Finding</th>
<th>Range</th>
<th>Mean</th>
<th>2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>0-1070</td>
<td>9</td>
<td>0-884</td>
</tr>
<tr>
<td>Polys</td>
<td>0-70</td>
<td>3</td>
<td>0-27</td>
</tr>
<tr>
<td>Lymphs</td>
<td>0-20</td>
<td>2</td>
<td>0-27</td>
</tr>
<tr>
<td>Protein</td>
<td>32-240</td>
<td>63</td>
<td>27-144</td>
</tr>
<tr>
<td>Glucose</td>
<td>32-78</td>
<td>51</td>
<td>35-64</td>
</tr>
</tbody>
</table>

CSF Values in First 24 hours in Full Term, Healthy Neonates

<table>
<thead>
<tr>
<th>CSF Finding</th>
<th>Range</th>
<th>Mean</th>
<th>2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>0-1070</td>
<td>9</td>
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</tr>
<tr>
<td>Glucose</td>
<td>32-78</td>
<td>51</td>
<td>35-64</td>
</tr>
</tbody>
</table>
### Choice of Antibiotics by Site of Infection

The choice of antibiotics needs to be tailored to the clinical situation. Below is a general guideline but predominant organisms being seen in the NICU and past exposures and treatments of the infant need to be taken into account when selecting a regimen pending identification of the organism.

<table>
<thead>
<tr>
<th>Site</th>
<th>Usual Organisms</th>
<th>Suggested Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset sepsis</td>
<td>GBS, Gm – esp. E coli, Listeria</td>
<td>Amp &amp; gent</td>
<td>Need to look at maternal cultures for possible unusual or resistant organisms</td>
</tr>
<tr>
<td>Late onset sepsis</td>
<td>Coag neg staph, Gm – rods, Enterococci, Other gm +</td>
<td>Amp &amp; gent if no central line Vanco should be used if central lines in place (with cefotaxime, ceftazidime or gentamicin)</td>
<td>Vermont Oxford Network defines late onset sepsis as over 3 days of age</td>
</tr>
<tr>
<td>NEC</td>
<td>Gm – rods, occ. Coag neg staph</td>
<td>Zosyn</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider adding vanco if CVL in place</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Gm + cocci, Gm – rods Colonizing organisms (ET aspirate)</td>
<td>Based on gram stain and colonizing organisms</td>
<td>CDC has diagnostic criteria but in face of lung disease often difficult to distinguish colonization from tracheitis from pneumonia</td>
</tr>
<tr>
<td>Meningitis</td>
<td>GBS, E coli, Gm – rods</td>
<td>Same as sepsis</td>
<td>Aminoglycosides have poor CSF penetration (synergy only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-14 days for GBS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14-21 days for listeria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 days for Gm – rods</td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>Gm – rods, Enterococci Coag neg staph, Fungus</td>
<td>Amp &amp; gent (early onset or no lines) Vanco &amp; cefotaxime (late onset)</td>
<td>Need renal ultrasound after treatment (during infection only if suspect obstruction)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Skin flora, Staph including MRSA</td>
<td>Naf &amp; gent Vanco &amp; gent (if MRSA suspected) Consider Zosyn if related to GI surgery wound breakdown</td>
<td>Drainage may be needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staph including MRSA, Other Gm + Gm -</td>
<td>Naf &amp; gent Vanco &amp; gent (if MRSA suspected) Consider Zosyn</td>
<td>Can progress to faciitis</td>
</tr>
<tr>
<td>Omphalitis</td>
<td>Any organism including GC and Chlamydia, Chemical conjunctivitis, Herpes</td>
<td>Topical usually sufficient – EES, gent, tobra Chlamydia needs oral EES for 14 days</td>
<td>Some will require systemic antibiotics – e.g. Pseudomonas</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Staph GBS E coli GC</td>
<td>Vanco &amp; gent Vanco &amp; cefotaxime</td>
<td>May need surgical drainage</td>
</tr>
<tr>
<td>Osteomyelitis or septic arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Candidal Infections

The most common fungal infection in the NICU is *Candida albicans*. Not all fungal infections are from *Candida albicans*, but may involve other species such as *C. parapsilosis* and *C. tropicalis*. Identification of the species is important as antifungal agent sensitivities vary from species to species. At the moment, all *C. albicans* are sensitive to Amphotericin B (AmB).

Incidence

- For unexplained reasons there has been a nationwide increase in the incidence of systemic Candida infections over the last decade. Incidence of 4% in infants with BW <1500 g and 10% with BW <1000 g have been reported. Most of these infections are acquired in the nursery rather than congenitally.
- Three forms have been identified in the newborn: Congenital candidiasis (onset at birth); Catheter related fungemia (onset usually >7 days); and systemic candidiasis (onset usually >7 days (See table below)
- The major risk factors for acquiring a fungal infection are: length of time on systemic antibiotics (esp. broad spectrum), use of parenteral nutrition and lipids, the presence of ET tubes, the use of gastric acid suppression medications and possibly indwelling NG/OG tubes.
- The organism typically comes from the infant’s own flora.

### Candidal Illness in the Newborn

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Congenital Candidiasis</th>
<th>Catheter-related fungemia</th>
<th>Systemic Candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Onset</td>
<td>Birth</td>
<td>&gt;7 days</td>
<td>&gt;7 days</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>None</td>
<td>Necessary</td>
<td>Necessary</td>
</tr>
<tr>
<td>Skin Involvement</td>
<td>Hallmark</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Respiratory involvement</td>
<td>Occasionally</td>
<td>Never</td>
<td>Frequent</td>
</tr>
<tr>
<td>Positive blood cx</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Multiorgan involvement</td>
<td>Never</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Treatment</td>
<td>Topical antifungals†</td>
<td>Catheter removal and parenteral AmB</td>
<td>Parenteral AmB</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Excellent</td>
<td>Good</td>
<td>Fair to Poor</td>
</tr>
</tbody>
</table>

†Death may occur in preterm infants with pulmonary involvement. AmB should be used in these infants.

From Bendel and Hostetter: Semin Pediatr Infect Dis, 1994

Clinical signs

- Rash/abscesses
- Temperature instability
- Respiratory deterioration
- Hyperglycemia or new onset glucose intolerance
- Hypotension
- Impaired renal function: anuria ("fungus balls" on renal ultrasound)
- New heart murmur
- Signs of NEC (feeding intolerance, abd. distention).
- These signs are also consistent with bacterial sepsis. Consider the diagnosis of fungal infection whenever bacterial sepsis is suspected and visa versa.

Diagnostic tests

- Cultures
  - Blood cultures (peripheral and line)
  - Urine culture (bladder tap or catheterization) and spun UA (to look for hyphae or yeast buds)
  - Lumbar puncture
  - Cultures are often not positive within 72 hours.
  - Isolation of positive culture from a bagged urine specimen or endotracheal tube does not necessarily indicate infection
- Chest Xray (sudden progression to "severe BPD") if have respiratory symptoms
• Renal ultrasound (r/o "fungal balls")
• Eye exam (ophthalmitis may be present in up to 50% of systemic infections, but rarer in strictly catheter related sepsis).
• Echocardiogram if have murmur

Treatment

• General Measures
• Treat systemic symptoms such as hypotension, respiratory failure etc.
• Remove catheters, perform any surgical procedures necessary (drain abscess, remove kidney fungus balls). Early treatment is crucial for success.

Antifungal therapy

Liposomal Amphotericin B

Dose: Day 1 dose 1 mg/kg then 3-5 mg/kg once a day over 2 hours infusion
Monitoring: Follow creatinine (renal function) and potassium levels (causes potassium wasting). Hepatotoxicity and bone marrow suppression are also seen as side effects. Identification and sensitivities of the infecting fungus are important. Medication is not compatible with anything but D5W (including saline)

Fluconazole

Use when fungus is resistant or unresponsive to amphotericin. 
Dose: See antibiotic section below
Toxicity: Thrombocytopenia, elevation of transaminases, may interfere with metabolism of methylxanthines and barbiturates.

Flucytosine (5-FC)

Use in combination with amphotericin for resistant organisms. Oral only 
12.5-37.5 mg/kg/dose q 6 hours po

Follow Up

Repeat cultures to document sterilization of the infected body compartment are needed. If positive cultures persist, the presence of an abscess must be suspected and echocardiography, head CT/MRI and/or abdominal CT/MRI might be indicated as well as repeat eye exams.

Other Fungal Infections

• Non candida albicans species are less common causes of fungal infection in the NICU.
• Itraconazole, voriconazole and caspofungin can be given to infants based on the likely (and then proven) sensitivities of the organism

Chemoprophylaxis for fungal infections when on Broad Spectrum Antibiotics

Fluconazole for prophylaxis against fungal infections should be considered for VLBW infants on long courses of broad spectrum antibiotics.

• Individual Dose: 3 mg/kg
• Interval: < 29 wk 3 times a week (Tu-Th-Sat or Mo-Wed-Fr)
  ≥ 29 wk every 48hrs
• Route: IV over 30 minutes
Hepatitis B Virus Infection and Vaccine

Background
The Center for Disease Control and the American Academy of Pediatrics recommend that all infants be immunized with the Hepatitis B vaccine regardless of the hepatitis status of the mother. However, because passive immunity may be important in infants delivered to Hepatitis B antigen positive women, it is important to identify pregnant women who are hepatitis B surface antigen positive during pregnancy. Universal screening for hepatitis status is done in our hospital.

Management

- The following protocol should be followed for all infants:
  - Delivery room and nursery personnel wear gloves when handling the infant initially. The infant is not infectious, but the maternal blood may be infectious.
  - All infants should receive hepatitis B vaccine prior to discharge from the hospital. Recommended doses and vaccine schedules are given in the table.

- For Infants of HBsAg positive women:
  - Wear gloves when handling infant until all maternal blood has been removed.
  - Bathe the infant immediately, taking care to remove all blood and secretions present on the skin or hair of the baby.
  - Give Hepatitis Immune Globulin 0.5 ml as soon as the infant is physiologically stable, within the first 12 hours of birth.
  - To avoid inoculation of the virus through the skin, cleanse the injection site well.

- For infants whose mother’s HBsAg status is unknown:
  - Order HBsAg on the mother. (Results should be available within 48 hours)
  - Give hepatitis vaccine within 12 hours of birth
  - If mother is HBsAg positive, give HBIG 0.5 ml as soon as possible, but at least within 7 days.

Recommended schedule and doses for hepatitis vaccine. (From Guidelines for Perinatal Care, AAP and ACOG, 2007) See below for recommendations if <2000 g birthweight

<table>
<thead>
<tr>
<th>Infants of</th>
<th>Dose</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg positive mothers*</td>
<td>HB vaccine #1 Recombivax 5 µg (0.5 ml) Engerix-B 10 µg (0.5 ml)</td>
<td>Birth to 12 hrs</td>
</tr>
<tr>
<td></td>
<td>HBIG 0.5 ml IM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HB vaccine #2</td>
<td>1-2 month</td>
</tr>
<tr>
<td></td>
<td>HB vaccine #3</td>
<td>6 months – anti-HBs levels should be checked after series done – if &lt;10 mIU/ml a repeat series of 3 doses (q 2 month) should be given</td>
</tr>
<tr>
<td>HBsAg-unknown mothers*</td>
<td>HB vaccine #1 Recombivax 5 µg (0.5ml) Engerix B 10 µg (0.5 ml)</td>
<td>Birth to 12 hours</td>
</tr>
<tr>
<td></td>
<td>HBIG 0.5 ml</td>
<td>If mother is HBsAg positive, give HBIG as soon as possible, not later than 1 week</td>
</tr>
<tr>
<td></td>
<td>HB vaccine #2</td>
<td>1-2 months</td>
</tr>
<tr>
<td></td>
<td>HB vaccine #3</td>
<td>6 months</td>
</tr>
<tr>
<td>HBsAg negative mother</td>
<td>HB vaccine #1 Recombivax 5 µg (0.5 ml) Engerix 10 µg (0.5 ml)</td>
<td>Preferred at birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>By two months of age</td>
</tr>
<tr>
<td></td>
<td>HB vaccine #2</td>
<td>1-2 months</td>
</tr>
<tr>
<td></td>
<td>HB vaccine #3</td>
<td>6 months</td>
</tr>
</tbody>
</table>
* There is some evidence that the vaccine is less effective in premature infants (AAP and the Redbook use 2000 g as a marker of prematurity.) If mother is HBsAg negative, vaccination may be delayed until the infant is >2000 gms or until discharge. If the mother is HBsAg positive, vaccine should be given within 12 hours of birth, and give a 4th dose of the vaccine (essentially the birth dose of vaccine is not counted in the series.) If mother is hepatitis B positive HBIG should be given in same dosing regimen as in term or larger infants.

Redbook section on Hepatitis B

**Hepatitis C**

- Mainly transmitted through blood
- 95% of post transfusion hepatitis is due to Hep C
- Sexual transmission is possible but rare
- Prevalence in general population is 1.8%
- Seroprevalence in pregnant women is 1-2%

The perinatal transmission and consequence of Hepatitis C infection is less well known than that of Hepatitis B. Just as for hepatitis B, a chronic carrier state exists for hepatitis C. In one large study 7698 pregnant women were tested for hepatitis C and 53 were positive for hepatitis C antibody (0.6%). 31/53 were also positive for Hepatitis C RNA. Of 54 infants delivered to these women, three (5.6%) became positive for HCV RNA during follow-up. No infants of HCV RNA negative women became positive. Thus, the rate of vertical transmission in chronically infected Hepatitis C positive women is about 5-6 %. Rate of transmission is highest in women with high titers of HCV RNA. (NEJM 1994; 330:744-50.) Co-infection with HIV increases the risk for vertical transmission to 14-17%. In 1/3rd of cases transmission is prenatal and 2/3rd are perinatal.

HCV virus can be found in colostrum and breast milk. The actual risk of transmission through breast milk alone is unknown, but at least one case has been reported. However, in another series none of the infants breast fed with known HCV RNA+ milk became infected after an average length of breast feeding of 2 months. The infectivity probably relates to viral load and length of breast feeding. CDC and AAP do not consider Hepatitis C a contraindication to breast feeding. AAP recommends that mothers should consider abstaining from breast feeding when nipples are cracked or bleeding.

**Suggested management**

- Hepatitis C antibody positive, RNA negative = no risk for transmission
- Hepatitis C antibody positive, RNA-positive = 5-10% risk for transmission
- Breast feeding - Consider testing breast milk for HCV RNA (using PCR). If negative, risk is low. If positive, counsel mother that there is a risk for transmission, but probably fairly low. If nipples are cracked or bleeding, counsel that risk of transmission is increased.
- Council against breastfeeding if coinfevted with HIV.

**Diagnosis**

- Incubation period is 2 weeks to 6 months with an average of 6-7 weeks
- No culture is currently available to test for Hepatitis C, diagnosis is made by presence of anti HCV antibody in the serum and infectivity is determined by testing for HCV-RNA by PCR.
- In infants born to HCV positive moms, NIH recommends testing HCV-RNA at 1-2 months of age
- If positive confirmatory testing should be done by repeating HCV-RNA by 4-6 months of age
- Infant tests positive for Anti HCV by 18 months of age (by then all maternal antibodies should have cleared)

**Prognosis**

- Effects on neonates are uncertain
- Overall 25 % of infected people may have jaundice and elevated liver enzymes
- Less than 10% of infected children develop chronic hepatitis
- Less than 5% may go on to cirrhoses and few may develop hepatocellular carcinoma.
- Infants are generally asymptomatic and no treatment trials with alpha interferon or Ribavarin in infants have been done.

Information can be obtained from [NIH website](https://www.niaid.nih.gov)

CDC has a toll free number to deal with issues on Hepatitis C: 1-888-4HEPCDC

[Redbook section on Hepatitis C](https://www.cdc.gov/hepc)
Congenital Syphilis

There was a rise in the number of cases of congenital syphilis starting in the 1990’s. This is a summary of disease – for infants with disease consult the AAP Redbook

Definitions (new 1989 CDC guidelines):

- **Confirmed:** You see the spirochetes (lesions, placenta, cord, autopsy)
- **Presumptive:** Suspect likely infection:
- **Mother with untreated or inadequately treated syphilis regardless of status of infant**
- **Any case in which the infant is reactive to a treponemal test (e.g. MHA-TP) for syphilis and has any one of the following:**
  - Any evidence of syphilis on physical exam (see below)
  - Any evidence of syphilis on long bone X-ray
  - Positive CSF VDRL
  - Elevated CSF WBC count or protein (without other cause)
  - Quantitative non-treponemal serologic titer (e.g. RPR) that is fourfold higher than the mother’s (both specimens drawn at birth)
  - Positive FTA-ABS 19S-IgM antibody
- "Syphilitic" stillbirth: fetal death after 20 weeks gestation where mom had untreated or inadequately treated syphilis
- All the above should be reported as cases

Who to evaluate

- Any infant born to a mother with a positive STS (serologic test for syphilis)
- Any infant with suspicious clinical findings
- All stillbirths
- Any infant born to an HIV positive women who was co-infected with syphilis during pregnancy regardless of treatment status.
- Any infant who is ill for unknown causes

Evaluation

- Maternal history/Maternal test results
- Physical exam
- Long bone radiographs
- Non-treponemal antibody titer
- Quantitative STS on baby and mom
- 19S-IgM FTA-ABS
- CSF analysis
- HIV antibody test
- Others as indicated (i.e. LFTs, platelet count, CXR, etc.)

Clinical findings

<table>
<thead>
<tr>
<th>Funisitis</th>
<th>Placentitis</th>
<th>Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrops</td>
<td>Growth retardation</td>
<td>Frontal bossing</td>
</tr>
<tr>
<td>Bone abnormalities</td>
<td>Hepatosplenomegaly</td>
<td>Pseudoparalysis</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Mucocutaneous lesions</td>
<td>Leptomeningitis</td>
</tr>
<tr>
<td>Snuffles</td>
<td>Nephrotic syndrome</td>
<td>Eye Abnormalities</td>
</tr>
</tbody>
</table>

Maternal treatment

- Adequate treatment of a syphilitic woman during pregnancy consists of meeting ALL of the following criteria:
  - History and documentation of adequate therapy for the stage of syphilis at the time of diagnosis.
  - Quantitative STS titers monitored during pregnancy.
Documentation of expected drop in titers.

Treatment

- Crystalline penicillin G 100,000-150,000 units/kg/d IV divided q8-12° for 10-14 days or
- Procaine pen G, 50,000 units/kg/d IM q day for 10-14 days
- If you're going to treat - use neurosyphilis regimens. CSF VDRLs are only positive 50-70% of the time with neurosyphilis.
- There are special cases when a single dose of Benzathine Penicillin G (BenPG) may be used. See evaluation and treatment algorithm below.
- Infants born to HIV positive women should NEVER be treated with BenPG.
- Syphilis is a reportable condition – discuss reporting requirements with local infection control person and make sure report is filed with the county health department.

A detailed algorithm is available in the Redbook

Follow Up

- Follow-up for untreated infants:
  - Do VDRL and FTA-ABS titers at 1, 2, 4, 6 and 12 months
  - Infant is declared uninfected IF
    - VDRL titer is decreasing by 3-4 months and
    - VDRL is negative by 6 months and
    - FTA-ABS is negative by 12 months
- If not: Reevaluate and treat with a regimen recommended for syphilis of more than one year's duration.

Follow-up for treated infants

- Do VDRL at 1, 2, 4, 6 and 12 months and CSF analysis every 6 months:
  - Infant is declared adequately treated IF
    - VDRL titer is decreasing by 3-4 months and
    - VDRL is negative by 6 months and
    - CSF VDRL is negative by 6 months and
    - CSF cell count is decreasing and
    - CSF cell count is normal by 2 years
- If not: Reevaluate and treat with a regimen recommended for syphilis of more than one year's duration.
Herpes Simplex Virus (HSV) Exposure and Infection

Herpes simplex virus is a rare (approximately 1 in 5,000 births – range 1/3000 to 1/20,000) but devastating disease in the newborn. Exposure to HSV should be minimized. Exposed infants should be isolated and cultured. Infected infants should be isolated and treated.

Presentation:
- A generalized systemic disease with liver, adrenal glands, respiratory tract and CNS involvement or DIC (25%)
- Isolated CNS disease (35%)
- Local skin, eye or mucous membrane involvement (45%)

- The diagnosis should be suspected in cases of overwhelming sepsis in the first weeks of life, especially if the maternal history is consistent with a primary infection (i.e. febrile illness without bacterial source even in the absence of lesions). Most overwhelming cases of herpes infection in infants occur in mothers with no history of herpes.

- Children should be observed carefully in the hospital for signs and symptoms of HSV infection. If discharged before the end of the first month of life their parents should be informed of the findings of HSV infection and the need to obtain immediate medical consultation if findings develop. Major findings are lassitude, irritability, fever, temperature instability, respiratory distress, apnea, hepatomegaly, jaundice, vesicles (in skin or mucous membranes), keratoconjunctivitis, or seizures. Shock and DIC may develop rapidly in the systemic disease.
- Vesicles are absent in over one third of cases; their absence should not lead to false sense of security.

Relative risk of infection:
- Most cases (85%) are peripartum; 5% are congenital and 10% are postnatal
- Primary herpes infection in mother (HSV antibody negative mother)
  - 33-50% attack rate in newborn.
  - 30% of infections are HSV -1 and 70% HSV-2.
- HSV antibody positive mothers:
  - 1% chance of shedding at delivery
  - 2% chance of neonatal HSV infection if shedding

Minimize exposure to HSV
- Mothers with history of genital HSV should be examined carefully for findings of active infection* during the pre-partum period.
- If there is active maternal genital HSV*, efforts should be made to deliver the child by C-section. C-section may be helpful even if there has been a rupture of membranes of greater than 4 hours.
- Mothers with active HSV lesions anywhere on the body should be in a private room.
- Parents with active HSV lesions anywhere on the body should be taught to use careful handwashing techniques before they touch their babies and lesions must be covered
- If parents have orolabial HSV, they must wash well, wear a mask, and not kiss their babies anywhere until their lesions have healed.

Isolate and Culture Exposed Babies
- Only babies meeting “high risk” criteria should be placed on precautions and cultured. These include:
  - Active maternal genital HSV* and vaginal birth.
  - Active maternal genital HSV* and C-section after 4 hours of ruptured membranes.
  - Active maternal genital HSV* and C-section after the onset of second stage of labor
  - Primary HSV infection in the mother, whether or not there is genital involvement.

*A diagnosis of active genital HSV in the mother requires one of the following at birth:
  - Positive viral culture of lesion
  - Positive fluorescent antibody test
  - Presence of ulcers or vesicles
  - Characteristically abnormal cytology

CPMC NICU Manual v7
- Precautions:
  - Well term infants: 24 hour rooming-in with mother with hand washing precautions for mother and personnel. Personnel should gown and glove for handling. If mother is unable to care for the infant, infant may remain in nursery but must be kept in an incubator for barrier, gowns and gloves used for handling and strict hand washing adhered to.
  - Sick Term and Preterm Infants: Maintain in Newborn Intensive Care Unit with hand washing precautions for mother and personnel. Personnel should gown and glove for handling.
- Duration of precautions: Length of hospitalization or 14 days of negative cultures, whichever is less.
- Direct contact with secretions from other HSV eruptions (kissing in the presence of cold sores, etc) should be avoided.

Culturing
- If asymptomatic: pharyngeal cultures at 12-24 hours (or before starting acyclovir if treatment is planned)
- If symptomatic: Viral cultures of pharynx, stool, CSF. If vesicles present, do the following tests:
  - Viral culture
  - Fluorescent antibody - Unroof vesicle and scrape base with wooden end of swab. Smear on slide and send slide for fluorescent antibody staining.
  - Positive cultures at birth may represent colonization; repeat cultures should be done at 24-48 hours. If these are positive viral replication is confirmed.
- Send CSF for PCR

Treatment
- Begin antiviral agents in the following cases:
  - Positive cultures obtained > 24 hours after birth
  - Frank findings of HSV infection
  - Primary HSV infection in mother at time of delivery in symptomatic infant
  - Premature infant meeting “high risk criteria”
  - Some experts recommend empiric acyclovir in infants born vaginally during the mother’s first episode of genital infection
- If antiviral agents are started:
  - Give Acyclovir 60 mg/kg/day divided q 8 hours IV. Duration of therapy is 14 days for SEM disease, 21 days for disseminated disease /meningitis.
- Obtain ophthalmological examination: If there is eye involvement give1% trifluridine 1 drop q 3 hours, or 3% vidarabine along with the systemic antiviral agents
- Provide supportive management as needed.
  MRI to determine extent of brain involvement. Some studies suggesting DW-MRI as the best study.

Management of infants born to mothers with a history of herpes but no active lesion
- Infants should be carefully examined at birth and monitored for the following 6 weeks for presence of symptoms, rashes, lesions.
- No isolation or cultures necessary in the infants.
- The value of intrapartum cultures in the mother is questionable.
- Consider delay of circumcision if risk of herpes to the infant is felt to be high

Consult the Redbook for more information on Herpes
Management of Infants Born to Tuberculin Skin Test Positive Mothers

No active disease in mother
- **Skin test newly found positive, chest radiograph negative**
  - Do not separate mother and infant
  - Usually begin INH therapy in mother (infant may breastfeed)
  - Skin test all household members before infant is discharged from hospital
- **Skin test positive, no chest radiograph done**
  - Infant must be separated from mother until results of X-Ray available.
  - If radiograph is negative, manage as above
- **Skin test positive, Chest radiograph abnormal**
  - Separate mother and infant until mother completely evaluated
  - Sputum examination and culture on mother
  - If negative (no evidence of active T.B., pulmonary or extrapulmonary)
  - Begin preventative therapy in mother (INH)
  - Skin test and evaluate all household members
  - Careful follow-up of infant and mother

Mother has active disease
- **Positive Radiograph or clinical evidence of disease**
  - Management of infants born to mothers with active disease is controversial. In general, in a population without a high rate of INH resistance, Guideline A is applicable. Otherwise, use Guideline B or follow the infectious disease consult recommendation.
  - **Guideline A:**
    - Place infant on prophylactic INH while evaluating mother (10 mg/kg/day)
    - Do not separate mother and infant unless:
      - Mother is ill enough to require hospitalization
      - Mother is expected to be noncompliant and directly observed therapy is unavailable.
      - Population being treated has a high rate of INH resistance
    - Continue INH in infant until mother is culture negative for 3 months
  - **Guideline B:**
    - Separate infant and mother until evaluation complete
    - Continue separation until mother is noninfectious (3 months of culture negative)
    - Test all household members for tuberculosis

- **Mother with Miliary Tuberculosis, bone disease, meningitis, endometrial TB**
  - **Evaluation of Infant:**
    - PPD
    - Chest radiograph
    - Culture of endotracheal secretions (if intubated)
    - Gastric washings
    - CSF
    - Acid fast stains on all above fluids, including urine
    - Do sensitivities on organisms
    - Test mother and infant for HIV
  - Baby appears to have congenital TB (e.g. symptoms, positive chest radiograph, positive smears)
    - Treatment: INH 10-15 mg/kg/day and Rifampin (10-20 mg/kg/day). If drug resistance is suspected, add pyrazinamide (PZA) or streptomycin. Treatment is usually for 9 months. If meningitis present, use 3 drugs. Some recommend adding Corticosteroids 1-2 mgs/kg/day of prednisone for 6-8 weeks.
  - No evidence of infection in baby
    - Separate mother from infant until mother not contagious
    - Treat infants: INH 10 mg/kg/day for 6 months
    - Repeat PPD at 4-6 weeks, 3 months, 6 months. If positive, treat for 9-12 months

- **BCG Vaccine:** In the USA only administered if infant is TST and HIV negative but is continually exposed to contagious pulmonary TB which is MDR or inadequately treated.

- Contact infection control to discuss reporting requirements to the health department
Care of Neonates at Risk for HIV Infection

In the U.S.A, approximately 150,000 women of childbearing age are infected with HIV and about 7000 give birth each year. The causative agent in acquired immunodeficiency syndrome (AIDS) is HIV-1 subtype B virus; HIV-2 is more common in West Africa. The virus can be isolated from various body fluids but is mainly transmitted in secretions (semen, cervical, breast milk and blood products.) The attack rate is lower than that of Hepatitis B. The infant's risk of infection from an HIV positive, untreated mother is approximately 30% in the U.S. This risk has been shown to decrease to 2% or less with implementing recent guidelines recommending universal HIV antibody testing of all pregnant women, Anti RetroViral (ARV) treatment in the antepartum, intrapartum and postpartum period, and prophylaxis of the neonate after delivery. The risk of infection appears to be higher in infants born at <34 weeks gestations. The risk to health care workers from an infected patient is <0.8%. Because of infectivity, high risk patients need special care.

Identification of "High Risk" Neonates

- Maternal history of
  - HIV positive blood test
  - AIDS
  - Intravenous drug use
  - Blood transfusion between 1/79 and 6/85
  - Donor inseminated unless donor has been screened
  - Sexual contact with high risk partner
    - IV drug abuser
    - Homosexual or bisexual
    - HIV positive or AIDS
    - Hemophiliac
  - Prostitution
- Screening by risk factor will identify only approximately 50% of HIV positive mothers hence universal screening both early and late in pregnancy (36 weeks) is currently recommended.
- Known sibling with HIV+ or AIDS

Mode of Transmission

- In utero: Probably 20%. Virus has been isolated from fetuses as early as 10 weeks gestation. Infection probably a result of maternal viremia or placental infection
- Peripartum: Probably predominant mode (may be as high as 80%). Possibly from exposure to virus in maternal blood and/or vaginal secretions.
- Postnatal: Breast feeding (15%)

Diagnosis

- Antibody screen
  - 100% of infants delivered to HIV+ mothers will have a positive antibody (HIV) test in the cord blood (not ideal for testing due to high rate of false positive results) or at birth because of passive transfer of antibody.
  - Uninfected infants will usually revert to seronegative between 6 and 18 months (median age = 9 months)
  - Presence of the antibody after 18 months is presumptive evidence of infection.
  - Confirm positive ELISA with Western blot or IFA.
  - If infant is positive and maternal status unknown, recommend testing mother, father and siblings.
- Viral tests (NAATS-nucleic acid amplification tests, are the gold standard)
  - Polymerase chain reaction for HIV virus DNA
    - May be negative at birth but >95% are positive by 4 weeks of age and 99+% positive by 6 months.
    - False positives are rare; the presence of a positive PCR within 48 hours of birth is strong evidence for in utero infection in the infant.
    - A negative PCR at birth does not rule out the infant becoming positive later, but sensitivity and specificity are very high by one month of age.
    - If negative, repeat at 2 weeks, 6 weeks and 4-6 months. It is less sensitive in detecting in non-B subtypes.
- Viral culture: May be negative at birth and become positive within first 6 months (expensive and results take 2-4 weeks)
- p24 antigen: May be negative at birth and become positive within first 6 months - usually not recommended for early testing.
- HIV – RNA assays to quantitative the viral load may be helpful in predicting clinical course. Also helpful in detecting non-subtype B infections (C, D and O)

Management

Prenatal
- CDC recommends that all pregnant women should be offered HIV testing early in pregnancy
  - Information should be provided about the risks of HIV and maternal child transmission
  - Must be informed that they can “opt out” of testing but should be encouraged to get tested
  - No written consent is required
- A second HIV test during the third trimester, preferably before 36 weeks of gestation, should be considered for all pregnant women, especially women who meet one or more high risk criteria listed above or
  - Women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women aged 15-45 years
  - Women who receive health care in facilities in which prenatal screening identifies at least one HIV-infected pregnant woman per 1,000 women screened
  - Women who are known to be at high risk for acquiring HIV (see above)
  - Women who have signs or symptoms consistent with acute HIV infection.
- When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection.
- If HIV positive, prenatal counseling regarding the risk of transmission is essential.
- If the mother chooses to continue the pregnancy, refer for treatment during pregnancy.
- Pregnant HIV+ woman should be offered treatment with Zidovudine and other HAART after 14 wks gestation and continued through entire pregnancy to decrease risk of viral transmission to their infant
- Screen for STD and treat aggressively
- Make sure prenatal care plan is in place to transmit information to baby’s care provider and check for any updates to treatment regimens for the infant at the Bay Area Perinatal AIDS Center (BAPAC) out of SF General. Their phone number is 415-206-8919.

Intrapartum
- Use universal precautions
- Rapid HIV antibody testing if HIV status unknown (results available within 20-30 minutes)
- Avoid scalp sampling, scalp electrodes, episiotomies
- C-Section is considered to help prevent transmission if arrive early in labor with no ROM, viral load unknown or greater than 1000 copies /ml and able to get intrapartum prophylaxis
- The CDC recommends that Zidovudine be offered to HIV+ women during labor, even if they have not received prenatal treatment. IV administration of a loading dose (2 mg/kg) followed by a continuous infusion of 1 mg/kg/hour until delivery is recommended. Other ARVs should be continued if being treated
- Alert pharmacy that infant will be born who needs treatment

Postpartum
- NO breast feeding if mother HIV positive
- Universal precautions when handling baby and mother (bathe immediately) – may be in regular nursery
- Begin oral administration of Zidovudine (ZDV, AZT) as soon as possible after birth (within 8 hours)
  - Infants 35+ weeks: 2 mg /kg / dose every 6 hours orally for first six weeks of life
  - 30-34 weeks: 2 mg / kg / dose given orally every 12 hours, advanced to every 8 hours at by 2 weeks of age and continued to 6 weeks
  - <30 weeks: 2 mg / kg / dose given orally every 12 hours, advanced to every 8 hours at 4 weeks of age and continued until 6 weeks
- Intravenous dose if Zidovudine: 1.5 mg / kg / dose over 1 hour given on same gestational schedule outlined above
- Additional ARV medications will depend on results of virologic (NAATS) testing repeated at 2 and 4 weeks
Before discharge confirm parents have medication for infant and are clear on it’s use
Do a baseline CBC prior to beginning therapy. Repeat hematocrit at 6 and 12 weeks to monitor ZDV toxicity
(cause anemia)
Follow laboratory tests as under Diagnosis
Careful physical exam (including measurements of growth) at least monthly during first year of life
Do CBC and lymphocyte subset measurements and IgG sometime during first 6 months, earlier if evidence of
poor growth, chronic or repetitive infections or opportunistic infection
PCP prophylaxis after 6 weeks of age in infected infants
Vaccines
  - May get Hep B vaccine after bath done
  - Should be given on schedule if infant is asymptomatic
  - MMR may be given (even though it is a live virus if CD4 T-lymphocyte are greater than 15%)
  - Varicella vaccine can also be administered but not in combination with MMR
  - Inactivated polio vaccine (Salk) rather than live (Sabin) should be used because of risk of transmission
to HIV-infected and immunocompromised parents or siblings.

Refer patient to UCSF Perinatal AIDS program

Discharge plans for high risk babies

Medical counseling should be given to those providing healthcare and medical follow-up of the child
Modified secretion precautions should be used at home. The child's HIV negative caretakers should wash their
hands well after handling the baby's secretions. If they have open wounds on their hands, they should wear
gloves when handling secretions. Surfaces at home contaminated with the baby's secretions should be washed
with soap and water and then disinfected with one-tenth strength sodium hypochlorite solution (diluted household
bleach).

HIV testing in California

The confidentiality of a patient's HIV status is protected by California law.

HIV tests can be obtained or released only after informed consent but written consent is no longer required.
The knowledge of the test results must be limited to those directly caring for the patient.
Release of test results to those not directly involved in the patient's care requires a special form (e.g. consent is
required to release the results to the Perinatal Coordinator of the San Francisco Dept. of Public Health for the
purpose of arranging foster care)
If blood and secretion precautions are needed, the reason for this cannot be written in the patient's room or on
the patient's bed. Specific risk factors may be listed in chart.
Name based reporting to California dept of Public Health is now mandated.

Linkage to care
Women who test positive for HIV shall also receive, whenever possible, a referral to a provider / institution specializing in
prenatal and post partum care for HIV-positive women and their infants.

Bay Area Perinatal AIDS Center (BAPAC) out of SF General. Their phone number is 415-206-8919.
Perinatal HIV hotline: 1-888-448-8765
CA, HIV/AIDS hotline: 1-800-367-2437
The National HIV Telephone Consultation Service Phone: 1-800-933-3413
Recommended Resources:

California State Office of AIDS
UCSF: [http://www.nccc.ucsf.edu/Clinical_Resources/Index.html](http://www.nccc.ucsf.edu/Clinical_Resources/Index.html)


**California Code of Regulations on HIV** and additional legal information

**San Francisco AIDS Foundation – Policy Watch**


**California Department of Health Services Perinatal HIV Testing Information and Consent Forms**

**Website on quality improvement in HIV care**:  
**California Perinatal Quality Care Collaborative** tool kit on HIV

**Redbook section on HIV**
Cytomegalovirus

Double stranded DNA virus found in secretions: urine, blood and breast milk

Primary CMV
- 2-3% of women sero-convert in pregnancy
- Transplacental spread is 30-40%
- 10% of in utero infected infants have symptoms (estimated 3 infants a year with CPMC birth rate)
- 20-30% mortality among those who are symptomatic at birth
- 90% of those with symptoms at birth have sequelae
- If asymptomatic at birth 5-15% will have sequelae

Secondary CMV (mom positive before becoming pregnant)
- 1% of fetus affected (will be positive)
- Almost all are asymptomatic
- Low morbidity and sequelae rates

Symptoms (sequelae)
- 90% of infants with congenital CMV are asymptomatic
- Hearing loss – may be progressive and pass hearing screen at birth
- Chorioretinitis
- Neurologic issues: microcephaly, periventricular calcifications, developmental delay, seizures
- IUGR
- Hepatosplenomegaly
- Blueberry muffin rash (dermal hematopoiesis)
- Thrombocytopenia

Postnatal acquisition
- Blood (unlikely in our population as use leukodepleted and CMV negative blood)
- Breast milk is most likely source
- Presents as a respiratory disorder, sepsis, hepatosplenomegaly, thrombocytopenia
- Most often infant is asymptomatic or has mild disease
- Freezing decreases transmission (kills cells in milk) but does not eliminate the risk
- Pasteurization eliminates risk (donor milk is pasteurized)

Diagnosis
- Urine culture for CMV
- Often need to send more than 1 culture

Treatment
- Controversial in asymptomatic infants
- If severe disease gancyclovir
Immunizations

For preterm or term infants with prolonged hospitalizations, vaccinations should be given at the appropriate chronological age, not at their corrected age. For extremely low birth weight infants (<1000 grams) it may be appropriate to wait until they are >34 weeks corrected age.

DTaP: 0.5 ml IM
IPV: 0.5 ml subcutaneous
Hepatitis B: first dose at birth if term or near term (>2000 g). If not given at birth either give before 1 month or age (typically at discharge) or begin with other vaccines: 0.5 ml of Engerix (10 microgram) or 0.5 ml of Recombinvax (5 microgram)
Hemophilus (HiB): 0.5 ml IM
Pneumococcal 7 valent conjugate: 0.5 ml IM

Combination vaccines:
Pediarix: DTaP, Hep B, inactivated polio: 0.5 ml IM.
Comvax: HiB conjugate and hepatitis B: 0.5 ml IM.

Rotavirus vaccine has not been approved for preterm infants and is an attenuated live virus.

Influenza Vaccine

Infants with congenital heart disease and chronic lung disease should be considered for vaccination against influenza strains expected during the upcoming influenza season if they are over 6 months of age. Use a split dose schedule. During the winter family members of all infants should be encouraged to get vaccinated against influenza.

Palivizumab (Synagis)

- Given for protection against respiratory syncitial virus infection during the RSV season (usually November through March). Approved by the FDA for use in any infant born at <35 weeks gestation.
- Recommended by AAP for following populations prior to discharge from ICN during RSV season (updated for 2009 season)
  - Infants < 29 weeks gestational age at birth and < 12 months of age at the start of RSV season get 5 doses.
  - Infants 29 0/7 - 31 6/7 weeks gestational age at birth and < 6 months of age at the start of RSV season get 5 doses.
  - Infants 32 0/7 - 34 6/7 weeks get treated based on risk factors. AAP suggests child care attendance OR sibling younger than 5 years as the 2 factors to consider. These infants are recommended for a maximum of 3 doses to finish treatment by 90 days of age (if born in August they may get 1 dose, if born in September they may get 2 doses, if born in October they may get 3 doses.)
  - Infants with chronic lung disease
  - Infants with hemodynamically significant congenital heart disease

- Dose is 15 mg/kg IM, given monthly during RSV season.
- Notification letters are sent to the follow up pediatricians each year in September to remind them about infants discharged from the CPMC NICU who might for potentially eligible for RSV prophylaxis.

For complete recommendations on Synagis use please see the AAP 2009 policy statement.
Respiratory Disorders

Non-Pulmonary Causes of Respiratory Distress and Apnea

Metabolic
- Hypoglycemia
- Hypocalcemia
- Hypermagnesemia (apnea)
- Hypothermia
- Hyperthermia
- Metabolic acidosis
- Hyperammonemia, hyperglycinemia (apnea/grunting respirations)

Circulatory Disorders
- Hypovolemia - with or without a low Hct
- Polycythemia
- Congenital heart disease – Truncus, Obstructed anomalous venous return
- Congestive heart failure
- Diaphragmatic hernia
- Cardiac arrhythmia – PAT or SVT
- Anemia

Neurological and CNS
- Meningitis
- Seizures
- Post-asphyxial
- Encephalopathy
- Extreme immaturity
- Intracranial bleed

Anatomical
- Choanal atresia
- Neuromuscular disease - myasthenia gravis, Werdnig-Hoffman, myotonic dystrophy
- Abdominal distention - any cause

Sepsis
- Group B strep, Listeria and E. Coli are the most common seen in first days

Iatrogenic
- Maternal drugs, local analgesics, heroin, barbiturates, methadone, prostaglandin infusion
- Reflex stimulation, rectal or nasopharyngeal
Apnea

**Definition:** Cessation in breathing of more than 10-20 seconds, often accompanied by bradycardia and oxygen desaturation. Occurs most often in infants ≤ 34 weeks gestation, associated with exaggerated periodic breathing. The 1986 NIH Consensus statement defines apnea as a respiratory pause of 20s in duration as the minimum criterion for a clinically relevant apnea, or a shorter duration if accompanied by bradycardia or cyanosis.

**Etiology**
- Cardiovascular
  - Hypoxia
  - PDA
  - Severe anemia
- Central Nervous System
  - Intracranial hemorrhage
  - Atypical Seizures
  - CNS malformations
- Infection
  - Sepsis
  - Meningitis
  - NEC
- Metabolic
  - Hypoglycemia
  - Hypo/hypernatremia
  - Hyperammonemia
- Mechanical
  - Feeding apnea (discoordinated suck and swallow)
  - Airway obstruction
    - Neck hyperflexed or hyperextended
    - Nose obstructed by bili goggles, CPAP mask, or dried secretions or swelling from nasal cannula
    - Airway obstructed by secretions or foreign material (e.g. milk, vomitus)
  - Vagal response (usually bradycardia only from gavage tube, deep oral or tracheal suction)
- Apnea of Prematurity
  - Usually onset is >24° of age in infants 28-34 weeks. Infants <28 weeks often have episodes of apnea from birth. The incidence and frequency is inversely related to gestational age. Most "grow out" of apneic spells by 37 weeks.
  - Probably associated with immaturity of the respiratory control mechanisms. Respiratory pattern is more irregular during REM (active) sleep.
  - Preterm infants may have central apnea, characterized by cessation of breathing movements and airflow, mixed apnea in which obstruction occurs after a central apnea, or obstructive apnea defined as lack of airflow in spite of inspiratory efforts.
- Gastroesophageal reflux (very rare: most apneas do not correlate with reflux and most reflux does not correlate with an apnea event)
- Miscellaneous
  - Temperature instability: too hot or too cold
  - REM sleep – associated with more periodic breathing
  - Drugs
  - Maternal medications: narcotics, magnesium
  - Infant medications: sedatives

**Treatment**
- Document - was it real? Ongoing nursing documentation of characteristics and interventions for each episode is critical. Almost all the monitors in the NICU have look back capability on them so spells that are in question can be looked at (at least last 24 hours)
- Stimulation - gentle tactile.
- Prone position. (Keep in mind once in open crib we follow Back to Sleep guidelines)
- Low flow cannula on room air often will work as breathing stimulant
Oxygen, ventilation with bag and mask or ET tube if not responding. (Ventilate in O₂ concentration that baby is usually requiring. Do not increase FiO₂ unless patient does not respond to stimulation and increased ventilation. Increase FiO₂ by 2-5% and observe for improvement. Do not use 100% routinely.)

- Diagnose and treat underlying cause (i.e. sepsis, metabolic problem). Avoid triggering reflexes that may cause apnea (e.g. deep oral suctioning).

- Methylxanthines
  - Caffeine citrate
    - load: 20 mg/kg IV or po (10mg/kg of caffeine base)
    - maintenance: 5-7 mg/kg q 24 hr/IV or po
    - desired level: 10-20 mcg/dl (higher levels may be tolerated in select infants)
    - tips: should be first line drug as once a day, well tolerated and low toxicity
  - Theophylline/Aminophylline
    - load: 5 mg/kg IV or po
    - maintenance: 1.5-3 mg/kg q 8-12 hr IV/po
    - desired level: 5-10 mcg/dl. If no response, may Î to levels of 10-15 mcg/dl.
    - tips: often difficult to maintain levels, high side effects

- Positive Airway pressure
  - NCPAP/face mask CPAP
  - high flow nasal cannula
  - low ventilatory rate using nasal prongs and Si-PAP machine
  - mechanical ventilation

Monitoring Respiratory Status

- Physical examination
- **Arterial blood gases** (normal values) - bedside technology is preferred method (iSTAT)
  - pH: 7.35-7.45
  - PCO₂: 35-45
  - PO₂:
    - <1000 g: 40-60
    - 1001-1500 g: 50-70
    - 1500-2500 g: 50-80
    - >2500 g: 70-90
  - Saturation beyond transition at term 95-100%
  - Saturation in preterm infants should be adjusted based on gestational age ranges

- Capillary blood gases
  - pH and PCO₂ are close to arterial values
  - PO₂ will be lower and cannot be used reliably to predict true arterial PO₂
- **Transcutaneous PCO₂ monitors**
- **Pulse Oximeters**
- The goal of therapy is not to achieve a NORMAL blood gas, it is to achieve an acceptable blood gas:
  - pH: >7.20
  - PCO₂: 45-55
  - Saturation maintained within set limits
    - ≤ 28 weeks corrected age limit set at 83-93%
    - 29-33 weeks corrected age limit set at 85-95%
    - ≥ 34 weeks corrected age limits set at 90-98%
Mechanical Ventilation

Indications for Ventilation
- Apnea
  - Severe or multiple, requiring mask and bag ventilation >6x/shift and not responding to CPAP
- Respiratory failure
- Hypoxemia PO₂ <60 in FIO₂ > 80% (<1500 gm, FIO₂ > 60%)
- Respiratory acidosis with pH <7.25 in infants <1500 gm, pH <7.2 in infants >1500 gm
- Profound shock (pH <7.0)
- Need for procedure where airway needs to be protected
- Certain surgical conditions (e.g. diaphragmatic hernia)

Management of Mechanical Ventilation
- The settings chosen (Peak [PIP] and End Pressure [PEEP], Rate and Inspiratory time [IT]) are tailored to:
  - size of infant
  - lung pathology (e.g. RDS vs. meconium aspiration vs. pulmonary edema vs. apnea)

FIGURE Respiratory wave forms obtained from ventilator pressure tracings, at pressures of 25/5 cm H₂O and rate of 60 breaths/min.

A = Inspiratory Time, (0.5 sec), B = Expiratory Time (0.5 sec), D = PEEP, Mean Airway Pressure = 12 cm H₂O

Respiratory orders
- Initial respiratory orders should specify PIP (determined by Pressure Control setting + PEEP setting on vent), PEEP, rate, IT and FIO₂. A monitoring device (such as pulse oximeter) should also be ordered along with alarm limits.
- If the computerized ordering pathway is not available, the RT will enter the orders, which should be signed in the computer as soon as possible.
- Subsequent orders should reflect desired changes and timing of the next blood gas. FIO₂ does not need to be reordered as it will be adjusted by the nursing staff to keep the infant within the ordered saturation limits.

Ventilatory changes for specific conditions
  Hypoxemia
  - Caused by hypoventilation, ventilation-perfusion abnormalities or right-to-left shunt.
  - Treat by:
    - Increasing FIO₂
    - Increasing mean airway pressure
    - Increase PEEP (especially helpful with RDS and atelectasis)
    - Increase inspiratory time (up to 0.5 sec) if increased for atelectasis, return to baseline once atelectasis is resolved.
- Increase PIP when there is concomitant hypercarbia
- Consider changing to high frequency mode

Hypercapnea
- Caused by hypoventilation, ventilation-perfusion abnormalities practically never by right-to-left shunt.
- **Treatment**
  - Increasing minute ventilation (tidal volume x rate)
    - Increase rate if chest movement appears adequate
    - Increase tidal volume if chest movement inadequate
      - Increase peak pressure by 2 cmH\textsubscript{2}O
      - Consider decrease PEEP by 1 cmH\textsubscript{2}O (if over 5 cm H\textsubscript{2}O)
      - Increase inspiratory time to 0.4 sec
      - Increase expiratory time (only if very short to begin with)
  - Consider changing to high frequency mode

Hyoxemia plus Hypercapnea
- Check tube position
  - Is it in? Use a CO\textsubscript{2} detector or look
  - Is it in proper position? All tubes have a tip to lip measurement on RT clipboard
- Check breath sounds => are they present and equal
  - Is there a pneumothorax? Transilluminate while you wait for an Xray
- Is ventilator functioning properly?
- **Treatment:**
  - Increasing F\textsubscript{I}O\textsubscript{2} and increasing rate or peak pressure
  - Increasing PEEP (if F\textsubscript{I}O\textsubscript{2} is > 80%) and increasing peak pressure and/or rate
  - If baby very hypoxic, take off ventilator and handbag until chest moves well and color improves

Metabolic Acidosis
- Caused by tissue hypoxemia, poor perfusion, excess acids or base losses.
- Compensated: pH normal, PCO\textsubscript{2} low, base deficit 7-10
- Uncompensated: pH <7.20, base deficit >10
- **Treatment**
  - Observe
  - Look for causes of acidosis such as hypotension, patent ductus, volume depletion and treat.
  - Consider getting more buffer into the TPN (esp. in preterms who waste bicarb in their kidneys)
  - Bicarbonate is frowned on. It likely only makes the gas and not the baby better. See article on topic by Aschner et al: Sodium bicarbonate: *Basically Useless Therapy*
  - For a half correction: deficit x wt (kg) x 0.25 = mEq HCO\textsubscript{3}

**General Guidelines for Changing Ventilator Settings**

The goal is not a normal blood gas
The goal is an acceptable blood gas
<table>
<thead>
<tr>
<th>Rate</th>
<th>PIP</th>
<th>PEEP</th>
<th>IT</th>
<th>FIO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>To increase PaCO₂</td>
<td>Decrease</td>
<td>Decrease</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>To decrease PaCO₂</td>
<td>Increase</td>
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<tr>
<td>To decrease PaO₂</td>
<td>NA</td>
<td>Decrease</td>
<td>Decrease</td>
<td>NA</td>
</tr>
</tbody>
</table>

Most important **bold**

NA, not applicable
NA<sup>b</sup> Not applicable unless the Inspiratory time is short (≤ 0.35)

### Modalities of Mechanical Ventilation

- **Assist / Control**
  Every spontaneous inspiratory effort is assisted with a mechanical breath. A back up rate is provided to assure a minimum number of breaths per minute.

- **Synchronized Intermittent Mandatory Ventilation (SIMV)**
  A set number of breaths per minute, when triggered by the patient, are synchronized with a ventilator breath. The patient may take additional breaths that are not mechanical. Should be used in conjunction with Pressure Support ventilation for spontaneous breathing to overcome resistance created by ETT.

- **Pressure support ventilation**
  Every spontaneous breath is “assisted” by an increase in airway pressure to a set degree.

The main goal of these techniques is to avoid baby breaths and ventilator breaths being out of sync. There is no evidence that these modalities decrease the complications of mechanical ventilation. However, they may help shorten the time on the ventilator by augmenting weaning.

### Guidelines for Specific Diseases

#### RDS - compliance is low
Respiratory distress syndrome defined by Vermont Oxford data set as:

- PaO₂ <50 mmHg in room air, central cyanosis in room air
- A requirement for supplemental oxygen to maintain PaO₂ >50 mmHg, or a requirement for supplemental oxygen to maintain a pulse oximeter saturation over 85% within the first 24 hours of life.
- A chest radiograph consistent with RDS (for example, reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) within the first 24 hours of life.

- Give surfactant early, within first 2 hours – ideally in the delivery room
- **Peak Pressure**
  - Use pressures which will adequately move chest wall, generally 20-30 cm H₂O
- **PEEP**
  - Oxygenation usually improves with increases in PEEP
  - If F<sub>I</sub>O₂ >60%, use PEEP's of 5-7
  - If F<sub>I</sub>O₂ 40-60%, PEEP's = 4-6
  - F<sub>I</sub>O₂ <40%, PEEP's = 3-4
  - As with CPAP pressure, optimum PEEP will change with time and lung status changes
- **Rate (IMV)**
  - Begin at 40-60/min
o Adjust to keep PCO$_2$ 45-55
o In severe RDS, hypercarbia and hypoxemia may respond better to increased peak pressure than to increased rate

- Inspiratory Time
  o Begin with 0.35 sec. Generally, do not use > 0.5 seconds to avoid barotrauma and gas trapping.
  o For infants with severe RDS with signs of interstitial emphysema or air leak, consider change to high frequency ventilation

- Weaning from ventilation – infants typically begin improving by 24-72 hours of age and the improvement is often associated with a brisk diuresis and often occurs rapidly. Surfactant may significantly shorten the time to improvement. Aggressive weaning is essential to protect from lung damage.
  o As F$_{1}$O$_2$ requirements drop (i.e. requiring <40-60% O$_2$) begin lowering the peak pressure. After administering Surfactant and improved lung compliance, it is especially important to watch delivered tidal volumes as these can increase quickly and result in overdistension.
  o Do not hyperventilate. Keep PCO$_2$ 45-55. If PCO$_2$ is at lower acceptable range, lower the rate or peak pressure
  o Lower the PEEP if >5 as F$_{1}$O$_2$ requirements drop
  o With severe RDS in small babies, lung damage may be lessened by allowing a pH of 7.25 - 7.30 and PCO$_2$ 50-60 mmHg instead of trying to maintain normal values.

**Meconium Aspiration: Uneven Ventilation and Perfusion**

- Oxygenation - keep well oxygenated (saturation > 95%); there is no benefit to hyperoxygenating – upper sat limit should be <100%
- Consider using surfactant
- Peak Pressure
  o Use the lowest peak pressure that will adequately oxygenate and ventilate the infant.
  o Usually begin with pressures of 20-30 cmH$_2$O.
  o In severe meconium aspiration, it may be necessary to use pressures as high as 40-50 cmH$_2$O. Consider change to HFOV.
- End Expiratory Pressure
  o Begin with low end-tidal pressure (2-3 cm H$_2$O).
  o Increase only if unable to oxygenate.
- Inspiratory Time
  o Keep short (< 0.25 seconds). Short IT may decrease risk of gas trapping. However, some babies with severe meconium aspiration do better with longer ITs. Consider trial and error approach.
- Rate: Individual infants may do better with rapid rates (60-100) or high frequency mode
- In large infants with severe aspiration it may be necessary to paralyze with pancuronium (0.1 mg/kg) Use caution as drug may cause hypotension and tachycardia.
- Weaning from ventilation
  o As infant improves with decreased F$_{1}$O$_2$ requirements (well oxygenated in <60% O$_2$) immediately begin lowering the peak pressure by 1-2 cm change if pressure is >35.
  o Make small changes only - no more than 2 cmH$_2$O of pressure or 2-4 cycles/min.

**Extubation**

- The reason for ongoing need for ventilatory support needs to be documented in the daily note
- Consider extubation in infants who are likely to be able to maintain:
  - adequate spontaneous ventilation
  - airway patency
- In general, if a baby tolerates ET CPAP for several hours, he will tolerate extubation. However, making smaller babies breath spontaneously through a small ET tube with high resistance may not be a fair test for extubation, even with the use of Pressure Support Ventilation.
Most often, extubation is done when ventilator rate and pressure and oxygen requirements are “low”. For example, an 1100 gram baby might be extubated at ventilator pressures of 16-18/4, a rate of 8-15, and an oxygen requirement of 35%.

Prior to extubation:
- evaluate need for respiratory stimulants
- consider need for CPAP
- suction the airway

After extubation:
- oxygen requirement may change (usually increases)
- upper airway stridor can occur
- segmental or global atelectasis can develop

Continuous Positive Airway Pressure (CPAP)

Indications for CPAP
- RDS
- Atelectasis
- Apnea and bradycardia
- Pulmonary edema
- Transient tachypnea
- Post-extubation

Methods of Delivering CPAP
- ET tube
  - Probably most effective, but invasive (including infection risks)
  - Usually works better than nasal flow or mask CPAP in infants >2000 grams
  - Do not use with 2.5 ET tube (resistance of tube is too high)
- Infant Flow Nasal CPAP
  - Correct size prongs or nasal mask must be used to achieve necessary pressure.
  - Pressures of 4-7cmH2O to increase FRC and improve oxygenation.
- Full Face Mask
  - Effective particularly in infants <1500 gm
  - Should not be used with high pressure (>5-6) as they may be transmitted and increase ICP.
  - May be used for the failure of nasal CPAP to improve oxygenation
  - May be needed if nasal prongs are causing nasal breakdown

Instituting CPAP

Begin CPAP in infants with mild to moderate RDS requiring >40% oxygen. Generally start with 5-6 cmH2O. There is an optimum CPAP which increases with worsening lung disease and decreases as the infant improves; the pressure used should be reassessed at least daily.
Considerations

- May be effective in infants with periodic breathing and apnea
- Probably not effective to treat high PCO₂ unless atelectasis or apnea/periodic breathing is the cause.
- Use with caution in aspiration syndromes (may increase risk of pneumothorax).
- When using CPAP, gastric distension may occur unless an orogastric tube is left in the stomach. This is particularly true with full face mask CPAP.

High Frequency Ventilation

High frequency ventilation (HFV) refers to techniques which deliver very low tidal volumes (sub-physiologic) at high rates. It is unclear how delivery of tidal volumes ≤ deadspace facilitates CO₂ removal. It was initially believed that HFV causes less barotrauma because there is less stretching of the lungs and airways. The majority of studies do not support his concept resulting in the Indications listed below.

Approved high frequency ventilators include, high frequency jet (HFJV), high frequency positive pressure using a flow interruptor (HFPP), e.g. Infant Star, and high frequency oscillatory ventilators (HFOV), e.g. SensorMedics 3100A. The latter two are available at CPMC. The Infant Star has limited usefulness for the larger infants and is being phased out as support from the manufacturer ends.

Basic theory for HFPP and HFOV is the same. The three components of HFV are: frequency, amplitude or deltaP (power-in arbitrary units) and MAP. The frequency remains constant (12-15 Hz) and is used primarily to dampen the amplitude at the alveolar level. Amplitude affects CO₂ removal and MAP is the prime determinant of oxygenation.

Indications are relative

- Failure of conventional ventilation
- Air leak
- Hypoplastic lungs

Procedure

Before starting high frequency ventilation

- Make sure conventional ventilator had been functioning appropriately
- Recent xray should be available to confirm pulmonary status, ET tube position, etc.
- Patient should be monitored with arterial line and continuous O₂ saturation, end-tidal or transcutaneous CO₂, and blood pressure.
- Sedation/muscle relaxation is usually not necessary
- RT will set up and calibrate HFV and place at bed side.

Starting high frequency ventilation

Infant Star

- Place infant on Infant Star ventilator using current settings; oscillator should be switched Off, amplitude knob should be in the full counter-clockwise position (minimum amplitude) and frequency should be set to 12 Hz.
- Have RT make sure that pop-off valve is set properly in maximum position)
- Turn oscillator switch on.
- Turn the IMV rate to at least half of current rate (< 30/min) while, at the same time, increase the amplitude until there is appropriate chest vibration.
- Adjust PIP so that there is appropriate (not excessive) chest expansion with conventional ventilator breath.
• Increase PEEP so that the MAP is at least as high as (up to 3 cmH₂O higher than) it was prior to HFV.
• Slowly decrease IMV rate to 0.

Sensormedics

• Preset Sensormedics ventilator to deliver frequency=12Hz, Tᵢ= 33%, minimum amplitude (Power setting 2.0).
• Starting MAP should be 3-5 cmH₂O higher than current for patients with low lung volumes (atelectasis, RDS). A starting MAP equal to or 2 cmH₂O higher than current is used for infants with airleak (PIE, pneumothorax)*
• Attach baby’s ET tube to Sensormedics tubing.
• Reset ventilator and start HFOV.
• Adjust amplitude to achieve appropriate chest vibration

* there is no background conventional ventilation with the Sensormedics (as there is with the Infant Star) to help establish and maintain lung volume. Using higher than baseline MAPs at the start of HFOV is very important to establish a good lung volume.

After high frequency ventilation is started

IMPORTANT SAFETY ALERT: The elevate function of the giraffe needs to be disabled to prevent accidental extubation by raising the bed.

• Desired result is improved oxygenation and a decrease in PCO₂. Changes in these parameters will be affected by MAP and Amplitude, respectively.

• Suctioning. Avoid unnecessary suctioning. The need for suctioning may be apparent from decreased chest vibration and/or increasing PCO₂. After suctioning, a few manual breaths (Infant Star) or a temporary increase in MAP (Sensormedics) may be helpful in reestablishing FRC.

• A chest xray should be done within 1-2 hr of initiating HFV. Usually, appropriate MAP is associated with a chest expansion of 8-9 ribs. Chest xray should be repeated x2 during the first 24 hours and then daily while on HFV.

• Guidelines for adjusting settings:

  Problem: | Try:
  --- | ---
  ↓PO₂ | Make sure ET tube patent; increase MAP by 1-2 cmH₂O increments
  atelectasis, ↓lung volume | increase MAP by 1-2 cmH₂O increments, then decrease after improvement; increase IMV of Infant Star
  ↓PO₂ ± hypercarbia, lung overexpansion by xray, poor cardiac output | decrease MAP by 1-2 cmH₂O increments until improved, repeat xray, consider placing back on conventional vent
  Hypercarbia without lung overexpansion | Increase amplitude, consider ↓ frequency if amplitude is at maximum
  ↓CO₂ | Decrease amplitude
  Hyperoxia | Decrease MAP, FIO₂

Weaning from HFV

Consider weaning from HFV when MAP is <8-10 cmH₂O and FIO₂ is <40%. With HFOV, wean to conventional ventilator or CPAP. With Infant Star, one can wean MAP and increase conventional rate at the same time.
Surfactant

The primary use of surfactant is in the treatment of respiratory distress syndrome (RDS). There are several surfactant formulations approved for use. Survanta is used at CPMC. It is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitoylphosphatidylcholine), palmitic acid, and tripalmitin are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant. The resulting composition provides 25 mg/mL phospholipids (including 11.0-15.5 mg/mL disaturated phosphatidylcholine), 0.5-1.75 mg/mL triglycerides, 1.4-3.5 mg/mL free fatty acids, and less than 1.0 mg/mL protein. It is suspended in 0.9% sodium chloride solution, and heat-sterilized. SURVANTA contains no preservatives. Its protein content consists of two hydrophobic, low molecular weight, surfactant-associated proteins commonly known as SP-B and SP-C. It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A.

Treatment of RDS is either “prophylactic” (surfactant given at birth, before the diagnosis of RDS is made) or “rescue” (surfactant given after there is evidence of RDS). Studies designed to determine whether there is an advantage to prophylactic or rescue have not shown any advantage. However, evidence does suggest that “early” treatment (before 2 hours of age) is more beneficial than later treatment. If possible, surfactant should be given in the delivery room as soon as infant is intubated.

Indications (both of the following needed if not a delivery room usage):
- Clinical and radiological evidence of RDS
- Intubation for ventilatory support

Giving Surfactant
- 4 ml/kg/dose
- Usually, 2-3 doses. There is no evidence of added benefit from >3 doses
- Scheduled 6-8 hours apart (depending on level of illness)
- ET should be suctioned before doses given in the NICU
- Needs to be given via catheter placed to safe suction distance in the trachea
- ½ the dose is given as bolus into each lung in a slightly lateral position

Possible Complications:

Prevention/Treatment:

Considerations:

Plugged ET tube
Suction prior to dosing; monitor TcCO2 and saturation

Transient hypoxia/hypercarbia
Pulse oximeter, TINA instill slowly

Lung overdistention/decrease in compliance
Consider empirical decrease in peak pressure

Pulmonary hemorrhage
Aggressive treatment of PDA

Surfactant for other diseases
There may be a clinical role for surfactant replacement therapy in
- meconium aspiration
- pneumonia
- severe pulmonary hypertension
- ARDS

Additional research needs to be done before surfactant is used routinely in these other diseases.
Guidelines for Tracheal Tube Lengths

<table>
<thead>
<tr>
<th>Birthweight (gms)</th>
<th>Tube Size</th>
<th>Oral</th>
<th>Nasal</th>
</tr>
</thead>
<tbody>
<tr>
<td>700</td>
<td>2.5 mm</td>
<td>6.0 cm</td>
<td>7.0 cm</td>
</tr>
<tr>
<td>1000</td>
<td>3.0</td>
<td>6.5</td>
<td>7.5</td>
</tr>
<tr>
<td>1250</td>
<td>3.0</td>
<td>7.0</td>
<td>8.0</td>
</tr>
<tr>
<td>1500</td>
<td>3.0</td>
<td>7.5</td>
<td>8.5</td>
</tr>
<tr>
<td>2000</td>
<td>3.5</td>
<td>8.0</td>
<td>9.5</td>
</tr>
<tr>
<td>3000</td>
<td>3.5</td>
<td>9.0</td>
<td>11.5</td>
</tr>
<tr>
<td>3500</td>
<td>3.5-4.0</td>
<td>9.5</td>
<td>12.0</td>
</tr>
<tr>
<td>4000</td>
<td>4.0</td>
<td>10.0</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Use of Transcutaneous Monitors

- Consider use of TCPCO₂ monitor in:
  - Infants needing frequent ventilator changes
  - Infants from whom ventilator is being weaned
  - Infants with pulmonary hypertension
  - Infants with hypercarbia when treatment response is being tested
  - Infants with thick secretions and frequent plugging of ET tube (rising CO₂ signal need to suction)

- Transcutaneous PCO₂ can be measured with a miniature glass pH electrode. The CO₂ measured at the skin is increased by two factors:
  - A constant factor related to the heating of the blood: At 43°C, this factor is PaCO₂/1.31.
  - A variable factor related to the skin CO₂ production: This is about 5 torr in newborns with RDS, 8 torr in older infants and 13 torr in babies with BPD.
  - The Radiometer TINA system is a combined PO₂/PCO₂ electrode that automatically corrects for the temperature effect. Get an arterial PCO₂ to estimate the skin metabolism factor.
  - Even if exact correlation can’t be obtained (typically larger infants with more subcutaneous fat) the monitor might help alert bedside care givers to rising CO₂

Oxygen Saturation and Pulse Oximeters

A transcutaneous oxygen saturation monitor (Pulse Oximeter) measures arterial oxygen saturation by a spectrophotometric technique. A beam of light is sent through a capillary bed to a photoreceptor and saturation is measured with each arterial pulsation.

The NICU routine is that oximeters are placed on all preterm infants and older infant with respiratory distress. Monitors may be removed after 34 weeks if infant has been on room air for >48 hours.

Limits set for the monitor vary with:
  - Amount of fetal Hgb present
  - Factors which shift to Hgb/O₂ dissociation curve.
  - Postnatal and gestational age of infant.
Saturation levels reported on blood gases are calculated values and may not correlate with pulse oximeter saturations. True arterial sample saturations can be measured by co-oximeter in the lab.

- Frequent blood transfusions will cause an earlier shift of the curve to the right as fetal hemoglobin is replaced with adult hemoglobin.

Estimate of PO\textsubscript{2} from Saturation  
(pH = 7.40, BE = 0, Temp = 37\degree)

<table>
<thead>
<tr>
<th>PO\textsubscript{2}</th>
<th>Adult Hgb</th>
<th>50% HgbF</th>
<th>100% HgbF</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>54%</td>
<td>60%</td>
<td>71%</td>
</tr>
<tr>
<td>40</td>
<td>71.5%</td>
<td>77%</td>
<td>86.6%</td>
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<tr>
<td>50</td>
<td>82%</td>
<td>87%</td>
<td>92.4%</td>
</tr>
<tr>
<td>60</td>
<td>89.2%</td>
<td>92%</td>
<td>95.4%</td>
</tr>
<tr>
<td>70</td>
<td>95%</td>
<td>94.9%</td>
<td>96.6%</td>
</tr>
<tr>
<td>80</td>
<td>95.3%</td>
<td>96.3%</td>
<td>97.6%</td>
</tr>
<tr>
<td>90</td>
<td>98%</td>
<td>98.3%</td>
<td>98.1%</td>
</tr>
</tbody>
</table>

**If pH is high, as in hyperventilated infants, the saturation is higher at lower PO\textsubscript{2}’s. For example, with a pH of 7.6 (BE = 0), 100% HgbF, the baby is 90% saturated at a PO\textsubscript{2} of 36.

**If pH is low, the baby will be more desaturated at higher PO\textsubscript{2}’s. For example, with a pH of 7.0 (BE = 20), 100% HgbF, the saturation is only 80% at a PO\textsubscript{2} of 50.

Saturation is maintained within set limits:

- < 28 weeks corrected age limits set at 83-93%
- 29-33 weeks corrected age limits set at 85-95%
- ≥ 34 weeks corrected age limits set at 90-98%
Use of End-Tidal CO2 Monitor

End-Tidal CO₂ Monitor is recommended for all intubated infants

- To trend PCO₂
- As an alarm to detect accidental extubation
- A module that hooks into the monitor is available

![Graph of CO₂ Expiration and Inspiration](image)

- Loss of the expiratory plateau (the B to D portion of graph is sloped up with no plateau)
  - Any obstruction that limits expiration
  - Kinked tube
  - Bronchospasm

- A sudden drop in end tidal CO₂ to zero
  - Kinked ET tube
  - Kinked or disconnected sampling tube
  - Patient extubated
  - The ventilator has failed

- A sudden drop in end tidal CO₂ but not to zero
  - Leak in circuit
  - Obstruction such as acute broncho-spasm
  - Leak in sampling tube drawing in room air
Treatment of Meconium Aspiration

Preparation in the DR or OR
- Use largest ET tube feasible for expected size of infant. Most often 3.5 mm for term infants.
- Be sure mechanical suction is working, and pressure reads 80-120 mmHg.
- Check CPAP and F1O2 concentration. Use 40% O2. Wean O2 as appropriate.
- Locate oximeter and have probe ready to open and place if infant needing support.

During Delivery
- Monitor FHR at time of second stage.
- Deep catheter suction of the infant by the OB is no longer recommended by NRP but the mouth should be cleared in same manner of deliveries without meconium stained fluid.
- Deep suctioning has been shown to have no benefit in large trials, however, it is not contraindicated. Suctioning on the perineum will probably not avoid MAS, but may make visualization of the cords and subsequent intubation easier.

Handling of the Infant
- In the Delivery room:
  - If the infant is not vigorous, the infant's trachea should be intubated and suction applied using wall suction attached to meconium aspirator device found in DR box.
  - If meconium is aspirated, repeat procedure again in rapid succession. (DO NOT take more than 30 seconds to clear trachea entirely of meconium). May repeat x 3. If meconium is still present, intubate and use sterile suction catheter.
  - If the baby is not breathing or has a heart rate < 100, proceed with NRP guidelines.
  - Place oximeter as soon as possible.
- In the NBICU:
  - If the infant is not completely recovered and in respiratory distress, admit to the NBICU.
  - Consider using surfactant in severe meconium aspiration.
  - Consider using antibiotics in severe meconium aspiration.
  - Ventilate as described in section on infants with persistent fetal circulation. (next section).
  - Use oximeter. Keep infant well oxygenated (not hyperoxgenated).
  - Consider associated conditions including potential candidate for cooling.

Complications
- Pneumothorax is the most common complication, immediately after birth as well as later. If infant does not respond to resuscitative efforts, needle aspiration of pleural space should be considered. Treat as described under treatment of pneumothorax.
- Pulmonary hypertension frequently occurs in neonates with aspiration syndrome.
Management of Infants with Persistent Pulmonary Hypertension

Definition
Persistent pulmonary hypertension (PPH) or persistent fetal circulation (PFC) is a condition in which the pulmonary vascular resistance fails to decrease after birth, resulting in increased pulmonary artery pressures, decreased pulmonary blood flow and, if severe, right to left shunting across the foramen ovale and/or patent ductus arteriosus. It is characterized by often profound hypoxemia which is unresponsive to oxygen administration and/or mechanical ventilation. The primary differential diagnosis in these infants is cyanotic heart disease versus pulmonary hypertension.

Associated conditions
- Intrauterine or perinatal asphyxia
- Meconium aspiration
- Parenchymal lung disease including RDS and pneumonia
- Diaphragmatic hernia
- Polycythemia
- Sepsis, particularly Group B streptococcal infections
- Shock
- May be idiopathic

Pathology
- **Chronic intrauterine hypoxia** may result in abnormal muscularization of the pulmonary arterioles, resulting in increased pulmonic vascular resistance. Other humoral factors released by damaged endothelial cells may produce intense vasoconstriction unresponsive to the usual vasodilatory stimuli of oxygen and lung expansion.
- **Postnatal pulmonary vasospasm** may be a response to hypoxemia, acidosis, or release of vasoconstrictive substances such as leukotrienes and thromboxanes in response to infection, inflammation and hypoxemia.
- **Abnormal lung growth** as seen in diaphragmatic hernia also results in abnormal pulmonary artery growth, with decreased total cross sectional area, and possibly increased vasoconstriction.

Diagnosis
- Suspect the possibility of PPH when
  - Associated conditions are present
  - Hypoxemia greater than expected by clinical findings such as X-Ray, pCO2 and pH
  - Differential between a right hand and a foot oximeter reading

- **Echocardiogram shows**
  - No structural heart disease (anomalous pulmonary venous return must be ruled out in particular)
  - Increased pulmonary artery pressure as assessed by Doppler
  - Right to left shunting across the foramen ovale
  - Tricuspid regurgitation
  - Right ventricular hypertrophy

- **Physical exam**
  - Cyanosis in room air
  - May have signs/symptoms of respiratory distress (grunting, retracting)
  - Some infants have a murmur loudest at the lower left sternal border consistent with tricuspid regurgitation and a prominent right ventricular impulse

- **Differential oxygenation in pre and post ductal distribution**
  - If there is right to left shunting across a ductus arteriosus, the pO2 in the temporal or right radial artery may be more than 10 mmHg higher than the pO2 in the abdominal aorta. This may be assessed by simultaneous blood gases drawn when the infant is quiet and not agitated or, noninvasively, by measuring the oxygen saturation of the right hand and a foot simultaneously.
  - The absence of a difference in pO2 does not rule out PPH if the right to left shunt is at the level of the atra instead of the ductus

CPMC NICU Manual v7
Lability of pO\textsubscript{2} (“flip-flop”) is characteristic of these infants

Management

- These are the sickest infants cared for in the ICN. Their clinical condition can change very rapidly and great vigilance is needed in evaluation.
- Minimal handling: Routine procedures such as examinations, IV placement, ET suctioning and weighing can cause the pO\textsubscript{2} to drop precipitously.
- Consider placing both UA and UV catheters to monitor blood pressure and CVP (consider double lumen UVC as often will require multiple medications and blood products.) CVP monitoring of the UVC must be ordered (not routine for UVC lines.)
- Many infants will need intubation and ventilation to treat hypoxemia. However, if the infant is well oxygenated in hood oxygen, without periods of hypoxemia (pO\textsubscript{2}<50) it is reasonable to watch carefully without instituting mechanical ventilation until absolutely necessary.
- Blood Gases:
  - Avoid hypoxia and acidosis
    - Maintain saturations above 87% as feasible; hyperoxia (PaO\textsubscript{2} >85 is not indicated)

- Ventilation
  - Avoid hyperexpansion of the lungs and decreased cardiac return
    - Inspiratory time short (<0.3 seconds)
    - Peak pressures moderate (<35 if possible)
    - PEEP low (2-3)
    - Ventilatory rate rapid (60-120 breaths/minute).
  - These infants often have markedly abnormal V/Q with parts of the lungs being relatively normal. They do not usually tolerate high PEEP's or longs inspiratory times.
  - Consider high frequency ventilation early if requiring Peak pressures >35 to ventilate or oxygenate or if interstitial air or pneumothorax is high risk. Consider beginning mechanical ventilation with High Frequency in infants with diaphragmatic hernia
  - Avoid alveolar hypoxemia.
  - Avoid hand ventilating these infants during periods of hypoxemia. This often induces excessive barotrauma.
  - Wean ventilation very cautiously once improvement is seen

- Sedation
  - Consider sedation for all infants who are being ventilated to avoid agitation. Fentanyl has less effect on blood pressure than morphine and may be the preferred sedative. Drip infusions may be more effective than intermittent bolus.
  - For infants who are fighting the ventilator and are on very high settings, neuromuscular blockade with pavulon may be necessary. Pavulon dose = 0.1 mg/kg for initial dose

- Nitric Oxide
  - Given as an inhaled gas, NO acts directly on pulmonary vessels to cause vasodilation without systemic vasodilation. May be given by endotracheal tube and by nasal cannula in babies who do not require mechanical ventilation. Start at 20 ppm and measure metHgb levels at least daily while being administered. MethHgb levels can be run off blood gases that are sent to the lab (same specimen.)
  - Specifics on use of nitric oxide at CPMC
  - Controversy exists on the proper dose of inhaled nitric oxide in preterm infants. Studies suggest restriction of dose to 5 ppm is prudent.

- ECMO
  - Consider sending infant to ECMO center if requiring excessive pressure to maintain either oxygen or carbon dioxide in acceptable range. Send early rather than after barotrauma has occurred. See below for ECMO criteria

- Fluids
  - Use volume expansion as necessary to maintain central venous pressure between 5 and 10. Adjust crystalloid infusion rates appropriately if renal function is poor and urine output decreased.
- **Blood pressure**
  - Dopamine 2.5-20 microgram/kg/minute. Keep mean blood pressure at high end of normal range. Avoid dobutamine.

- **Pulmonary vasodilators**
  - iNO is the drug of choice.

When conventional therapy fails, these infants may be candidates for ECMO (extracorporeal membrane oxygenations) or a trial of inhaled nitric oxide.

**ECMO criteria are as follows:**
- >2000 grams
- No intraventricular hemorrhage
- No congenital heart disease or anomalies inconsistent with survival
- Failure of conventional ventilation and/or high frequency ventilation to maintain PO2 >50 in 100% oxygen on maximum support.

You may be asked for an "oxygenation" index. Commonly used ones are as follows:

- **Oxygenation index**: \( \frac{\text{MAP} \times \text{FiO}_2 \times 100}{\text{post ductal pO}_2} \)
  - **Criteria for ECMO**: >40

- **AaDO\(_2\) (Alveolar/arterial oxygen difference)**: \( 713 - 47 - \text{PO}_2 - \text{pCO}_2 \)
  - **Criteria for ECMO**: >610 for >8 hours or >605 for 4 hours with PIP >38
Treatment of Pneumothorax

Infants at Risk
- Resuscitated infants (iatrogenic from high pressures or intubation of right main steam bronchus during resuscitation)
- Severe RDS requiring high peak and peep pressures for ventilation
- Infants with meconium aspiration
- Infants with pulmonary intestinal emphysema
- Diaphragmatic hernia
- Infants with hypoplasia of lungs

Diagnosis
- Sudden drop in PO$_2$ initially, and later hypercapnea and acidosis
- Hypotension or hypertension (early) or decrease in pulse pressure
- Shift in cardiac impulse, asymmetric chest
- Bradycardia or tachycardia
- Acute narrowing of pulse pressure
- Physical diagnosis: Unequal breath sounds, uneven chest size, transillumination of chest should be performed while waiting for the Xray
- Chest x-ray

Therapy
- Prevention – aggressive weaning, close attention to bag pressures used, limit suctioning and use of in line suctioning (to avoid bagging)
- For acute deterioration, transilluminate chest. Needle pleural space with 22 or 24 gauge needle. (If transillumination was positive, needle that side first. If side not known, needle both pleural spaces.)
- Place chest tubes. In general, 15 cm of negative suction is sufficient for infants less than 1000 grams being ventilated on relatively low pressures, and 20 cms of negative pressure for infants greater than 1000 grams.
- Repeat chest x-ray, both AP and lateral for reduction.
- If infant is stable and not on mechanical ventilation, a chest tube may not be necessary for a non-tension pneumothorax.

Washout with 100% is contraindicated. Washout takes too long in a symptomatic infant and can cause oxidative stress. If the baby needs treatment, it should be mechanical with drainage.
Treatment of Pulmonary Interstitial Emphysema

Associated Conditions
- Severe RDS
- Meconium aspiration
- Group B strep sepsis
- Ventilation for any reason in very immature infants

Management
- Consider high frequency ventilation early
- If using conventional ventilator, keep mean airway pressure as low as tolerated.
- Keep inspiratory time low, <0.25 sec.
- If emphysema is focal (e.g. RML) or on one side, position infant so that emphysematous side is dependent and less well ventilated. To effectively work infant must stay in this position for 12-24 hours.
- Keep infants dry - limit fluids to insensible water loss and urine output.
- Be alert for signs of pneumothorax and pneumomediastinum.
Care of Infants with Chronic Lung Disease

Incidence and Etiology

- The incidence of CLD in the NBICU at CPMC is 20% of infants with RDS requiring mechanical ventilation for over 24 hours. CLD occurs most frequently in infants ventilated for RDS with B.W.’s <1250 gms and may reach an incidence of 60% in infants <750 g. CLD has also been seen in term infants and in preterms ventilated for apnea without RDS.
- Clinical factors implicated in the development of CLD are immature lungs, oxygen, mechanical ventilation and subsequent barotrauma, pulmonary edema, patent ductus arteriosus, excessive fluid administration and deficient antioxidant mechanisms. Infants who are ventilated to maintain low or normal pCO2’s in the first days of life also have an increased incidence of RDS.

Prevention

- Avoiding mechanical ventilation is probably the single most important factor in prevention. As this is obviously not always possible, when ventilating use minimal pressure and rate to maintain oxygenation. Ventilate to acceptable pCO2, not necessarily normal pCO2 (e.g. 50-60). Wean the ventilator aggressively.
- Early or prophylactic surfactant treatment may be more helpful than rescue treatment, although not all CLD will be prevented with surfactant
- Avoid nosocomial infections

Diagnosis

- Clinical
  - F1O2 and/or ventilation dependency (usually >30% O2 after 4 weeks, or still ventilated)
  - Retractions, rales, tachypnea, wheezing
  - CO2 retention
  - Need for oxygen at 36 weeks corrected age
- Radiological
  - Persistent granularity beyond 2 weeks of age
  - Areas of atelectasis, hyperinflation, strands of increased density, “bubbly lungs”

Treatment

- Patience! Supportive Care, Time
- Oxygen
  - Maintain PO2 between 55 and 75. Avoid hypoxemia as that may increase pulmonary artery pressure and therefore increase shunting
  - When possible, keep F1O2 <60%
  - Nasal Cannula Oxygen: In infants with chronic lung disease it is occasionally desirable to change the infant to nasal cannula oxygen (e.g. infants in open cribs, home oxygen). The fractional concentration of oxygen delivered by this route is variable and depends on inspiratory flow rate, minute ventilation, position of cannula in the nares and percentage of nasal vs. oral breathing. Although estimates of approximate oxygen delivery are listed below (J Peds 103:929, Dec. 1983) frequent monitoring of saturations by pulse oximetry or PO2 by transcutaneous monitors is advised.

<table>
<thead>
<tr>
<th>Flow Rate of 100% O2 (per minute)</th>
<th>Appropriate O2 Delivered (F1O2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/16 L</td>
<td>26%</td>
</tr>
<tr>
<td>1/8 L</td>
<td>27%</td>
</tr>
<tr>
<td>1/4 L</td>
<td>31%</td>
</tr>
<tr>
<td>1/2 L</td>
<td>35%</td>
</tr>
<tr>
<td>3/4 L</td>
<td>40%</td>
</tr>
<tr>
<td>1 L</td>
<td>44%</td>
</tr>
</tbody>
</table>

Do not use flow rate >2 L/min with wall nasal cannula. This is very drying to the mucosa. If higher flows are needed use high flow modalities (be aware these may cause distending pressure.)
Ventilation
- Infants who require ventilation for hypercapnea should be ventilated at lowest possible pressures to minimize barotrauma.
- Wean from ventilator as soon as possible.

Fluids
- Moderate fluid restriction (usually <150 ml/kg/day of oral feeds or <120/kg/day of I.V. fluid. Balance need for fluid restriction with need for adequate caloric intake.

Calories
- Give maximal calories in minimal fluid (at least 120 cal/kg/day - often require 140 cal/kg/day for growth)
- Use 24 to 28 cal/oz formulas. In theory, providing extra calories as fat instead of carbohydrates lowers the respiratory quotient, decreasing CO2 production.
- Supply adequate calcium, phosphorus and Vitamin D

Medications
- Diuretics: Some infants appear to respond to diuretics. Consider a trial of diuretics. If no response within 3-7 days, discontinue or use intermittently.
  - Lasix (1 mg/kg/dose q 12’ IV or IM, 2-4 mg/kg/dose q 8-12’ po)
  - Add Diuril 20-40 mg/kg/day po divided q 12’ if Lasix is given for >5 days. Conserves calcium.
  - The risk of nephrocalcinosis is higher in infants on furosemide. Monitor carefully.
  - For infants with severe electrolyte disturbances (e.g. low sodium and chloride, use a combination of Diuril and Aldactone (2.5 mg/kg/day).
- Bronchodilators
  - Aminophylline and aerosols may be useful if bronchospasm is evident.
  - Albuterol aerosols. Doses range from 0.02 ml/kg/dose of 0.5% (5 mg/ml) solution to 0.2 ml/kg/dose. Begin with lower dose and increase if no response. Give q 6-8 hours.
  - Side effects: Tachycardia, arrhythmias, agitation
  - If side effects are pronounced:
    - Decrease dose of medication
    - Increase duration of treatment (e.g. concentration and length of inhaling)
- Inhaled steroids have been used, though no clinical trials are available to show effectiveness. Beclovent or Vanceril are available in MDI form. Dose is 1-2 puffs every 8-12 hours. Consider using nystatin swabs to prevent thrush.
- Systemic Steroids
  - Start with hydrocortisone trial: 1 mg/kg/dose every 8 hours. Initial dose for 3 days, then reduce by 50% for 3 days, then reduce by 50% for 3 days then off – weaning dose will need to be based on response
  - If refractory to weaning ventilation consider short pulse of dexamethasone
    - 0.05-0.1 mg/kg/dose given q 12 hours. Initial dose for 3 days then cut by 50% for 3 days then cut by 50% for 3 days then off
  - Consider impact of reflux, fatigue with feeds and episodes of aspiration in the course of the disease

Prevent ventilator associated pneumonias by strict adherence to VAP bundle (slide set on VAP prevention)
- Treat infections aggressively. Most common pulmonary infections in these infants are ventilator associated infections of colonizing organisms (coag negative staph, gram negative rods.) Culture periodically for CMV. Culture ET aspirates if clinical condition deteriorates.
- Keep hematocrit >35. Begin EPOGEN when receiving >50 cal/kg enterally. Continue epogen treatment to 40 weeks corrected age.
- Some infants may require sedation for extreme irritability. Consider lorazepam as needed.

Monitoring
- Blood Gases
  - Use saturation monitor to adjust FIO2 when possible. If infant is >36 weeks adjusted age and eyes are mature, keep saturation > 92%.
Do ABG’s as indicated or when changes in O₂ or ventilation are made. Babies not requiring mechanical ventilation also require periodic blood gasses to look for CO₂ retention.

- Keep PO₂ 55-75, PCO₂ 50-60 or higher if tolerated, pH 7.35-7.45. If pH is normal, and PCO₂ high, do not increase ventilation

- **EKG, Echocardiogram**
  - At least one/month to look for RVH, LVH, increased pulmonary pressure.

- **Blood pressure:** Infants with CLD have a higher incidence of hypertension. Captopril is first line drug if blood pressure ≥ 2 S.D. above norm for age.

- **Growth and Development**
  - Daily weights and calorie counts
  - Weekly lengths and head circumference PLOT on curve
  - Developmental assessments when at term and monthly thereafter

- **Metabolic Panels**
  - Check x-rays for signs of osteopenia, rickets, fractures
  - Measure serum Ca and PO₄ q 2-3 weeks. Keep serum Ca 8-10 mg%, PO₄ 5-7 mg%. Infants on furosemide are particularly prone to lose large amounts of calcium in the urine. Diuril will help block Lasix induced calciuria.

- Renal ultrasounds beginning at six weeks to look for nephrocalcinosis.

**Environment**

- As these infants may require prolonged hospitalization beyond the corrected age of 40 weeks, it is helpful to provide an “age appropriate” environment. Allow the babies undisturbed rest periods. Keep in quiet area. Try to have consistent caretakers. Encourage frequent parental visiting and care. Get OT/PT and play therapist involved to provide appropriate toys, music, etc. for age.
Hematologic

Anemia

Traditionally anemia in a “just born” baby was defined as a hematocrit of less than 40%. Mean cord blood hematocrit is 50.2% with an SD of 6.9%.

What is more important than the actual hematocrit are
1) Why is the baby anemic?
2) Is the baby symptomatic?

Causes of anemia

- Blood loss:
  - Fetomaternal, Twin to Twin
  - Rupture of umbilical vessels or abnormalities of the vessels (velamentous insertion)
  - Loss into or via the placenta (abruption, placenta previa, surgical incision)
  - Internal hemorrhage: subgaleal, giant cephalhematoma/caput, intracerebral or intra-abdominal bleed (retroperitoneal, rupture of liver/spleen)

- Hemolysis:
  - Immune: Rh incompatibility, other incompatibility
  - Infection: sepsis, syphilis, TORCH
  - DIC
  - Macro/microangiopathic: cavernous hemangioma, AV malformation, Large vessel thrombi, renal arterial stenosis, Coarctation of the aorta
  - Red cell membrane disorders
  - Red cell enzyme deficiencies
  - Hemoglobinopathies

- Low production:
  - Diamond-Blackfan syndrome
  - Pearson’s syndrome
  - Congenital dyserythropoietic anemia
  - Congenital viral infections: rubella, CMV, parvovirus, adenovirus
  - Trisomy 21

Initial diagnostic tests:

- Careful history, physical exam
- CBC, retic, red cell indices, direct antibody test (Coomb’s, DAT), smear
- If fetomaternal transfusion is suspected: Kleihauer-Betke on mother (looking for fetal cells in maternal circulation).
- Examine the placenta if indicated
- Evaluate for coagulopathy if indicated

Symptoms of anemia

- Acute blood loss:
  - Clinical findings may include: acute distress, pallor, shallow, rapid respiration (may be irregular), tachycardia, signs of shock.
  - Hematocrit may be normal if intravascular volume has not yet equilibrated. Hematocrit may fall over time.
  - Treatment: volume expansion, red cell transfusion, supportive therapy, may need treatment of coagulopathy, DIC

- Chronic blood loss:
  - Clinical signs may include: pallor disproportionate to degree of distress, tachypnea, tachycardia, signs of congestive heart failure (rapid, weak pulses, poor perfusion, hepatomegaly)
  - Hematocrit will be low.
If baby has a very low hematocrit and is euvolemic and/or has signs of congestive failure, volume expansion and simple red cell transfusion may not be a safe method to increase the red cell volume. In these cases an augmentation exchange transfusion with packed red cells is often required.

The amt of packed cells to be used for *isovolemic* augmentation exchange:

Volume (ml) of packed cells to be exchanged =

\[
\frac{\text{Weight in kg} \times \text{blood volume per kg} \times (\text{desired Hct} - \text{observed Hct})}{\text{Hct of PRBC unit} - \frac{\text{desired Hct} + \text{observed Hct}}{2}}
\]

Blood volume for most newborns is 80 – 95 ml/kg
Hct of packed red cell units is 70-80%

- Do push-pull method via appropriate vascular access in appropriate aliquots (10 mls in term babies). May also do isovolemically using 2 lines – for example pull out from UAC and run blood in PIV as constant infusion.
- As in all exchange transfusions this volume is only an estimate. Other factors such as speed of the exchange, actual blood volume of the baby, actual hct of the packed cells, equilibration time etc, will effect the end hematocrit. It may be useful to check a hematocrit near the end of the exchange and make appropriate adjustments to the volume to be exchanged.

Be sure to collect blood for any and all testing (i.e. State Newborn Screen, G6PD, hemoglobin electrophoresis etc.) prior to any transfusion of red cells.

Nathan and Oski, Hematology of Infancy and Childhood, Saunders, 7th Ed. 2009, pg 36.
Bleeding Newborn

Babies are born in a state characterized by decreased coagulation and anticoagulation factors. The coagulation system can be easily overwhelmed. The system can be overwhelmed by trauma, thrombosis, sepsis and DIC.

There can also be bleeding because of the absence of various clotting factors.

Initially the approach can be separated by the clinical status of the baby:

- Well appearing infant:
  - Factor deficiency
  - Neonatal alloimmune thrombocytopenia

- Sick infant:
  - DIC
  - Underlying cause for the coagulation system to be overwhelmed

- Getting a complete history of the pregnancy, mother’s medical condition and delivery may also be revealing. Was the mother on Dilantin, have ITP, pre-eclampsia, a viral infection?

- A thorough exam looking for signs of trauma, thrombosis or DIC may also be helpful.
- Make sure the baby received vitamin K.
- Get a CBC, PT, PTT and fibrinogen level (at CPMC a coag panel II in PCIS gets you a PT, PTT, fibrinogen and a platelet count)
- If specific factor deficiency is suspected, draw these labs.
- If liver malfunction is suspected evaluate for this.

Treat according to what is revealed by lab determinations.

- Be sure to send diagnostic/confirmatory tests prior to the infusion of blood products that may interfere with such testing.
- Fresh Frozen Plasma contains all clotting factors.
- Cryoprecipitate contains mainly Factor VIII, XIII, Fibrinogen, von Willebrand's factor, Fibronectin. Use this product when the PTT is prolonged and the PT is normal and/or Fibrinogen/Fibronectin is needed
- Transfuse platelets in a bleeding baby if the platelet count is less than 50,000 per microliter. If NAIT is suspected and PLA-1 negative platelets are not available, random donor platelets may be used. Continue to transfuse platelets in 10 ml/kg aliquots until platelet levels rise and are stable (all the anti-platelet antibodies are used up by the platelets infused).

Look for underlying causes and treat these as well.

The following tables are adapted from Nathan and Oski’s Hematology of Infancy and Childhood, Saunders, 7th edition, 2009, pp 148-154.

### TABLE 5-1 -- Coagulation Screening Tests and Coagulation Factor Levels in Fetuses, Full-Term Infants, and Adults

<table>
<thead>
<tr>
<th>Parameter</th>
<th>19-23 (n = 20)</th>
<th>24-29 (n = 22)</th>
<th>30-38 (n = 22)</th>
<th>Newborn (n = 60)</th>
<th>Adult (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>32.5 (19-45)</td>
<td>32.2 (19-44)</td>
<td>22.6 (16-30)</td>
<td>16.7 (12.0-23.5)</td>
<td>13.5 (11.4-14.0)</td>
</tr>
<tr>
<td>PT (INR)</td>
<td>6.4 (1.7-11.1)</td>
<td>6.2 (2.1-10.6)</td>
<td>3.0 (1.5-5.0)</td>
<td>1.7 (0.9-2.7)</td>
<td>1.1 (0.8-1.2)</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>168.8 (83-250)</td>
<td>154.0 (87-210)</td>
<td>104.8 (76-128)</td>
<td>44.3 (35-52)</td>
<td>33.0 (25-39)</td>
</tr>
<tr>
<td>TCT (sec)</td>
<td>34.2 (24-44)</td>
<td>26.2 (24-28)</td>
<td>21.4 (17.0-23.3)</td>
<td>20.4 (15.2-25.0)</td>
<td>14.0 (12-16)</td>
</tr>
<tr>
<td>Factor I von Clauss (g/L)</td>
<td>0.85 (0.57-1.50)</td>
<td>1.12 (0.65-1.65)</td>
<td>1.35 (1.25-1.65)</td>
<td>1.68 (0.95-2.45)</td>
<td>3.0 (1.78-4.50)</td>
</tr>
<tr>
<td>Factor I Ag (g/L)</td>
<td>1.08 (0.75-1.50)</td>
<td>1.93 (1.56-2.40)</td>
<td>1.94 (1.30-2.40)</td>
<td>2.65 (1.68-3.60)</td>
<td>3.5 (2.50-5.20)</td>
</tr>
</tbody>
</table>
**FETUSES (WEEKS’ GESTATION)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>19-23 (n = 20)</th>
<th>24-29 (n = 22)</th>
<th>30-38 (n = 22)</th>
<th>Newborn (n = 60)</th>
<th>Adult (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor IIc (%)</td>
<td>16.9 (10-24)</td>
<td>19.9 (11-30)</td>
<td>27.9 (15-50)</td>
<td>43.5 (27-64)</td>
<td>98.7 (70-125)</td>
</tr>
<tr>
<td>Factor VIIc (%)</td>
<td>27.4 (17-37)</td>
<td>33.8 (18-48)</td>
<td>45.9 (31-62)</td>
<td>52.5 (28-78)</td>
<td>101.3 (68-130)</td>
</tr>
<tr>
<td>Factor IXc (%)</td>
<td>10.1 (6-14)</td>
<td>9.9 (5-15)</td>
<td>12.3 (5-24)</td>
<td>31.8 (15-50)</td>
<td>104.8 (70-142)</td>
</tr>
<tr>
<td>Factor Xc (%)</td>
<td>20.5 (14-29)</td>
<td>24.9 (16-35)</td>
<td>28.0 (16-36)</td>
<td>39.6 (21-65)</td>
<td>99.2 (75-125)</td>
</tr>
<tr>
<td>Factor Vc (%)</td>
<td>32.1 (21-44)</td>
<td>36.8 (25-50)</td>
<td>48.9 (23-70)</td>
<td>89.9 (50-140)</td>
<td>99.8 (65-140)</td>
</tr>
<tr>
<td>Factor VIIIc (%)</td>
<td>34.5 (18-50)</td>
<td>35.5 (20-52)</td>
<td>50.1 (27-78)</td>
<td>94.3 (38-150)</td>
<td>101.8 (55-170)</td>
</tr>
<tr>
<td>Factor XIIc (%)</td>
<td>13.2 (8-19)</td>
<td>12.1 (6-22)</td>
<td>14.8 (6-26)</td>
<td>37.2 (13-62)</td>
<td>100.2 (70-135)</td>
</tr>
<tr>
<td>Factor XIIc (%)</td>
<td>14.9 (6-25)</td>
<td>22.7 (6-40)</td>
<td>25.8 (11-50)</td>
<td>69.8 (25-105)</td>
<td>101.4 (65-144)</td>
</tr>
<tr>
<td>PK (%)</td>
<td>12.8 (8-19)</td>
<td>15.4 (8-26)</td>
<td>18.1 (8-28)</td>
<td>35.4 (21-53)</td>
<td>99.8 (65-135)</td>
</tr>
<tr>
<td>HMWK (%)</td>
<td>15.4 (10-22)</td>
<td>19.3 (10-26)</td>
<td>23.6 (12-34)</td>
<td>38.9 (28-53)</td>
<td>98.8 (68-135)</td>
</tr>
</tbody>
</table>


All values are given as means followed in parentheses by the lower and upper boundaries including 95% of the population.

Ag, antigen; APTT, activated partial thromboplastin time; HMWK, high-molecular-weight kininogen; INR, international normalized ratio; PK, prekallikrein; PT, prothrombin time; TCT, thrombin clotting time.

* $P < .01.$

† $P < .05.$

**TABLE 5-2 -- Reference Values for Coagulation Tests in Healthy Full-Term Infants during the First 90 days of Life with the ACL Analyzer**

<table>
<thead>
<tr>
<th>Coagulation Tests</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 30</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>13.0 (10.1-15.9)</td>
<td>12.4 (10.0-15.3)</td>
<td>11.8 (10.0-14.3)</td>
<td>11.9 (10.0-14.2)</td>
</tr>
<tr>
<td>INR</td>
<td>1.00 (0.53-1.62)</td>
<td>0.89 (0.53-1.48)</td>
<td>0.79 (0.53-1.26)</td>
<td>0.81 (0.53-1.26)</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>42.9 (31.3-54.5)</td>
<td>42.6 (25.4-59.8)</td>
<td>40.4 (32.0-55.2)</td>
<td>37.1 (29.0-50.1)</td>
</tr>
<tr>
<td>TCT (sec)</td>
<td>23.5 (19.0-28.3)</td>
<td>23.1 (18.0-29.2)</td>
<td>24.3 (19.4-29.2)</td>
<td>25.1 (20.5-29.7)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.83 (1.67-3.99)</td>
<td>3.12 (1.62-4.62)</td>
<td>2.70 (1.62-3.78)</td>
<td>2.43 (1.50-3.79)</td>
</tr>
<tr>
<td>Factor II (U/mL)</td>
<td>0.48 (0.26-0.70)</td>
<td>0.63 (0.33-0.93)</td>
<td>0.68 (0.34-1.02)</td>
<td>0.75 (0.45-1.05)</td>
</tr>
<tr>
<td>Factor V (U/mL)</td>
<td>0.72 (0.34-1.08)</td>
<td>0.95 (0.45-1.45)</td>
<td>0.96 (0.62-1.34)</td>
<td>0.90 (0.48-1.32)</td>
</tr>
<tr>
<td>Factor VII (U/mL)</td>
<td>0.66 (0.28-1.04)</td>
<td>0.89 (0.35-1.43)</td>
<td>0.90 (0.42-1.38)</td>
<td>0.91 (0.39-1.43)</td>
</tr>
<tr>
<td>Factor VIII (U/mL)</td>
<td>1.00 (0.50-1.78)</td>
<td>0.88 (0.50-1.54)</td>
<td>0.91 (0.50-1.57)</td>
<td>0.79 (0.50-1.25)</td>
</tr>
<tr>
<td>VWF (U/mL)</td>
<td>1.53 (0.50-2.87)</td>
<td>1.40 (0.50-2.54)</td>
<td>1.28 (0.50-2.46)</td>
<td>1.18 (0.50-2.06)</td>
</tr>
<tr>
<td>Factor IX (U/mL)</td>
<td>0.53 (0.15-0.91)</td>
<td>0.53 (0.15-0.91)</td>
<td>0.51 (0.21-0.81)</td>
<td>0.67 (0.21-1.13)</td>
</tr>
<tr>
<td>Factor X (U/mL)</td>
<td>0.40 (0.12-0.68)</td>
<td>0.49 (0.19-0.79)</td>
<td>0.59 (0.31-0.87)</td>
<td>0.71 (0.35-1.07)</td>
</tr>
<tr>
<td>Factor XI (U/mL)</td>
<td>0.38 (0.10-0.66)</td>
<td>0.55 (0.23-0.87)</td>
<td>0.53 (0.27-0.79)</td>
<td>0.69 (0.41-0.97)</td>
</tr>
<tr>
<td>Factor XII (U/mL)</td>
<td>0.53 (0.13-0.93)</td>
<td>0.47 (0.11-0.83)</td>
<td>0.49 (0.17-0.81)</td>
<td>0.67 (0.25-1.09)</td>
</tr>
<tr>
<td>PK (U/mL)</td>
<td>0.37 (0.18-0.69)</td>
<td>0.48 (0.20-0.76)</td>
<td>0.57 (0.23-0.91)</td>
<td>0.73 (0.41-1.05)</td>
</tr>
<tr>
<td>HMWK (U/mL)</td>
<td>0.54 (0.06-1.02)</td>
<td>0.74 (0.16-1.32)</td>
<td>0.77 (0.33-1.21)</td>
<td>0.82 (0.30-1.46)</td>
</tr>
<tr>
<td>Factor XIIa (U/mL)</td>
<td>0.79 (0.27-1.31)</td>
<td>0.94 (0.44-1.44)</td>
<td>0.93 (0.39-1.47)</td>
<td>1.04 (0.36-1.72)</td>
</tr>
<tr>
<td>Factor XIIb (U/mL)</td>
<td>0.76 (0.30-1.22)</td>
<td>1.06 (0.32-1.80)</td>
<td>1.11 (0.39-1.73)</td>
<td>1.16 (0.48-1.84)</td>
</tr>
</tbody>
</table>

All factors except fibrinogen are expressed as units per milliliter, with pooled plasma containing 1.0 U/mL. All values are expressed as means followed by the lower and upper boundary encompassing 95% of the population. Between 40 and 77 samples were assayed for each value in newborns. Some measurements were skewed because of a disproportionate number of high values. All infants received 1 mg vitamin K intramuscularly at birth. The following reagents were used for coagulation screening tests: prothrombin time (Dade C rabbit thromboplastin), activated partial thromboplastin time (Dade FS). Measurements were made with an ACL analyzer.

APTT, activated partial thromboplastin time; HMWK, high-molecular-weight kininogen; INR, international normalized ratio; PK, prekallikrein; PT, prothrombin time; TCT, thrombin clotting time; VWF, von Willebrand factor.

**Values indistinguishable from those of adults.**

**TABLE 5-4 -- Reference Values for Coagulation Tests in Healthy Premature Infants (30 to 36 Weeks' Gestation) during the First 90 Days of Life**

<table>
<thead>
<tr>
<th>Coagulation Tests</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 30</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>13.0 (10.6-16.2)</td>
<td>12.5 (10.0-15.3)</td>
<td>11.8 (10.0-13.6)</td>
<td>12.3 (10.0-14.6)</td>
</tr>
<tr>
<td>INR</td>
<td>1.0 (0.61-1.70)</td>
<td>0.91 (0.53-1.48)</td>
<td>0.79 (0.53-1.11)</td>
<td>0.88 (0.53-1.32)</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>53.6 (27.5-79.4)</td>
<td>50.5 (26.9-74.1)</td>
<td>44.7 (26.9-62.5)</td>
<td>39.5 (28.3-50.7)</td>
</tr>
<tr>
<td>TCT (sec)</td>
<td>24.8 (19.2-30.4)</td>
<td>24.1 (18.8-29.4)</td>
<td>24.4 (18.8-29.9)</td>
<td>25.1 (19.4-30.8)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.43 (1.5-3.73)</td>
<td>2.80 (1.6-4.18)</td>
<td>2.54 (1.5-4.14)</td>
<td>2.46 (1.5-3.52)</td>
</tr>
<tr>
<td>Factor V (U/mL)</td>
<td>0.45 (0.20-0.77)</td>
<td>0.57 (0.29-0.85)</td>
<td>0.57 (0.36-0.95)</td>
<td>0.68 (0.30-1.06)</td>
</tr>
<tr>
<td>Factor VII (U/mL)</td>
<td>0.88 (0.41-1.44)</td>
<td>1.00 (0.46-1.54)</td>
<td>1.02 (0.48-1.56)</td>
<td>0.99 (0.59-1.39)</td>
</tr>
<tr>
<td>Factor XII (U/mL)</td>
<td>0.67 (0.21-1.13)</td>
<td>0.84 (0.30-1.38)</td>
<td>0.83 (0.21-1.45)</td>
<td>0.87 (0.31-1.43)</td>
</tr>
<tr>
<td>Factor VIII (U/mL)</td>
<td>1.11 (0.50-2.13)</td>
<td>1.15 (0.53-2.05)</td>
<td>1.11 (0.50-1.99)</td>
<td>1.06 (0.58-1.88)</td>
</tr>
<tr>
<td>VWF (U/mL)</td>
<td>1.36 (0.78-2.10)</td>
<td>1.33 (0.72-2.19)</td>
<td>1.36 (0.66-2.16)</td>
<td>1.12 (0.75-1.84)</td>
</tr>
<tr>
<td>Factor IX (U/mL)</td>
<td>0.35 (0.19-0.65)</td>
<td>0.42 (0.14-0.74)</td>
<td>0.44 (0.13-0.80)</td>
<td>0.59 (0.25-0.93)</td>
</tr>
<tr>
<td>Factor X (U/mL)</td>
<td>0.41 (0.11-0.71)</td>
<td>0.51 (0.19-0.83)</td>
<td>0.56 (0.20-0.92)</td>
<td>0.67 (0.35-0.99)</td>
</tr>
<tr>
<td>Factor XI (U/mL)</td>
<td>0.30 (0.08-0.52)</td>
<td>0.41 (0.13-0.69)</td>
<td>0.43 (0.15-0.71)</td>
<td>0.59 (0.25-0.93)</td>
</tr>
<tr>
<td>Factor XII (U/mL)</td>
<td>0.38 (0.10-0.66)</td>
<td>0.39 (0.09-0.69)</td>
<td>0.43 (0.11-0.75)</td>
<td>0.61 (0.15-1.07)</td>
</tr>
<tr>
<td>PK (U/mL)</td>
<td>0.33 (0.09-0.57)</td>
<td>0.45 (0.25-0.75)</td>
<td>0.59 (0.31-0.87)</td>
<td>0.79 (0.37-1.21)</td>
</tr>
<tr>
<td>HMWK (U/mL)</td>
<td>0.49 (0.09-0.89)</td>
<td>0.62 (0.24-1.00)</td>
<td>0.64 (0.16-1.12)</td>
<td>0.78 (0.32-1.24)</td>
</tr>
<tr>
<td>Factor XIIa (U/mL)</td>
<td>0.70 (0.32-1.08)</td>
<td>1.01 (0.57-1.45)</td>
<td>0.99 (0.51-1.47)</td>
<td>1.13 (0.71-1.55)</td>
</tr>
<tr>
<td>Factor XIIb (U/mL)</td>
<td>0.81 (0.35-1.27)</td>
<td>1.10 (0.68-1.58)</td>
<td>1.07 (0.57-1.57)</td>
<td>1.21 (0.75-1.67)</td>
</tr>
</tbody>
</table>


All factors except fibrinogen are expressed as units per milliliter, with pooled plasma containing 1.0 U/mL. All values are given as means followed by the lower and upper boundary encompassing 95% of the population. Between 40 and 96 samples were assayed for each value in newborns. Some measurements were skewed because of a disproportionate number of high values. All infants received 1 mg vitamin K intramuscularly at birth. The following reagents were used for coagulation screening tests: prothrombin time (Dade C rabbit thromboplastin), activated partial thromboplastin time (Dade FS). Measurements were made with an ACL analyzer.

APTT, activated partial thromboplastin time; FactorVIII, factorVIII procoagulant; HMWK, high-molecular-weight kininogen; INR, international normalized ratio; PK, prekallikrein; PT, prothrombin time; TCT, thrombin clotting time; VWF, von Willebrand factor.

*Values indistinguishable from those of adults.*

†Values skewed because of a disproportionate number of high values.
**Polycythemia**

**Definition**
- Central venous hematocrit greater than 65% on at least two samples in a term infant (taken from a large, free-flowing antecubital vein.) Hct should be measured at 6-8 hours.
- Umbilical venous hematocrit greater than 63%

**Diagnosis**
- Infants who are SGA, IDM, twins or have a history of perinatal asphyxia (Apgar < at 5 minutes or history of perinatal blood loss), have a screening capillary hematocrit at 4-6 hours of age. Any infant who appears plethoric or has symptoms should have a screening hematocrit done.
- If capillary hematocrit is >70%, a central venous hematocrit is drawn.

**Infants at Risk**
- SGA infants
- Infants of diabetics (including gestational diabetes)
- Post-mature infants
- Infants of mothers with pre-eclampsia
- Twin-twin transfusion
- Iatrogenic (large placental transfusion from delay in cord clamp)
- Down syndrome and other trisomies
- Beckwith syndrome
- Congenital adrenal hyperplasia

**Symptoms and Signs**
- CNS
  - Lethargy and hypotonia
  - Jitteriness or extreme tremulousness
- Cardiopulmonary:
  - Tachypnea and respiratory distress
  - Congestive heart failure
  - Apnea
  - Pulmonary hypertension
- Gastrointestinal
  - Significant feeding difficulty and/or vomiting
  - Abdominal distension
  - Necrotizing enterocolitis
- Metabolic
  - Hypoglycemia
  - Hypocalcemia
  - Hypomagnesemia
- Hematologic
  - Jaundice
  - Thrombocytopenia
  - Fragmented red cells
- Renal
  - Oliguria
  - Renal vein thrombosis

**Therapy**
Consult with attending before treating. Values given below are not absolute. There is no clear evidence that therapy is useful in an asymptomatic infant.

**Central Hct 65-70% and asymptomatic**
• Screen for hypoglycemia with glucometer
• Consider need to hydrate p.o. or I.V.
• Recheck central venous hct in 6-8 hours
• Watch carefully for development of symptoms

Central Hct >65% and symptomatic
• Hydrate for 4 hours and repeat central hematocrit. SCREEN for hypoglycemia (glucose <45 mg/dl)
• If still greater than 65%, hyperviscosity should be suspected and infant should be prepared for a partial exchange to bring hct to less than 60.

Central venous Hct >70% (symptomatic or asymptomatic)
• Immediately repeat the hct to avoid errors
• Prepare to do partial exchange

Partial Exchange
• Use umbilical vein catheter. (Check position by x-ray before proceeding). Do not exchange in the liver. If unable to pass beyond liver, pull back and use for blood removal, and give colloid by I.V. or use umbilical artery catheter.
• Check umbilical venous hematocrit as soon as catheter is inserted.
• If UV hct is less than 63, the exchange is probably not necessary.
• If UV hct is greater than 63, proceed with exchange.

Volume of saline to exchange =

\[
\text{Blood volume (85 ml/kg) } \times (\text{Observed Hct - Desired Hct})
\]
\[
\text{Observed Hct}
\]

Another way to look at it

\[
(\text{Weight in kg } \times 85) \times (\text{Observed Hct - Desired Hct})
\]
\[
\text{Observed Hct}
\]

• Use normal saline for the exchange
• In term infants, exchange blood for plasma in 10 - 20 ml aliquots
• Remove catheter after exchange. Monitor in ICN for minimum of 6 hours.
Thrombocytopenia

Principles

- Definition: <150,000 platelets per microliter
- Without clinical evidence or with petechiae, purpura, bruising
- Thrombocytopenia may occur alone, or may be associated with DIC.

Causes

Immune disorders

- Maternal immune disorders
  - Maternal ITP with passive transfer of antibodies
  - Systemic lupus erythematosus
  - Drug-induced platelet destruction quinine, quinidine, PAS, sulfonamides
- Alloimmune neonatal thrombocytopenia: Transfer of antibodies against platelet antigens, usually Pl\(\text{A}^1\). Mother is usually Pl\(\text{A}^1\) negative and baby is Pl\(\text{A}^1\) positive. (Note: this condition follows a similar pathophysiology to rH sensitization)

Increased platelet consumption

- DIC
- Giant hemangiomia
- Necrotizing enterocolitis
- Stasis: renal vein thrombosis, polycythemia
- Hypertension

Injury to platelets

- Hypoxia, ischemia
- Sepsis, acidosis
- Drug injury: Chlorothiazides, aspirin, hydralazine

Obstetrical complications

- Pregnancy induced hypertension (pre-eclampsia), maternal hypertension
- Placental abruption
- Amniotic fluid
- Dead twin fetus

Decreased production

- Viral or bacterial infections. Including congenital infections such as toxoplasmosis, CMV, rubella, herpes, syphilis, ECHO and enterovirus.
- Leukemia
- Congenital megakaryocytic hypoplasia: (Fanconi’s, Trisomy 13, 18 and 21)
- Inherited: Wiskott-Aldrich, May-Hegglin anomaly, Bernard Soulier Syndrome

Miscellaneous

- Metabolic disorders: glycinemia, methylmalonic acidemia, isovaleric acidemia
- Congenital thyrotoxicosis
- Cold stress
### Approach to the Thrombocytopenic Infant

- **Maternal**
  - History (see causes)
  - Prenatal diagnosis by PUBS may be indicated with maternal ITP and low platelet count, and/or history of allo immune thrombocytopenia in previous newborn.
  - Platelet count
- Clinical examination: Look for Petechiae, jaundice, hepatosplenomegaly, congenital anomalies.
- Laboratory investigation: CBC, platelet count, smear, Coombs test, PT, PTT, fibrinogen (coag panel II at CPMC)
  - Consider:
    - Torch titers - toxoplasmosis, CMV, rubella, herpes, syphilis, ECHO and enterovirus
    - Bacterial and viral cultures

### Therapy
- Treat underlying or predisposing illnesses.
- Platelet transfusions:
  - In general, keep platelet count ≥ 50,000.
  - For **well term** infants, if **not bleeding**, transfuse if platelet count is <20,000
  - If NAIT is suspected and PLA-1 negative platelets are not available, random donor platelets may be used. Continue to transfuse platelets in 10 ml/kg aliquots until platelet levels rise and are stable (all the anti-platelet antibodies are used up by the platelets infused).

---

**Thrombocytopenia in *Sick* Infant**

<table>
<thead>
<tr>
<th>Normal PT, PTT</th>
<th>Abn PT, PTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Infection (no DIC)</td>
<td>- DIC</td>
</tr>
<tr>
<td>- Hypersplenism</td>
<td>- Sepsis</td>
</tr>
<tr>
<td>- Necrotizing enterocolitis</td>
<td>- Cold stress</td>
</tr>
<tr>
<td>- Marrow infiltration</td>
<td>- Acidosis</td>
</tr>
<tr>
<td>-</td>
<td>- Hypoxia</td>
</tr>
<tr>
<td>-</td>
<td>- Severe liver disease</td>
</tr>
</tbody>
</table>

**Thrombocytopenia in *Healthy* Infant**

<table>
<thead>
<tr>
<th>Mother's platelet count normal</th>
<th>Mother's platelets LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Neonatal alloimmune thrombocytopenia (NAIT)</td>
<td>- Maternal ITP</td>
</tr>
<tr>
<td>- Neonatal drug</td>
<td>- Maternal drugs</td>
</tr>
<tr>
<td>- Hemangioma</td>
<td>- Familial</td>
</tr>
<tr>
<td>- Congenital thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>- Maternal ITP in remission</td>
<td></td>
</tr>
<tr>
<td>- Congenital viral infection</td>
<td></td>
</tr>
</tbody>
</table>

*From Cloherty & Stark, Manual of Neonatal Care, 3rd ed., 1991*
Treatment of Anemia of Prematurity with Erythropoietin

Principle
Genetically engineered human erythropoietin is used to stimulate production of red blood cells and decrease the need for erythrocyte transfusions in high risk preterm infants (usually those with B.W. < 1200 grams and/or gestational age <31 weeks)

Background
- Infants born prematurely have limited ability to produce erythropoietin, even in the face of severe anemia. This results in anemia in the very low birth weight infants, frequently requiring multiple red cell transfusions. Numerous controlled clinical trials have shown that premature infants are capable of responding to exogenous erythropoietin with increased red cell production. Infants begin to make erythropoietin at 35 weeks gestation.
- Epoieten alpha is a product manufactured with recombinant DNA technology that has the same biological effects of endogenously produced erythropoietin. It acts on erythroid progenitors in the bone marrow, stimulating differentiation and cell division. Measurable effects on hematocrit and reticulocyte counts occur within two weeks of treatment.
- The only adverse side effect in preterm infants is neutropenia which occurs rarely and resolves with discontinuation of the drug.

Dose and Administration
- The dose of epogen is 250 units/kg three times/week given subcutaneously
  - Eligible infants may begin to receive epogen when they are receiving at least half their calories enterally and are able to tolerate oral iron.
  - Iron is started at 3 mg/kg/day and increased to 6 mg/kg/day when full feeds are tolerated.
  - All infants on epogen need additional Vitamin E (15 units/kg/day) because of increased erythropoiesis.

Monitoring
- Hematocrit and reticulocyte counts should be monitored weekly beginning one week after onset of therapy. The reticulocyte count should have increased to 200,000 by two weeks of treatment.
- Consider increasing Epogen dose if no response in two weeks.

Length of Treatment
- Discontinue treatment if hematocrit >45%
- Discontinue treatment at 35-36 weeks gestation in most infants.
- Continue treatment to 40 weeks corrected age in infants with chronic lung disease

Post-treatment
- The infant’s hematocrit is expected to drop after discontinuing epogen. Native erythropoietien will not be produced until the infant’s hemoglobin is low enough to stimulate production (often less than hct=28%). If infant is to be discharge, be sure that follow-up pediatrician knows the hematocrit and when the drug was stopped.
- Continue iron at 4 mg/kg/day after epogen is discontinued. Vitamin E may be discontinued.
Transfusion Therapy

Various blood products are given to infants in the NICU for a wide range of indications. The following outlines guidelines for their judicious usage.

How blood products are processed and supplied:

- **Irradiation**: Prevents lymphocytes from replicating and removes risk of graft vs. host disease
- **CMV negative**: If donor tests negative for antibodies to CMV, there is a decrease in the likelihood that the transfused blood will transmit latent CMV to the baby.
- **Leucodepletion**: Leucodepletion (removal of the majority of white blood cells) of the blood at collection is now relatively standard as it decreases transfusion reactions and also reduces CMV carrier risks.
  - The CMV virus can lie dormant in the white cells of persons who have been infected with CMV (and are now asymptomatic). It seems that a “critical” number of CMV containing cells are needed to convey infection in a transfusion recipient. Leucodepletion may bring the number of white cells below that critical number and this is the method that high CMV positive donor prevalence areas (such as parts of the Eastern Seaboard of the US) are using to lower CMV infection risk from PRBC transfusion. CMV positive donor prevalence in the San Francisco Bay Area is about 55-60%. It is still possible to get CMV donor negative units. Leucodepletion is seen as a second safeguard measure.
- **Designated or directed donor**: Family recruited blood donor who donates specifically for a given infant.
  - Necessary steps: (call the San Francisco Branch of Blood Centers of the Pacific at 415 567-6400 for questions)
    - Ask parents if they want to supply directed donor blood.
    - If they do, fill out the form. Request packed red cells, in 8-packs, irradiated and CMV negative. Neither type specific nor sickle dex negative blood is required. Make sure you fill out the baby’s blood group and type.
    - Inform parents that up to 5 days may be needed for processing and testing once the blood is collected. Also that up to 50% of donors are rejected because of positive CMV titers, so multiple donors are recommended.
    - Give parents the number for the Blood Center so the donor(s) can make an appointment to donate (special handling requires special staff).
    - The Blood Bank will charge a special collection/tracking fee for each directed donation (Medi-Cal patients are exempted) because these units require special handling.
- **Dedicated unit**: Unit set aside for infant's sole use. May be directed unit or from the blood bank. If unit is divided into multiple packs, use of dedicated units will decrease the number of different donors to which an infant will be exposed (donor exposures).
- **Washing**: Packed red cells may be rinsed and then resuspended in saline. This is done to remove the storage solution and its contents: potassium, antibodies, buffer, WBC. This is probably not necessary except under special circumstances. Once washed, red cells are only usable for 24 hours prior to being discarded.
- **Split Unit**: Division of unit into smaller “packs” so a single unit can be used for multiple transfusions. Once a pack is opened the blood is discarded after 24 hours because of FDA mandated precautions safeguarding against contamination. Split packs may also be referred to as “Quad Packs” when they contain packed red cells.
- **Satellite bags** (previously known as “8-packs”): A single unit of red cells can have multiple satellite bags attached with a sterile docking device (California campus blood bank does this for us and dispenses the needed aliquot in a sterile bag.) Even though the blood is not stored in these tiny bags, blood from the main unit can be drained into these bags when blood is ordered and thus multiple transfusions can be yielded per unit (the number is related to the volume of the transfusion and the outdate of the blood). The use of this system decreases donor exposures in infants likely to receive many transfusions. A dedicated pack should be ordered for infants that are very ill or have birth weights <1500 grams. This blood should be type specific or one of the O negative units we keep on hand for emergencies and cannot be washed prior to administration.
Packed Red Blood Cells (PRBC’s)

Uses:
- Symptomatic anemia at birth (Hct <40%)
- Replacement of iatrogenic losses (consider this in unstable tiny babies with >10% total blood volume over a week) and Hct <39%
- Hct <35-40% in infants with severe pulmonary or cardiac illness
- Hct <30% in stable preterm infants with signs and symptoms of anemia (this includes: tachycardia, tachypnea, poor weight gain, lethargy and perhaps apnea)

Product: Packed red cells (usual Hct 68-75%), unwashed (unless special circumstances require washing), leukocyte depleted, irradiated, CMV antibody negative, type specific or O negative. If only type compatible available consider washing.

Dose: 15 ml/kg, infused over 1-4 hours. Ideally given as continuous infusions but if access is an issue may be given as small pushes via umbilical lines. Maximum 10 ml/kg hour.

Estimation of transfusion volume for simple transfusion:

Volume (ml) of packed cells to be transfused =

\[
\frac{\text{Weight in kg} \times \text{blood volume per kg}}{\text{Hct of PRBC unit}} \times (\text{desired Hct} – \text{observed Hct})
\]

Blood volume for most newborns is 80 – 95 ml/kg
Hct of packed red cell units is 70-80%

The amt of packed cells to be used for isovolemic augmentation exchange:

Volume (ml) of packed cells to be exchanged =

\[
\frac{\text{Weight in kg} \times \text{blood volume per kg} \times (\text{desired Hct} – \text{observed Hct})}{\text{Hct of PRBC unit} – \frac{\text{desired Hct} + \text{observed Hct}}{2}}
\]

Blood volume for most newborns is 80 – 95 ml/kg
Hct of packed red cell units is 70-80%

Complications:
- Hemolytic transfusion reaction (shock, hemolysis, hemoglobinemia and hemoglobinuria) – if you see what you think is a reaction contact the blood bank at Cal immediately as specific lab testing is required
- Non hemolytic reactions: Reaction to proteins, WBC's, fragments, rash, changes in vital signs, bronchospasm (rare in infants)
- Hypothermia in small infants if blood is not warmed (blood is stored in refrigerator in blood bank)
- Fluid overload, congestive heart failure
- Hypoglycemia: secondary to interrupted glucose infusion during blood administration
- ? increased risk of ROP
- Suppression of infants own red cell production
- Infection risks and testing done on units to prevent
### Infection Risk per unit exposure Screening of US Donors

<table>
<thead>
<tr>
<th>Infection</th>
<th>Risk per unit exposure</th>
<th>Screening of US Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV 1 &amp; 2</td>
<td>1 / 1.8 million</td>
<td>Anti HIV ½; nucleic acid testing for HIV-1</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 / 2 million</td>
<td>Surface antigen, anti-HBcore</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 / 800,000</td>
<td>Anti-HCV, nucleic acid testing</td>
</tr>
<tr>
<td>CMV</td>
<td>Infrequent with leukoreduced and CMV negative</td>
<td>Anti-CMV</td>
</tr>
<tr>
<td>West Nile</td>
<td>Rare</td>
<td>Nucleic acid testing</td>
</tr>
<tr>
<td>Chagas</td>
<td>Rare</td>
<td>T cruzi antibody</td>
</tr>
<tr>
<td>Malaria</td>
<td>0.027 / million</td>
<td>Donors deferred for history or travel risk</td>
</tr>
<tr>
<td>Parvo B19</td>
<td>1 / 3,000-40,000</td>
<td>No routine screening done, varies on population</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>RBC: 1 / 30,000 Platelets: 1 / 200,000</td>
<td>All platelets are screened for bacterial growth before release</td>
</tr>
</tbody>
</table>

**Comments:**
If a large volume of red cells is needed (e.g. euvoletic infant with very low hct) consider a partial volume exchange with PRBC's. Once an infant's blood is typed and screened for antibodies, crossmatch is not necessary until the infant is greater than 4 months old.

### Platelets

**Use:**
- Platelet count < 50,000 with bleeding or at high risk for bleeding or very ill.
- Platelet count < 20,000 if asymptomatic

**Product:** Irradiated type (AB0) compatible single donor unit concentrated to 35-50 ml/unit dose (soft spun). Each unit contains 7.0 x 10^10 platelets. Kept at room temperature. Must be used within 5 days of collection.

**Dose:** 10 ml/kg to raise platelet count by 100,000.

**Complications:**
- Infection (same as with PRBC's)
- Transfusion reaction from WBC's in platelet prep (always a few left behind).

**Comments:**
- To test response, check platelet count 1 hour after infusion.
- There are “dried” platelet products that are very concentrated, but it is very difficult to use these from a practical standpoint (hard to get the product out of the bag).
- If isoimmunization is suspected, use maternal platelets or PlA1 negative platelets. If neither of these is available, you can just keep transfusing random donor platelets until you get a response (soak up the anti-platelet antibodies with infused platelets, or you may get PlA1 negative platelets by chance).

### White Blood Cells

**Use:** Controversial. Some studies show that WBC administration may be helpful for infants with sepsis and severe neutropenia (ANC < 1000). Optimally WBC's would only be given after documented bone marrow granulocyte depletion.

**Product:** Irradiated, ABO compatible, single donor unit, spun down.

**Dose:** 10 - 15 ml/kg.

**Complications:**
- Infection
- Systemic reactions
Graft vs. host disease

Comments:
WBC's take time to get (may be up to 8 hours). WBC units also have PRBC's (Hct about 30%). May need to give repeated doses q 12 hours.

Fresh Frozen Plasma ("FFP", contains ALL clotting factors)

Use: Coagulopathy
Product: Frozen pack from single compatible donor
Dose: 10 ml/kg
Complication: Infection
Comments:
FFP administration is a donor exposure. FFP should not be used for simple volume expansion or for routine exchange transfusions. Must be thawed just before use, takes at least 30-40 minutes.

Cryoprecipitate (Factor VIII, XIII, Fibrinogen, von Willebrand's factor, Fibronectin)

Use: Coagulopathy associated with above factors (prolonged PTT and normal PT). Need for fibronectin or fibrinogen
Product: Frozen pack from single donor
Dose: 10 ml/kg
Complications: Infection
Comments:
Need time to thaw prior to use. Contains three times as much fibrinogen as FFP. Avoid use in hemophiliacs because of risk of antibody formation. Counts as a donor exposure.

Albumin

Use: Volume expansion, hypoproteinemia
Product: Heat treated in saline, 5% and 25% concentration
Dose: 10 ml/kg for volume expansion of 5% albumin, 1 gm/kg for hypoproteinemia
Complications: No infectious risk (product is heat treated)
Comments:
25% concentration should be diluted with saline prior to use as a volume expander. 25% concentration can be used for hypoproteinemia when volume administration is an issue, but infuse VERY slowly. Salt content of 5% albumin is 130-160 mEq/liter.
Neonatal Jaundice – Unconjugated Hyperbilirubinemia

Unconjugated hyperbilirubinemia: direct bilirubin fraction ≤ 2.0 mg/dL and no bilirubin in urine

**Etiology:** Unconjugated hyperbilirubinemia occurs routinely in the neonatal period due to:
- Increased bilirubin load after birth
  - Shortened RBC life span (fetal hemoglobin)
  - Sequestered RBC’s (e.g. bruising, cephalhematoma, swallowed blood, occult hemorrhage)
- Inefficient transfer of bilirubin from blood into the liver (especially in the premature infant)
- Inefficient metabolism of bilirubin by the liver
  - Low levels of bilirubin binding proteins (ligandin or glutathione S-transferase and Z protein).
  - Decreased levels of glucuronyl transferase which conjugates bilirubin
- Increased enterohepatic circulation due to decreased gastrointestinal motility

**Evaluation:**
- All mothers should have blood type and group.
- Infants with any of the following danger signs should be considered at risk for bilirubin toxicity:
  - Family history of hemolytic disease
  - Prematurity
  - Vomiting, lethargy or poor feeding
  - Fever
  - Onset of jaundice after the third day of life
  - High-pitched cry
  - Hepatosplenomegaly

**Diagnostic cascade:**
- Order blood type and group (cord blood) of infants of Rh-negative or O mothers
- Order DAT or direct antibody test (previously known as Coombs’) on cord blood, if possible maternal-infant isoimmunization
- Order serum bilirubin (total/direct) and albumin levels if an infant:
  - Appears jaundiced within 24 hours of birth or marked jaundice (jaundice which extends to lower extremities) is present
  - Coombs’ test is positive (also order HCT, reticulocyte count, RBC morphology)
  - Infant is ill or premature and ≥ 24 hours of age
  - Transcutaneous bilirubin value falls into risk category on curve
- Order HCT, reticulocyte count, RBC morphology, blood type, Rh and Coombs’ ordered if bilirubin or bilirubin/albumin ratio exceeds 50% of exchange level (see Table) in first 24 hours of life or 65% of exchange level thereafter
- Order G-6-PD if Asian or Mediterranean or if can’t easily explain reason for the jaundice
- Consider the following if unconjugated hyperbilirubinemia out of proportion to circumstances, lacks a good explanation (e.g. preterm, bruising) or persists longer than a week:
  - Breast milk jaundice (most likely)
  - Hypothyroidism
  - Undetected hemolysis or sequestrated blood
  - Crigler-Najjar syndrome (may respond to phenobarbital)
  - UTI or sepsis (very rare)

- Bilirubin levels in the first week of life should be interpreted relative to post-natal age
- Online bilirubin interpretation toll: [bilibool](#)

**Treatment:**

**Phototherapy Pointers**
- The effectiveness of phototherapy relates to the surface area covered and the intensity of the lights used
- Lights in the blue range are most effective
- Some providers experience nausea when viewing blue lights and white lights can be used to counteract this effect
• For term infants may need 2 lights to adequately cover surface area
• Bili bed (neoBlue Cozy Bili bed) can’t be used if infant is on oxygen (may use fiberoptic bili blankets but they have limited irradiance)
• Aim is for photometer reading of spectral irradiance of at least 30 \( \mu \text{W/cm}^2/\text{nm} \)
• Irradiance can be increased by adding lights, moving lights closer to infant (acceptable if using blue lights that do not generate heat), changing out light bulbs as they do lose strength over time
• Check [CPMC policy for other nuances of phototherapy](#)

Otherwise well term infant
• Bilirubin 16-25 mg/dL or bilirubin/albumin ratio exceeds 5.2 (65% of exchange level — may need earlier Rx if falls into risk area)
  • Interrupt nursing for 24-28 hours (may alternate nursing and bottle feeding; water supplement not helpful)
  • Phototherapy – intensive using double surfaces (blue light overhead and using bili bed)

• Bilirubin 25-30 mg/dL
  • Phototherapy if bilirubin/albumin ratio less than 8 mg/g (blue light overhead and using bili bed) – see above
  • Exchange transfusion

• Exchange transfusion if bilirubin exceeds 30 mg/dL, auditory brainstem evoked potentials are absent or symptomatic

Term infant with active hemolysis (see Table)
• Make sure pH \( \geq 7.35 \) and hematocrit/hgb and oxygenation are adequate
• Phototherapy – intensive using two surfaces (blue light overhead and using bili bed)
• Give IVIG if bilirubin level is nearing or you anticipate it will accelerate towards the exchange level for the baby’s age/GA/risk category (see “Figure 4” below), IVIG may block/absorb the maternal antibodies in the baby’s body and slow the hemolytic process. The dose given is 0.5 – 1 gm/kg. Follow the IVIG infusion protocol for infusion rates.
• Exchange transfusion
  • If bilirubin is rising faster than 0.5 mg/dL per hour
  • Bilirubin/albumin ratio exceeds 6.5 mg/g
  • Total bilirubin reaches 18 mg/dL and rising despite IVIG
  • Auditory brainstem evoked potentials are absent or symptoms are present

Preterm infants (see Table)
• Phototherapy at 50% of exchange total bilirubin or bilirubin/albumin ratio (whichever comes first if infant is ill)
• Phototherapy at 65% of exchange total bilirubin or bilirubin/albumin ratio (whichever comes first) for standard risk infants.

### Table

Total Bilirubin (mg/dL) and Bilirubin/albumin ratio (mg/g) as Criteria for Exchange Transfusion* or Phototherapy**

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>&lt;1250</th>
<th>1250-1499</th>
<th>1500-1999</th>
<th>2000-2499</th>
<th>( \geq 2500 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Risk</td>
<td>13</td>
<td>15</td>
<td>17</td>
<td>18</td>
<td>25-29</td>
</tr>
<tr>
<td>or Bilirubin/albumin ratio</td>
<td>5.2</td>
<td>6.0</td>
<td>6.8</td>
<td>7.2</td>
<td>8.0</td>
</tr>
<tr>
<td>High Risk</td>
<td>10</td>
<td>13</td>
<td>15</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>or Bilirubin/albumin Ratio</td>
<td>4.0</td>
<td>5.2</td>
<td>6.0</td>
<td>6.8</td>
<td>7.2</td>
</tr>
</tbody>
</table>

*Exchange transfusion recommended at whichever variable comes first.
**Phototherapy recommended at 50% of exchange level variable (total bilirubin/albumin ratio, whichever comes first) for high risk group and 65% of exchange level variable for standard risk group.
Risk factors: 
Apgar <3 at five minutes; PaO₂ <40 mm ≥ 2 hrs, pH ≤ 7.15 ≥ 1 hr, birth weight <1000 g, hemolysis; clinical or CNS deterioration.

Another approach to treatment of hyperbilirubinemia in babies that are greater than or equal to 35 weeks gestation is to use the curves published by the AAP in 2004 (AAP Guidelines for the Management of Hyperbilirubinemia (Pediatrics, 114:297–316, 2004). The age of the baby when the sample was collected is plotted on the graph and compared to the appropriate age/condition curve. If the bilirubin value is at or above the curve, then phototherapy/exchange transfusion is to be considered. Please note that there are two similar graphs. The first graph is for the initiation of intensive phototherapy and the second for exchange transfusion.

- Data on these curves is also available using on line bilirubin interpretation tools such as found at Bili Tool™.

![Graph showing guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.](image)

- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, GBD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dl. (If measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dl (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Fig 3. Guidelines for phototherapy in hospitalized infants of 35 or more weeks’ gestation.

Note: These guidelines are based on limited evidence and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy which should be used when the TSB exceeds the line indicated for each category. Infants are designated as “higher risk” because of the potential negative effects of the conditions listed on albumin binding of bilirubin,56-57 the blood-brain barrier,58 and the susceptibility of the brain cells to damage by bilirubin.59

Intensive phototherapy” implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 μW/cm² per nm (measured at the infant’s skin directly below the center of the phototherapy unit) and delivered to as much of the infant’s surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system.

See Appendix 2 for additional information on measuring the dose of phototherapy, a description of intensive phototherapy, and of light sources used. If total serum bilirubin levels approach or exceed the exchange transfusion line (Fig 4), the sides of the bassinet, incubator, or warmer should be lined with aluminum foil or white material.60 This will increase the surface area of the infant exposed and increase the efficacy of phototherapy.61

If the total serum bilirubin does not decrease or continues to rise in an infant who is receiving intensive phototherapy, this strongly suggests the presence of hemolysis.

Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice) may develop the bronze-baby syndrome. See Appendix 2 for the use of phototherapy in these infants.
REFERENCES

AAP Clinical Practice Guideline on Jaundice


Neonatal Jaundice – Conjugated Hyperbilirubinemia (Cholestatic Jaundice)

Conjugated hyperbilirubinemia (direct bilirubin ≥ 2 mg/dL, urine bilirubin positive).

Direct hyperbilirubinemia is significant and may represent:
- Congenital infection (TORCH)
- Sepsis
- Biliary atresia or giant cell hepatitis
- Galactosemia
- Cholestasis (inspissated bile syndrome)
- Choledochal cyst
- Alpha-1-antitrypsin deficiency
- Rotor’s syndrome, Dubin-Johnson syndrome

Direct hyperbilirubinemia indicates a need for diagnostic work-up but rarely requires therapy (phototherapy is contraindicated and results in bronzing).

See Parenteral Nutrition section for treatment recommendations.
Exchange Transfusions

Indications:
Treatment of hyperbilirubinemia or anemia associated with hemolytic disease
- Single Volume exchanges 63% of blood volume
- Double Volume exchanges 87% of blood volume

Use Packed Red Blood Cells:
- Freshest possible, must be <7 days old, washed, irradiated, CMV negative, sickle prep negative
- Resuspend with fresh frozen plasma to desired Hct (40-45%)
- Warmed

**Volume of Exchange** = 2 x blood volume
Blood volume varies from 80-95 ml/kg  higher volumes are for lower birth weight

Volume PRBC’s = \frac{\text{total exchange volume} \times \text{desired Hct}}{\text{Hct PRBC’s}}

Volume FFP = \text{total exchange volume} - \text{PRBC volume}

A unit of PRBC’s usually holds 300-350 ml

Method:
- Single line (push/pull)
- 2 lines (isovolemic)
- Aliquot size: 5-10 ml, Smaller in micropreemies
- Time: over 1-2 hours

- **Checklist for exchange transfusion**
- There is a detailed nursing policy and procedure on how to set this up

Complications:
- Anemia
- Temperature
- Volume overload
- Hyperkalemia
- Hyperglycemia with rebound hypoglycemia
- Hypernatremia
- Hypocalcemia (due to CPD buffer)
- Rebound hyperbilirubinemia
- Thrombocytopenia, coagulopathy
- Possibly Necrotizing enterocolitis
- Emboli/thrombosis from lines
- Infection from lines, blood
- Graft vs. host disease (if not irradiated blood)
- Transfusion reactions
- Modifications of serum drug levels (especially antibiotics)

Remember to draw any necessary tests before exchange. This is your last chance to draw unaltered serologies, enzyme tests, chromosomes and metabolic tests. (Consider need for TORCH titers, G6PD tests).

“Just in case” save a red, purple and green top for later consideration.

*Must Do State Newborn Screen before Exchange*
Gastrointestinal Disorders

Abdominal Distension and/or Vomiting

Obstructive Causes
- Bowel atresias or stenoses
- Bands or annular pancreas
- Strangulated hernia
- Imperforate anus
- Meconium ileus, meconium plug or meconium peritonitis
- Small left colon syndrome (IDM's)
- Malrotation, volvulus or duplication
- Hirschsprung's disease
- T-E fistula
- Abdominal mass
- Perforation
- Constipation
- Preterm
- Hypothyroidism

Non-mechanical Causes
- Sepsis
- Electrolyte imbalance
- Acute necrotizing enterocolitis
- Respiratory distress with aerophagia
- Ascites
- Adrenal insufficiency - may simulate pyloric stenosis because of delayed gastric emptying time
- Pneumoperitoneum
- Assisted ventilation, especially with mask or nasal CPAP
- Overfeeding

Failure to Pass Meconium
- Delayed passage
- Anal atresia
- Anal stenosis
- Hirschsprung’s
- Meconium plug
- Meconium ileus
Gastroesophageal Reflux Disease (GERD)

- GERD occurs in most premature infants
- The association between GERD and apnea has not been proven (several well controlled studies)
- It is usually not pathological
- A 24-hour pH probe study is the gold standard for the diagnosis of occult GERD, but requires the gastric contents to be acidic
- Non-pharmacological measures should be adopted first in the treatment of GERD
- Pharmacological treatment of GERD should only be undertaken where there is proven, pathological reflux

Gastro-esophageal reflux disease (GERD) may be defined as the spontaneous effortless regurgitation of gastric contents into the oesophagus. This may or may not result in vomiting. Although some (physiological) reflux occurs in most premature infants, the total amount of reflux in a 24-hour period is usually not grossly abnormal. Preterm infants appear to have fewer and shorter episodes of reflux than term infants. Therefore, the investigation and management of GERD in the neonatal nursery should be reserved for those infants in whom the reflux is considered to be pathological.

When might GERD be pathological?
- Delayed acid clearance resulting in
  - Bleeding
  - Stricture (incidence unknown)
- Pulmonary complications
  - Apnea (however, most apnea is not due to GERD)
  - Aspiration and pneumonia
  - Microaspiration and reactive airway disease
  - Hoarseness or weak cry from chronic aspiration
  - Exacerbation of chronic lung disease in some cases
- Failure to thrive, secondary to poor intake
- Apparent life-threatening events and SIDS (controversial)
- Infants with underlying problems – examples: post esophageal atresia repair, infants with severe neurologic disorders, infants with high intra-abdominal pressures, infants on ventilation
- GERD may be made worse by some medications (xanthines and beta agonists relax GE junction, xanthines increase acid production)

Differential Diagnosis (of vomiting)
- Bowel obstruction (usually bile-stained vomiting) – malrotation and volulus as cause of bilious emesis is a surgical emergency and requires immediate diagnostic evaluation
- Drugs e.g. theophylline and caffeine
- Inborn errors of metabolism
- Pyloric stenosis (GERD usually not projectile)
- Sepsis (especially UTI)
- Necrotizing enterocolitis

Diagnosis of GERD
- Usually clinical
- Barium swallow and ultrasound nonspecific (only useful to rule out congenital or acquired structural abnormalities such as malrotation, stenosis, web, fistula, dysmotility)
- 24-hour pH probe gold standard, although gastric contents must be acid
  - Values used in analysis: # GER episodes, # episodes > 5 min, duration of episodes, duration of longest episode, time acid pH <4
- White oral secretions may be differentiated from milk
- Endoscopy little data available for preterm infants
- Radio-nucleotide studies not standardized in preterm infants
- Esophageal manometry catheter size limits usefulness in VLBW
- Lipid laden macrophages on bronchoscopy
Management

- **Non-pharmacological**
  - Prone +/- 30-degree elevation (beware increased risk of SIDS if prone - apnea monitoring required).
  - Alternatively right side down
  - Avoid seated positioning (car seat, infant swings) as increases intraabdominal pressures
  - Increased frequency (thus decreased volume) of feeds
  - Consider intermittent tube insertion
  - Continuous feeding (gastric or transpyloric)
  - Thickeners of feeds (rice cereal / various commercial products that are cornstarch based)
  - Fundoplication (reserved where intractable or life-threatening proven GERD and failed pharmacological therapy)

- **Pharmacological only for proven, pathological GERD**
  - H2 blockers e.g. Ranitidine
    - Famotidine (Pepcid):
      - IV or oral dose: 0.5 mg/kg/dose q 12 h
    - Ranitidine (Zantac):
      - Oral dose: 2mg/kg/dose po every 8 h
      - Preterm IV dose: 0.5 mg/kg/dose every 12 h
      - Term IV dose: 1.5 mg/kg/dose every 8 h
    - Caution: higher pH of gastric contents may change gut flora
  - Proton pump inhibitors e.g. lansoprazole (Prevacid)
    - Dose: 0.03 - 0.1 mg/kg/dose every 8 h
    - Clinical data mixed: narrow dose range 2˚ CNS toxicity and long term usage has been linked to tardive dyskinesia in adults.

- **Fundoplication**
  - Increases LES pressure, and functions as valve
  - Success rate > 90%: eliminate or reduce GERD
  - Complications - (more common in neurologically impaired)
    - herniation: hiatal or paraesophageal
    - gas bloat: inability to burp/vomit, dysphagia, dumping, retching

Areas of Uncertainty in Clinical Practice

- The role of GERD in the etiology of SIDS
- Reflux-specific behavioral criteria (e.g. discomfort, head retraction and mouthing) may be inappropriate as diagnostic criteria for GER in premature infants

References

- Gastroesophageal Reflux – Emedicine May 13 2009
- Author: Steven M Schwarz, MD, FAAP, FACN, AGAF, Professor of Pediatrics, Children's Hospital at Downstate, SUNY-Downstate Medical Center
  Coauthor(s): Andre Hebra, MD, Chief, Division of Pediatric Surgery, Medical University of South Carolina; Professor of Surgery and Pediatrics, Medical University of South Carolina
Necrotizing Enterocolitis (NEC)

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in neonates. Ninety percent of babies with NEC are preterm. It is predominantly a disease of the very low birth weight infant and is most common in babies < 1000 g or those that are both preterm and growth restricted. The incidence of NEC is inversely proportional to birth weight. In general, the age of onset is inversely proportional to gestation; therefore smaller babies present later. Approximately 50% of babies developing NEC require surgery. The mortality rate of NEC is 20-40%. Of those who survive, approximately 25% develop long term sequelae.

The Vermont Oxford Network defines NEC as:

- Necrotizing Enterocolitis (NEC) diagnosed at surgery
- NEC diagnosed at postmortem examination
- NEC diagnosed clinically and radiographically using the following criteria:
  - One or more of the following clinical signs present:
    - Bilious gastric aspirate or emesis
    - Abdominal distention
    - Occult or gross blood in stool with no apparent rectal fissure
  - AND One or more of the following radiographic findings present:
    - Pneumatosis intestinalis
    - Hepato-biliary gas
    - Pneumoperitoneum

Etiology

- Exact etiology remains unknown
- Research suggests that it is multifactorial
- Abnormal bacterial flora
  - Gram-positive and gram-negative bacteria, fungi, and viruses have all been isolated from affected infants but many infants have negative culture findings.
  - In healthy individuals, the intestinal milieu is characterized by a predominance of bifidobacteria. Such colonization is enhanced by the presence of oligofructose, a component of human milk, in the intestinal lumen. Infants who receive formula feedings without oligofructose as a constituent have been noted to have a predominance of clostridial organisms.
  - Many preterm infants receive frequent exposure to broad-spectrum antibacterial agents, further altering the intra-intestinal bacterial environment.
  - Evidence suggests that exogenous administration of the probiotics bifidobacteria and lactobacilli or prebiotics (nondigestible substances that selectively promote the growth of beneficial probiotic like bacteria normally present in the gut) may moderate the risk and severity of NEC in preterm infants.
- Intestinal ischemia
  - Epidemiologically, some have noted that infants exposed to intrauterine environments marked by compromised placental blood flow (ie, maternal hypertension, preeclampsia, cocaine exposure) have an increased incidence of NEC.
  - Infants with postnatally diminished systemic blood flow, such as is found in patients with patent ductus arteriosus or congenital heart disease, also have an increased incidence.
  - Intestinal necrosis results in breach of the mucosal barrier, allowing for bacterial translocation and migration of bacterial endotoxin into the damaged tissue.
- Reperfusion injury with activation of proinflammatory cellular cascades
  - Activated leukocytes and intestinal epithelial xanthine oxidase may then produce reactive oxygen species, leading to further tissue injury and cell death.
- Intestinal mucosal immaturity/dysfunction
  - In the preterm infant, mucosal cellular immaturity and the absence of mature antioxidative mechanisms may render the mucosal barrier more susceptible to injury.
- Substrate: Experimental and epidemiologic studies have noted that feeding with human milk has a protective effect; however, donor human milk that has been pasteurized is not as protective. Human milk contains secretory immunoglobulin A (IgA), which binds to the intestinal luminal cells and prohibits bacterial transmural translocation.
Risk factors

- Prematurity
- Enteral feeding (although approx. 10% of cases occur in infants never fed)
- Formula feeding (6 times more common than if only breast milk fed)
- Often occurs in clusters (although organisms vary)
- Bowel ischemia
- in term infants
  - Polycythemia
  - Cardiac surgery
  - Abdominal surgery (esp. gastrochisis, intestinal atresia)
  - Endocrine abnormalities

Clinical Presentation (highly variable and often non-specific)

- GI dysfunction
- Abdominal distension
- Vomiting
- Bilious drainage from enteral feeding tubes
- Blood in stool
- Abdominal tenderness, erythema, discoloration or mass
- Systemic signs
  - Temperature instability
  - Apnea and/or bradycardia
  - Worsening respiratory status and increasing support needs
  - Lethargy
  - Metabolic acidosis
  - Hypotension
- Lab abnormalities
  - Shifted CBC or neutropenia
  - Thrombocytopenia
  - Coagulation disorders

Differential Diagnosis of suspected NEC

- Dysmotility of prematurity
- Septic ileus
- Bowel obstruction
- Gastroenteritis
- Anal fissure
- Cow’s milk protein sensitive enterocolitis

Radiographic findings

- Nonspecific
  - Diffuse gaseous distension
  - Asymmetric, disorganized bowel pattern
  - Dilated bowel loops
  - Bowel wall thickening
  - Increased peritoneal fluid
- Diagnostic signs
  - Persistent loop
  - Pneumatosis intestinalis (virtually pathognomonic)
  - Submucosal – bubbly or cystic appearance (may be confused with stool, although stool usually moves on serial x-rays)
  - Subserosal – linear or curvilinear appearance
Portal venous gas
Pneumoperitoneum: left lateral decubitus (left side down) often helpful in determining if free air (shows between liver and abdominal wall)

Management (see 'Modified Bell’s Staging Criteria' table below for duration of recommended treatment)
- NPO
- Vented gastric tube for suction – keep track out output and replace if high volume
- Blood culture (2 sets if have indwelling central line – 1 from line, 1 peripheral)
- Antibiotics - variable combination depending upon central line use and surgeon preference but mostly Gram + and Gram – coverage.
  - Vancomycin - with central line
  - Zosyn – covers most gram negative organisms and good Gram +
  - 3rd Generation Cephlasporin if used in combo with Vanco
  - metronidazole (only for definite NEC) and also surgeon dependent
- Bowel rest for 10-14 days
- Total parenteral nutrition
- Fluid management - resultant 3rd spacing and hypovolemia
- DIC clinical picture and coagulation disruption
- Pressors for hypotension
- Ventilation
- Pain management – consider continuous drip infusion
- Serial radiographs – consider doing single left lateral decubitus view to limit Xray exposure
- Surgery (25% to 50% of cases) - indicated if perforation occurs (but not necessarily if portal air is seen) or if metabolic derangements cannot be managed with medical therapy. A drain may be only surgical procedure selected if perforation.
- Handle infant using strict Body Secretion Precautions

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SYSTEMIC SIGNS</th>
<th>INTESTINAL SIGNS</th>
<th>RADIOLOGIC SIGNS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Suspected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Temperature instability, apnea, bradycardia</td>
<td>Elevated residuals, mild abdominal distension, occult blood in stool</td>
<td>Normal or mild ileus</td>
<td>NPO, antibiotics x 3 days</td>
<td></td>
</tr>
<tr>
<td>B: Same as IA</td>
<td>Same as IA, plus gross blood in stool</td>
<td>Same as IA</td>
<td>Same as IA</td>
<td></td>
</tr>
<tr>
<td>II. Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Mildly ill</td>
<td>Same as IA</td>
<td>Same as I, plus absent bowel sounds, abdominal tenderness</td>
<td>Ileus, pneumatosis intestinalis</td>
<td>NPO, antibiotics x 7 to 10 days</td>
</tr>
<tr>
<td>B: Moderately ill</td>
<td>Same as I, plus mild metabolic acidosis, mild thrombocytopenia</td>
<td>Same as I, plus absent bowel sounds, definite abdominal tenderness, abdominal cellulitis, right lower quadrant mass</td>
<td>Same as IIA, plus portal vein gas, with or without ascites</td>
<td>NPO, antibiotics x 14 days</td>
</tr>
<tr>
<td>III Advanced</td>
<td>SYSTEMIC SIGNS</td>
<td>INTESTINAL SIGNS</td>
<td>RADIOLOGIC SIGNS</td>
<td>TREATMENT</td>
</tr>
<tr>
<td>A: Severely ill, bowel intact</td>
<td>Same as IIB, plus hypotension, bradycardia, respiratory acidosis, metabolic acidosis, disseminated intravascular coagulation, neutropenia</td>
<td>Same as I and II, plus signs of generalized peritonitis, marked tenderness and distension of abdomen.</td>
<td>Same as IIB, plus definite ascites</td>
<td>NPO, antibiotics x 14 days, fluid resuscitation, inotropic support, ventilator therapy, paracentesis</td>
</tr>
<tr>
<td>B: Severely ill: bowel perforated</td>
<td>Same as IIIA</td>
<td>Same as IIIA</td>
<td>Same as IIB, plus pneumoperitoneum</td>
<td>Same as IIA, plus surgery</td>
</tr>
</tbody>
</table>

**Complications**

- Mortality rate ranges from:
  - 0-20% in babies who weigh more than 2500 g.
  - 10% to more than 50% in infants who weigh less than 1500 g
  - 40-100% in extremely premature infants <1000 g
- Surgery requiring ileostomy
- Short bowel syndrome
  - Diarrhea from poor water absorption or bile salt induced
  - High risk dehydration – esp. with gastroenteritis
  - Salt and fluid losses due to high output = dumping
  - Failure to thrive due to poor absorption or metabolic acidosis
  - Vitamin deficiency $2^0$ to fat malabsorption or resections (proximal bowel-iron and folate, distal bowel B$_{12}$)
  - Zinc deficiency
  - "Blind loop" syndromes of bacterial overgrowth
- Stricture
  - 20-30%
  - most commonly in large bowel
  - 80% on left side
  - may not develop for weeks to months post-NEC
  - presents with recurrent abdominal distension
  - surgical consultation and contrast enema required
- Prolonged parenteral nutrition risks
  - Central venous catheters thromboembolic events and nosocomial infections
  - Cholestasis, direct hyperbilirubinemia, and other metabolic complications.

**Prevention**

- Antenatal corticosteroids
- Early intervention with early stoppage of feeds for suspected NEC
- Breast milk
- Infection control practices may limit the size of disease clusters
- Probiotics

**Controversies**
- Effect of rate of feed upgrade in the prevention of NEC
- Prophylactic antibiotics (proven to reduce NEC risk but concern re development of antibiotic-resistant organisms)
- Enteral IgA (enteral IgG refuted)

**References**

Neurologic Disorders

Perinatal or Neonatal Asphyxia

Definition
The diagnosis of asphyxia should be reserved for those infants in whom there is strong evidence of a period of oxygen deprivation and acidosis. Historical factors such as meconium staining of the amniotic fluid, fetal distress in utero or respiratory depression at birth do not necessarily mean that the infant is or has been “asphyxiated.” The Perinatal Guidelines (American Academy of Pediatrics & American College of Obstetrics and Gynecology, 1992) state “the term asphyxia should be reserved for a clinical context of damaging acidemia, hypoxia, and metabolic acidosis. A neonate who has had hypoxia proximate to delivery severe enough to result in hypoxic encephalopathy will show other evidence of hypoxic damage, including all of the following:

- Profound metabolic or mixed acidemia (pH<7.00) on an umbilical cord arterial blood sample
- Persistence of an Apgar score of 0-3 for longer than 5 minutes
- Neonatal neurologic sequelae, e.g., seizures, coma, hypotonia
- Multi-organ system dysfunction, i.e., cardiovascular (62%), gastrointestinal, hematologic, hepatic (85%), pulmonary (86%) or renal system (70%).

Other criteria which have been used to substantiate the diagnosis of asphyxia include:

- Arterial pH in the infant >one hour old of <7.20 with a base deficit >12 mEq/L
- Need for complicated resuscitation including CPR and drugs other than Narcan
- Delayed onset of spontaneous respirations >15 minutes

Vermont Oxford Network requires the presence of all three of the following criteria to diagnose HIE:

- Presence of a clinically recognized encephalopathy within 72 hours of birth. Encephalopathy is defined as the presence of 3 or more of the following findings within the first 72 hours after birth.
  - Abnormal level of consciousness: hyper alertness, lethargy, stupor or coma
  - Abnormal muscle tone: hypertonic, hypotonic or flaccidity
  - Abnormal deep tendon reflexes: increased, depressed or absent
  - Seizures: subtle, multimodal or focal clinic
  - Abnormal Moro reflex: exaggerated, incomplete or absent
  - Abnormal suck: weak or absent
  - Oculomotor or pupillary abnormalities: skew deviation, absent or reduced Doll's eyes or fixed unreactive pupils

- Three or more supporting findings from the following list:
  - Arterial cord pH <7.00
  - APGAR score at 5 minutes of 5 or less
  - Evidence of multiorgan system dysfunction (see below)
  - Evidence of fetal distress on antepartum monitoring: persistent late decelerations, reversal of end-diastolic flow on Doppler flow studies of the umbilical artery or a biophysical profile of 2 or less
  - Evidence on CT, MRI, technetium or ultrasound brain scan performed within 7 days of birth of diffuse or multifocal ischemia or of cerebral edema
  - Abnormal EEG: low amplitude and frequency, periodic, paroxysmal or isoelectric
  - The absence of an infectious cause, a congenital malformation of the brain or an inborn error of metabolism, which could explain the encephalopathy.

- Multiorgan system dysfunction requires evidence of dysfunction of one or more of the following systems within 72 hours of birth:
  - Renal: oliguria or acute renal failure
  - GI: necrotizing enterocolitis, hepatic dysfunction
  - Hematologic: Thrombocytopenia, disseminated intravascular coagulopathy
  - Endocrine: hypoglycemia, hyperglycemia, hypercalcemia, syndrome of inappropriate ADH secretion (SIADH)
  - Pulmonary: persistent pulmonary hypertension
  - Cardiac: myocardial dysfunction, tricuspid insufficiency
Findings & Treatment by System after Birth in Severe Asphyxia

Neurologic

- **See HIE Hypothermia protocol.**
- Staging of hypoxic ischemic encephalopathy has been suggested by Vermont Oxford Network to allow comparisons across centers. Staging is based on the worst stage seen in the first 7 days of life.
  - **Severe** if the infant is in deep stupor or coma. Infants in this category are not arousable in response to arousal maneuvers.
  - **Moderate** if the infant is lethargic or in mild stupor. Infants in this category are arousable but have a diminished response to arousal maneuvers.
  - **Mild** if the infant is alert or hyperalert, with either a normal or exaggerated response to arousal

- Preterm infants may not follow the classical pattern
- Most infants who suffer an “asphyxial” episode recover with no neurologic or developmental sequelae.
- Poor prognosis is associated with the following:
  - Severe prolonged asphyxia
  - Seizures unresponsive to usual medications
  - Sarnat Stage 3 encephalopathy
  - Abnormal neurologic exam, especially absent Moro at 2 weeks
  - Cystic encephalomalacia on CT or leukomalacia on ultrasound

**Treatment**

- **See Hypothermia protocol if > 36 weeks.**
- Document serial neurologic examinations
- Treat seizures with Phenobarbital.
- Head Ultrasound or CT to rule out hemorrhage and/or edema prior to cooling if indicated

Renal

- Acute renal failure (creatinine >1.5mg/dL) may be non-oliguric oliguric or anuric. About 50-60% of asphyxiated infants have oliguria (< 0.5 ml/Kg/hour).
  - May be “pre-renal” from diminished renal perfusion (responds to 10-20 ml/Kg fluid challenge and lasix.) Pre-renal oliguria usually resolves in 48-72 hours and will usually give FENa< 1.
  - May be a result of acute tubular and/or cortical necrosis. ATN may take 4-6 days to resolve and will give values of FENa > 2.5.

- Urinary retention may occur.
  - Examine for bladder distention and place bladder foley if urinary retention is a concern.
- Acute tubular necrosis
  - Initial oliguria often followed by polyuria
  - Large losses of sodium, water and other electrolytes in urine
  - Urine positive for blood, protein
  - Decreased glomerular filtration

- Cortical necrosis may occur in severe asphyxia

**Treatment**

- Restrict fluids to 50-80 ml/kg/day or insensible water loss+urine output
- Sodium, potassium and phosphorus intake should be restricted and electrolytes monitored closely.
- Medication dosing and levels should be closely monitored and adjusted if signs of renal impairment
- Low dose Dopamine can be used to improve pre-renal impairment.

Cardiac and circulatory effects

- Myocardiac ischemia—usually transient, but can result in hypotension, cardiac shock and death.
- May be 2˚ to poor cardiac output or relatively a peripheral vascular resistance.
- Pulmonary hypertension may lead to right ventricular failure with tricuspid regurgitation
- Physical exam shows congestive heart failure:
  - tachypnea, tachycardia, cardiomegaly, hepatomegaly
  - systemic BP low and capillary refill delayed
  - TR murmur (systolic murmur loudest at LLSB)
• EKG: Elevated ST in precordial leads, inverted T in left precordial leads
• CXR: Cardiomegaly
  o left side predominantly affected will have hazy lungs
  o right side predominantly affected pulmonary congestion absent
• Evidence of either left or right ventricular dysfunction on echocardiogram
• Laboratory:
  o Creatine kinase (MB isoenzyme) elevated 5-10% after birth
  o Cardiac troponin T levels useful marker for myocardial necrosis

Treatment
• Treat hypotension with inotrope (start Dopamine at 5 microgram/kg/min and titrate up to 20-25 microgram/kg/min)
• Correct any metabolic abnormalities.
• If asphyxia is severe or perfusion impaired, do a cardiac echo to assess ventricular function.
• Try to keep MAP on ventilator as low as possible to prevent impairment of venous return.
• May need after load reduction medication and diuresis.
• Watch for late hypertension if renal failure present

Pulmonary
• May have combination of acute RDS, meconium aspiration, pulmonary edema from congestive heart failure and/or PPHN
• ↑ pulmonary capillary permeability to plasma proteins
• Inactivation of surfactant
• Exam: cyanosis, grunting, nasal flaring, retraction
• CXR: normal to ↑ lung volume, ↑ risk pneumothorax, diffuse bilateral alveolar opacification with air bronchograms

Treatment
• Keep well oxygenated and maintain normal ventilation parameters. Avoid hyperoxia and hypocarbia.
• May benefit from surfactant if meconium aspiration syndrome

Gastrointestinal
• Severely asphyxiated infants may have nonspecific GI bleeding
• Ileus, ulceration or perforation, potentially colonic necrotizing enterocolitis.
• In severe asphyxia feedings should be withheld for 5-7 days (until intestinal motility normalizes) with the presumption that intestinal ischemia may have occurred.
• Feeding intolerance is common due to delayed gastric emptying and transient disturbances in intestinal motor activity due to ischemic injury and loss of neuronal regulation and motor control.
• Hepatic: “Shock” liver
  • Abnormal synthetic, excretory and detoxifying functions
  • Abnormal Liver function tests
  • Deficient production of clotting factors: PT, PTT, Fibrinogen,
  • Hyperammonemia
  • Deficient glucose production (prone to hypoglycemia)
  • Poor hepatic clearance of medications
  • Cholestatic jaundice may develop

Treatment
• Hold feeds until bowel function normalizes
• Follow for signs of perforation or colonic NEC.
• Follow liver enzymes and anticipate need for phototherapy and possible cholestasis to develop.
• Investigate for and treat coagulopathy

Metabolic
• Hypoglycemia (although in acute phase due to stress the glucose may be very elevated and it may drop quickly)
Hypocalcemia
- Hypomagnesemia

**Treatment**
- Normalize blood glucose and calcium.
- May need high doses of calcium gluconate initially.
- One small RCT suggests neuro-protective effect of Mg if given in first six hours of life with use of hypothermia normalizing Mg should also be done early if Mg levels are low.

**Hematological**
- High risk for DIC – a low index of suspicion should be used to check coagulation labs
- There may be a markedly increased white blood count with left shift secondary to the intense adrenergic surge associated with asphyxia
- Nucleated red cells are increased
- Platelets are frequently decreased due to DIC and decreased production

**Treatment**
- Follow labs for DIC
- Use FFP for coagulopathy, Cryoprecipitate for low fibrinogen and platelets as needed

**Whole Body Cooling for Neonatal Encephalopathy**

The rationale for whole body cooling for Hypoxic Ischemic Encephalopathy comes from evidence from multiple randomized controlled trials suggests that mild hypothermia following perinatal hypoxia-ischemia may reduce mortality and disability without adverse effects.

**Summary of Cooling Plan**
- Within 6 hours of birth
- Aim for core temperature of 33.5°C.
- The total period of cooling will be 72 hours.
- Upon completion of 72 hours of body cooling, infants will be gradually re-warmed over a 6-hour period.
- Cooling provided by The Blanketrol III Hyper/Hypothermia System servo-controlled to the infant’s esophageal temperature

**Patients Who Meet Criteria for Cooling**
Infants are evaluated in two steps: evaluation by clinical and biochemical criteria and neurological exam

- ≥ 36 weeks gestational age
- ≤ 6 hours of age
- Infant meets **biochemical** criteria
  - Cord pH or any postnatal blood gas pH within 1 hour of birth ≤ 7.0
  - OR Base Deficit on cord gas or any postnatal blood gas within 1 hour of birth ≥ 16 mEq/dL
  - OR pH 7.01-7.15 or base deficit 10-15.9 mEq/L with history of perinatal event AND APGAR score ≤ 5 at 10 minutes OR need for ventilation for > 10 minutes
- Infant meets **neurologic** exam criteria
  - Seizures
  - Moderate to severe encephalopathy defined as positive findings in 3 or more categories of the Sarnat Encephalopathy Scale:
    - Level of Consciousness (lethargic and/or stupor)
    - Spontaneous Activity (decreased or no activity)
    - Posture (distal flexion/complete extension or decerebration)
    - Tone (focal or general hypotonia or flaccid)
    - Primitive Reflexes (weak or absent)
- Autonomic System (Abnormal Pupils reaction, Bradycardia/variable HR, periodic breathing or apnea)
  - Infant does not meet exclusion criteria
    - <36wk gestational age
    - IUGR (<1800 gm)
    - Severe PPHN (at discretion of attending physician)
    - Severe hemodynamic compromise/perfusion sensitive states (sepsis)
    - Coagulopathy with active bleeding.
    - Need for transfer for possible ECMO
    - Severe congenital anomalies/syndromes/known metabolic disorders
    - Confirmed Sino-venous thrombosis.

Management of Inborn Infants Eligible for Cooling
- Turn off/down overhead heaters and external heat sources. Infants should not be warmed.
- Resuscitate and support per NRP guidelines otherwise.
- Order HUS, EEG and neurology consult as soon as possible, but do not delay cooling for these studies.
- If indicated, head CT or other studies should be done to rule out intracranial bleeding prior to cooling.
- Monitor core temperature closely. Continuous core temperature monitoring should be initiated as soon as possible, using either esophageal (preferred) or rectal temperatures.
- Skin temperature may be 1-2 lower than rectal temperature, so not reliable for monitoring.
- Secure vascular access before cooling causes peripheral vasoconstriction. Umbilical catheters (UAC and double lumen UVC preferred) or at least 2 PIV if not able to get umbilical lines. Do not use scalp vessels.

- Maintain adequate sedation. Infant should not shiver (this generates heat.)
  - Morphine is the drug of choice.
  - Loading dose 0.1 mg/kg IV
  - Repeat 0.05 mg/kg/dose prn discomfort or shivering
  - Start continuous infusion as soon as possible. 0.01 mg/kg/hr IV drip. Titrate for shivering and increased by 0.005 mg/kg/hr increments
  - Avoid Benzodiazepines. Use of Benzodiazapines with morphine will likely result in hypotension.
  - Cooling blanket set up specifics are available in the on line protocol.
  - Place foley catheter for monitoring of urine output and prevention of urinary retention due to sedative medications.

- Laboratory/blood work Blood Work Prior To Cooling
  - Cord blood gases.
  - Arterial blood gas with electrolytes (to get Ionized Calcium) and with “core temp” clearly labeled
  - Ionized calcium level – on the iSTAT
  - Baseline metabolic panel, including Ca, Mg, liver function and BUN/Cr
  - CBC with differential, platelets
  - Coags with DIC panel (PT/PTT/D-dimers/Fibrinogen)
  - Ammonia and Lactate – lactate can be run on blood gas sent to lab
  - Blood Glucose (glucometer okay)
  - Any metabolic work up for encephalopathy that is also warranted based on clinical picture.

- Follow-up Blood Work
  - Blood gases minimum q 6hrs x 24 hrs, then q12 - 24hrs as needed.
  - Remind RT to run blood gases for “core temperature” of infant.
  - Ionized Calcium: Levels may rapidly fall with acidosis and prolonged resuscitation, blood product administration as well as reperfusion during rewarming. Maintaining normal Ca++ as an inotrope is especially important during the bradycardia associated with cooling. Encephalopathy can be confused with hypocalcemic seizures. Monitor ionized Ca++ levels with blood gases.
  - Magnesium levels may fall with acidosis
  - Potassium levels may increase due to intracellular K+ shifts with acidosis, particularly with initiation of cooling and during reperfusion with warming.
  - Glucose levels need to be followed closely. Hypoglycemia associated with hypoxia, however glucose metabolism may be altered with cooling, leading to glucose intolerance.
  - Serum lactate q6-12hrs x 24hrs, then daily (send blood gas on ice to lab to get lactate with the gas)
  - BUN and Creatinine within 6-24 hours of life. Lower GFR with cooling due to decrease in renal blood flow.
  - AST and ALT within 6-24 hours of life.
- Serum ammonia levels within 6-24 hours of life. (1 green microtainer on ice)
- Cortisol—consider baseline level if cardiovascularly unstable (1 green microtainer)
- CBC with platelets Watch for thrombocytopenia, neutropenia and polycythemia (more likely to be symptomatic due to sludging with vasoconstriction.)

- Obtain Pediatric Neurology Consult as soon as practically possible.
- Place Amplitude Integrate EEG (aEEG)
- Order placement of 12-lead EEG electrodes as soon as practically possible. EEG leads can be placed around aEEG leads.

**Medical Management by Systems**

- **Fluids and nutrition**
  - NPO - during entire period of cooling and rewarming.
  - Place Foley for monitoring of urine output and to avoid urinary retention.
  - Total Fluids of 80 ml/kg/day
  - Starter TPN or D10W (or D5W if hyperglycemic)
  - Management of Acidosis – Try to avoid base replacement therapy if circulation is re-established and patient can self correct over time. Treat hypovolemia with volume administration as needed.

- **Respiratory**
  - Ventilator Support - Provide any respiratory support as usual.
  - Avoid hypocapnea. Cooling can decrease pCO2. Maintain blood gas pCO2 goal: 45-50 mmHg
  - Avoid hyperoxia.
  - Maintain goal Oxygen saturations: < 98% and PaO2 should be < 100mmHg
  - Monitor both pre and post-ductal saturations if ANY concern for pulmonary hypertension.
  - Consider if baby should be re-warmed if pre/post ductal saturations have greater than 10% difference or frequent desaturations while on maximum therapy for pulmonary hypertension.

- **Cardiovascular**
  - Maintain blood pressure in normal range, despite bradycardia.
  - Treat hypovolemia with volume administration, as needed.
  - Dopamine (1st choice agent) or Dobutamine (2nd choice agent) as needed
  - Expect bradycardia (<100 bpm) when temperature <34 °C.
  - For deep bradycardia (<80 bpm) – Don’t over react. It may be tolerated, if blood pressure is maintained adequately. Raising core temperature to 34°C alone may be adequate.
  - If sustained profound bradycardia (<60 bpm) consider atropine before using epinephrine
  - Atropine dose: 0.01-0.03 mg/kg/dose, q 10-15min
  - Monitor for arrhythmias. Obtain rhythm strip if unusual pattern develops.

- **Infectious Diseases**
  - Start antibiotics (Ampicillin and Gentamicin) after cultures obtained. Hypothermia reduces immune function, increasing risk for overwhelming sepsis.

- **Neurologic**
  - Maintain adequate sedation as above
  - Treat seizures (clinical or confirmed sub-clinical). Phenobarbital (1st choice agent) and follow serum levels
  - aEEG and video EEG as outlined above
  - Head Ultrasound only if clinically indicated.
  - MRI on DOL #4-5, at least 24 hours after re-warming and EEG electrodes removed. Request “neonatal brain protocol with MR spectroscopy and diffusion imaging.”

- **Skin**
  - Skin breakdown in dependent areas is seen in cooled patients, adjusting position to avoid pressure points
  - Check EEG and aEEG probes minimum of every 24 hours.
Guidelines for Rewarming after Cooling

- Complete 72 hours of cooling at 33.5°C. Warm by 0.5°C increments every hour.
- This is a high risk period. Monitor closely during rewarming, then at least 24 hrs after for:
  - Seizures
  - Rebound hyperthermia
  - Acidosis
  - Hypocalcemia
  - Hypoglycemia
  - Hyperkalemia
  - Hypomagnesemia
  - Diuresis/oliguria
  - Vasodilatation and hypotension
- Monitor laboratory results
  - Send blood gas and metabolic panel/electrolytes, including Mg and Ca 1 hour after start of rewarming.
  - Glucose - Q1-2 hours until stable
  - Arterial blood gas with electrolytes - Send 3 hours after rewarming has begun.

See protocol on line for specifics of cooling including blanket use and trouble shooting the system
**Neonatal Seizures**

**Incidence**
- 1-5% of full term births
- 60 in 1000 preterm birth
- One of the highest risk periods for seizures in human life and major risk factor for neurologic disability

**Seizure Types**
- **Subtle**
  - Eye: deviation, staring spells, blinking or fluttering eyelids
  - Oral-Buccal-lingual movements: Chewing, drooling, tongue thrusting
  - Extremities: Cycling/swimming movements
  - Vitals: Apnea, desaturations, autonomic changes in BP, HR
  - Both term and preterm
- **Generalized tonic**
  - PRETERM infant - Most uncommon type
  - Associated with IVH
- **Multifocal/Focal clonic**
  - Rhythmic jerking different from overall jitteriness or Benign Sleep Myoclonus
- **Seizures**--rarely involve all extremities, typically slow clonic jerking that rarely can be stimulated, does not stop with passive flexion or restraint, commonly with ocular and autonomic signs
- **Jitteriness**--commonly all extremities, fast tremor, commonly inducible and stops with flexion or restraint, rarely associated with ocular or autonomic signs
- **Benign Sleep Myoclonus**: Never when awake, always normal neurologic exam and EEG, stops with restraint and rarely associated with ocular or autonomic signs.

**Etiology of Early Onset (<3 days)**
- **CNS**
  - Hypoxia Ischemic Encephalopathy (65%)
  - Cerebral bleed
    - Subdural or Epidural - Traumatic delivery
    - Subarachnoid—“Well baby” with seizures
    - Intraventricular (10%)—Prematurity or AVM
  - Cerebral Infarction—Arterial or thrombosis with edema
  - Intrinsic developmental brain defects (6%)
  - Tuberous sclerosis
  - Benign Familial neonatal seizures (“Fifth Day Fits”)
- **Metabolic derangements**
  - Hypoglycemia—SGA, IDM, asphyxia
  - Hypocalcemia—IDM, asphyxia, DiGeorge/cardiac anomalies, prematurity
  - Hypomagnesemia
  - Pyridoxine dependency
- **Hematologic**
  - Extreme anemia
  - Polycythemia
- **Toxins**
  - Narcotic or barbiturate withdrawal
  - Local anesthetics—Lidocaine or Mepivacaine with paracervical/pudendal block
- **Cardiovascular Hypertension**
Etiology of Later Onset (>3 days)

- CNS
  - Benign Idiopathic neonatal seizures ("Fifth Day Fits")
  - Kernicterus
- Metabolic derangements
  - Hyponatremia—SIADH complicating meningitis, IVH
  - Hypernatremia—Dehydration, hyperammonemia
  - Hypocalcemia
  - Inborn errors of amino acid metabolism

- Infections
  - Meningitis – bacterial
  - Meningoencephalitis – viral
  - TORCH association

- Rare Disorders of glucose transport, metabolic disorders (Organic acidemias, urea cycle defects, Mitochondrial and peroxisomal disorders)

Evaluation

- History: maternal drugs, prenatal course, birth history, family history
- Physical: neurologic state, skin lesions, trauma signs, hepatosplenomegaly
- Bedside glucose test immediately, then blood glucose if <40 (send on ice and run STAT)
- Lumbar puncture (cell count, glucose, protein, HSV PCR if HSV suspected, save 1 ml for further diagnostics)
- Sodium, potassium, calcium, magnesium, BUN, Hct, blood gas
- CAT scan or head ultrasound for suspected hemorrhage or hydrocephalus screen.
- MRI for suspected HIE, stroke, cerebral dysgenesis, MRA/MRV if venous thrombosis
- EEG - consider pyridoxine infusion if no obvious etiology (remember the bedside aEEG machine)
- CBC, blood culture, TORCH titers, urine CMV
- Urine Toxicology
- Blood Ammonia, lactate, pyruvate, pH, serum amino acids and urine organic acids for initial metabolic screen
- Consider serum creatine kinase, biotinidase, serum carnitine and acylcarnitine profile, serum transferring, copper and ceruloplasmin screen, cholesterol, fatty acids (short, medium and long-chain), pipecolic acid. Urine acylglycine, uric acid, CSF lactic and pyruvic acids, CSF amino acids, CSF organic acids.

Immediate Therapy

- Establish adequate ventilation and perfusion
- Correct metabolic disturbance
- Hypoglycemia: D10W 2 ml/kg I.V. then continue infusion with D10W 100 ml/kg/day
- Hypocalcemia: Calcium gluconate 100-200 mg/kg as slow bolus. DO NOT give through arterial line if perfusion is poor or BP is low
- Hypomagnesemia: Magnesium sulfate, 50% 0.2 ml/kg I.M. or 25-50 mg/kg I.V. over 1-2 hour infusion, every 8-12 hours for 2-3 doses
- Pyridoxine dependency: Pyridoxine 50 mg I.V.
  - Note this is not a per kg dose.
  - Should be given while EEG in progress to document response

Medications

- aEEG suggested for monitoring effectiveness of medication
- Phenobarbital and phenytoin will stop > 80% of neonatal seizures.

First Line Drugs

- Phenobarbital - Enhances GABA inhibition and limits glutamate excitation
  - Monitor for respiratory depression
  - Loading: 10-20 mg/kg Slow I.V. or I.M.
  - Repeat with 5 mg/kg in Q30 minutes if necessary.
● Total dose = 30-40 mg/kg = level 40 mcg/ml
● Maintenance: 5 mg/kg/day I.V. or I.M., or PO, once daily
● Follow blood levels to adjust dosage. Therapeutic trough level 20-40 mcg/ml

● Pyridoxine: 50 mg IV bolus every 10 minutes up to 500 mg/kg if seizures on maximum Phenobarbital and no obvious etiology

Second Line Drugs: Suggest Neurology consult

● Phenytoint
  ● Blocks voltage dependant Na+ channels
  ● May cause respiratory depression
  ● Loading: 10-20 mg/kg. Slow I.V. (maximum infusion rate: 1 mg/kg/min)
  ● May repeat x1. Maximum dose = 40 mg/kg
  ● Monitor EKG during administration for heart block or V-fib. More common with rapid administration
  ● Maintenance: 2-4 mg/kg/dose IV or p.o. every q 12 hours.
  ● Therapeutic level 10-20 mcg/ml
  ● Oral absorption is poor
  ● Give I.V. in normal saline only

  ● Fosphenytoin (refrigerated) may be given IM when there is no IV access or in patients that are hypotensive

Third line drugs

● Lorazepam: 0.05-0.1 mg/kg IV over several minutes
  ○ Maintenance Q8-12 hours.
  ○ Continuous infusion 0.3 to 0.8mg/Kg/hour.
  ○ Good for neonatal tetany and narcotic withdrawal.
  ○ NOT a good choice for preterm infant given long half life of metabolite.

● Diazepam also NOT a good choice due to preservative displacing bilirubin from albumin
● Monitor closely for respiratory depression, hypotension, apnea
● Half life up to 54 hours in asphyxiated babies, duration of action 6-24 hours!

● Lidocaine 2 mg/kg, then 6 mg/kg per hour - Narrow therapeutic range and cardiac side effects.
● Valproic acid
  ○ 10 to 25 mg/kg then 20 mg/kg/day in 3 doses
  ○ Monitor drug levels.

● Non-status recurrent seizures:
  ○ Levetiracetam (Keppra®)
  ○ Inhibition of voltage-dependent N-type calcium channels; facilitation of GABA-ergic inhibitory transmission.
  ○ Loading: 10-20mg/kg/dose IV/PO
  ○ Maintenance 10-20 mg/kg/dose q12hr
  ○ No drug levels needed (maximum dose: 60mg/kg/day)

Neurodevelopmental Outcome

● HIE encephalopathy 50% normal
● IVH 10% normal
● Subarachnoid hemorrhage 90% normal
● Hypocalcemia
  ○ Early onset 50% normal
  ○ Late onset 100% normal
● Hypoglycemia 50% normal
● Bacterial meningitis 50% normal
● Developmental malformations 0% normal
● Fifth Day Fits 100% normal
Intraventricular Hemorrhage

Incidence
Reported incidence ranges from 20 to 60%. More recently, there appears to be a decrease in the incidence, with most centers reporting 15-40% incidence of hemorrhage in infants <1500 grams. There is an inverse relationship between incidence of hemorrhage and gestational age. It is rare in infants >32 weeks gestation and may be as frequent as 60% in infants of 24 weeks gestation.

Timing
Most hemorrhages (>80%) occur in the first three days of life, with approximately 50% occurring on the first day of life. Almost all hemorrhages are seen by seven days of life, although later bleeding has been reported in a small number of infants. In addition, a small, but significant number of hemorrhages occur before birth.

Pathogenesis
- Impaired cerebral auto-regulation
- Fluctuating cerebral blood flow (related to fluctuating arterial blood pressure)
- ↑ Cerebral blood flow
- ↑ Cerebral venous pressure (with pneumothorax, asphyxial heart failure)
- Hypotension and reperfusion
- Coagulation abnormalities

Most hemorrhages begin as bleeding in the subependymal layer of the ventricles (SEH or germinal matrix hemorrhage). This area is highly vascular with poor capillary support before 35 weeks, involves “hairpin loop” configuration of venous drainage and is very vulnerable to hypoxia.

The germinal matrix then ruptures into the ventricles and may proceed to dilation of the ventricular system or the development of hydrocephalus. In addition to the bleeding, some are associated with ischemia, resulting in intraparenchymal hemorrhages which may reflect bleeding into an ischemic area of the brain, rather than extension of the ventricular blood into the brain, or be result of venous hemorrhage from obstructed intracerebral veins.

Some infants may also develop periventricular leukomalacia, which is a result of ischemia of the white matter adjacent to the ventricles. This ischemia may be a pressure phenomena from over distension of the ventricles or a result of decreased perfusion to that area during the episode of hemorrhage.

Associated Clinical Factors
- Asphyxia
- Respiratory distress syndrome
- Pneumothorax
- Hypernatremia
- Rapid volume expansion
- Gestational Age <34 weeks, particularly <30 weeks
- Hypertension, hypotension
- Thrombocytopenia

Symptoms
Most are “silent” hemorrhages, diagnosed only by ultrasound. In catastrophic hemorrhage, infants may present with
- Hypotension, shock
- Drop in hematocrit
- Severe, persistent metabolic acidosis
- Cyanosis
- Seizures
- Bulging fontanel, split sutures
- Sudden deterioration of ventilatory status, apnea
- Bradycardia
- Lethargy, change in consciousness, papillary and cranial nerve abnormalities
- DIC
- SIADH

**Diagnosis**

The best descriptive method is an actual description of the location, size, laterality, presence or absence of ventricular dilation and/or hydrocephalus and presence of PVL. The Papile grading system is the universal grading system as follows:

- **Grade I:** Germinal matrix hemorrhage only
- **Grade II:** Germinal matrix + intraventricular blood with normal size ventricles (10-50% of ventricular area on sagittal view)
- **Grade III:** Ventricular blood + dilatation of ventricles
- **Grade IV:** Intracerebral blood (periventricular hemorrhage) and/or hydrocephalus

Periventricular leukomalacia is an important finding on ultrasound. The presence of extensive PVL correlates more strongly with neurodevelopmental impairment than the grade of the hemorrhage. PVL may be present as early as birth and as late as 3 weeks after a hemorrhage. Serial ultrasounds are necessary for the diagnosis.

**Timing of Imaging**

**Head Ultrasounds:** The majority of hemorrhages occur within the first 3 days of life, 35-50% on day 1 and 86% by day 3. Ninety-one percent of all hemorrhages will be apparent by day 7 of life. However, occasional hemorrhages do occur both prenatally and after the first week of life. If an ultrasound is positive, repeat ultrasounds should be done every 1-2 weeks and a final ultrasound as close to 40 weeks gestation as possible.

Minimum Screening:
- **<27 weeks**
  - HUS on day 3 (sooner if suspect large bleed but be cautious as very early can be normal as the bleed is just starting)
  - Repeat HUS at 7-14 days of age
  - Repeat HUS between 36-40 weeks

- **27-29 weeks gestation**
  - HUS between 7-14 days of life
  - If early HUS done repeat HUS at 7-14 days of age
  - Repeat HUS between 36-40 weeks

- **30-32 weeks gestation**
  - HUS between 7-14 days of life

- **> 32 weeks**
  - HUS if multiple risk factors for IVH
  - CT (immediately) if need to rule out hemorrhage
  - MRI (DOL #5-7) for encephalopathy

**Premie MRI:**

- For detection of white matter injury
- Infants with Grade III or IV IVH, cystic PVL and/or moderate to severe ventriculomegaly on US
- History of significant hypotension/sepsis.
- Use tensor-weighted imaging (TWI) allows for better quantification of brain size and myelination
- Study to be done > 36 weeks CGA
- Baby should not be sedated if possible, but feeding just prior to MRI with tight swaddle and ear muffs usually is sufficient.

**Prognosis**

In general, outcomes with IVH Grade I and II are similar without IVH
35% morbidity with Grade III
90% morbidity with Grade VI

Treatment

- Grades I and II: No treatment is necessary. Repeat head ultrasounds weekly until resolved. Do weekly head circumference measurement.
- Grade III and IV: IVH with ventricular dilatation frequently resolves with no treatment. However, it must be followed closely as it may result in rapidly progressive hydrocephalus.
- IVH with hydrocephalus: Neurosurgical consult
- Serial lumbar punctures may be effective in decreasing ventricular size if >8 ml of CSF are removed. The therapeutic value of serial taps is controversial
- Ventricular reservoir for ventricular taps: In rapidly progressive hydrocephalus in infants who are too small to shunt or whose CSF protein is extremely high, a ventricular reservoir may be a temporizing treatment to prevent further loss of brain substance in high pressure hydrocephalus

- Medical management
  - Do nothing: spontaneous resolution is common
  - Diamox: May decrease CSF production. Not of proven value. Usual dose 5-25 mg/kg/day (IV or po q 8 hours). Side effects are very common, including metabolic acidosis and GI intolerance with vomiting and diarrhea.
Intracranial Bleeding

See section above for germinal matrix and intraventricular hemorrhage in preterm infants

- Intracranial bleeding can occur at any level (see graphic below) and often is associated with evidence of trauma
- Presentation can include silent, irritability, lethargy, seizures, full fontanel, focal neurologic signs
- Type of imaging is dependent on the stability of the infant and the urgency of testing (after hours CT is the most readily available test as technician is in house)
- Coagulation factors should be checked if lesions are of significant size or expanding
- Although surgery is seldom needed Neurosurgical consult is recommended for large lesions (exception = subgaleal bleeds)
- With significant intracranial bleeding follow up imaging is indicated to look for post hemorrhagic hydrocephalus and persistent effusions
- Outcome is dependent on associated illness (e.g. HIE) and presence and extent of parenchymal injury

From Wiki Doc.com
<table>
<thead>
<tr>
<th>Type of Hemorrhage</th>
<th>Source of Bleeding</th>
<th>Population</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgaleal</td>
<td>Trauma (often vacuum with rotation) Shearing of bridging veins of scalp Can be extensive and associated with DIC</td>
<td>Term (primarily due to not using vacuum in preterm deliveries)</td>
<td>May not need routine imaging – base imaging on other clinical features and history</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Subdural</td>
<td>Rupture of draining veins &amp; sinuses in subdural space Often associated with trauma</td>
<td>Term</td>
<td>CT or MRI Ultrasound may give clues if subdurals are large but most are outside the normal port of HUS</td>
</tr>
<tr>
<td>Epidural</td>
<td>Between skull and dura Much rarer than subdural and often associated with skull fracture</td>
<td>Term</td>
<td>CT or MRI Ultrasound may give clues if lesion is large but most are outside the normal port of HUS</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>Common – “normal trauma of birth” Rupture of bridging veins of subarachnoid space</td>
<td>Preterm</td>
<td>CT or MRI or LP Ultrasound may give clues if extensive (see brightness into the sulci of brain) but most are outside the normal port of HUS</td>
</tr>
<tr>
<td>Germinal matrix and IVH</td>
<td>See above</td>
<td>Preterm</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Intraparenchymal hemorrhage – cerebrum</td>
<td>Preterm see above Extension of IVH AV malformations Ruptured aneurysms Coagulopathy Post infarction or embolic Venous or sinus thrombosis with bleeding</td>
<td>Preterm</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Intraparenchymal hemorrhage – cerebellar</td>
<td>Traumatic Venous infarction Extension of IVH Was associated with use of full mask CPAP in past</td>
<td>Preterm</td>
<td>Ultrasound if get proper cuts</td>
</tr>
</tbody>
</table>
Retinopathy of Prematurity

Background and Definition

Retinopathy of Prematurity (ROP) is an alteration in the normal vascular development of the retina, usually seen in premature infants whose vasculature is not developed at the time of birth. Low concentrations of insulin-like growth factor-1 (IGF-1) and relative hyperoxia in the early postnatal period lead to delayed retinal blood growth. Later, increased concentrations of IGF-1 permit VEGF-induced angiogenesis. Treatment with laser ablation of the peripheral avascular retina leads to rapid reduction of VEGF concentrations. It occurs most frequently in infants <1000 grams and are at risk for low levels of IGF-1 following birth. The incidence increases with decreasing birth weight and gestational age.

Diagnosis

Diagnosis is made by indirect ophthalmoscopy. Table below shows recommended times of examination. Most infants < 28 weeks develop some degree of ROP, although in most it regresses spontaneously. Other than prematurity, intrauterine growth restriction (IUGR), poor postnatal weight gain, poor head circumference growth and high oxygen needs after birth are also associated risk factors for ROP.

Classification has increased emphasis on dilatation and tortuosity of the posterior retinal blood vessels or “plus” disease as the key criterion for treatment decision. The degree of ROP is described in stage, location and extent.

Categories

- No ROP: mature vascular pattern to ora serrata.
- Immature, at risk: Avascular zones still exist on the preterm retina with transition to the vascular zone.
- ROP: Active neovascularization is present, stable or regressing.

Classification

- Location: See Figure for examination.
  - Zone I, II and III.
  - Retinopathy in Zone I much worse prognosis than retinopathy observed more peripherally
- Extent of Disease: How much of the retina is involved as total clock hours (of worst stage involved)
- Severity
  - Stage 1: A flat demarcation line exists between the vascular and avascular zones
  - Stage 2: The demarcation line is elevated above the plane of the retina
  - Stage 3: Neovascularization has invaded the vitreous. This may produce scars which place traction on the retina or optic disc
Stage 4: A subtotal retinal detachment has occurred. 4A: Extrafoveal involvement; 4B: Foveal involvement

Stage 5: Total retinal detachment (previously called retrolental fibroplasia)

- **Plus Disease**: Refers to vascular dilation and tortuosity of the peripheral vessels in at least two retinal quadrants. Suggests that active changes are present. Iris vascular engorgement, poor papillary dilation with dilating eye drops and vitreous haze may occur in more severe cases.
- **Pre-Plus disease**: Changes in vascular abnormalities that are insufficient for the diagnosis of plus disease but not considered normal.
- **Aggressive Posterior ROP (AR-ROP)** occurs in zone I and in posterior zone II and does not progress through stages 1-3 like classic ROP. Appears as a flat network of neovascularization with severe plus disease, needing urgent treatment.

**Screening**
- Taken from 2006 AAP recommendations (with errata correction of 2009) and 2008 United Kingdom guidelines:
  - All infants whose birth weights are less than 1500 grams
  - All infants gestational age less than 32 weeks
  - Select infants whose birth weights are between 1500 and 2000 grams or whose gestational ages are 32 weeks or more and have unstable courses, requiring cardiovascular support or at high risk (ie: SGA).
  - No exam needed if > 1800 grams and no oxygen needed
  - See chart for when the first screening should be done and follow up exams.
  - Screening examinations can be discontinued when the retina is fully vascularized, when vascularization has progressed into zone III without prior ROP, when ROP has regressed and at 45 weeks postmenstrual age when prethreshold disease is absent.

**Treatment Criteria**
- Current recommendations based on CryoROP study showing “prethreshold” ROP treatment led to better outcomes, thus lowering treatment threshold.
- The use of number of clock hours is no longer used as criteria for treatment.
- Treatment should be performed within 72 hours of the decision to treat.
- Threshold ROP is defined as:
  - Zone I, any stage of ROP with plus disease
  - Zone I, Stage 3 ROP without plus disease
  - Zone II, stage 2 or 3 ROP with plus disease

**Prognosis**
- Stage 1 and 2: Most regress completely. Higher incidence of refractive errors, amblyopia and strabismus.
- Stage 3: High incidence of myopia requiring corrective lenses. Strabismus common. May progress to late retinal detachment and vitreal hemorrhage
- Stage 4: 4A: As above. Functional vision usually preserved. 4B: Functional vision often not preserved.
- Stage 5: Poor prognosis for vision.

**Prevention:**
- Increasingly studies are showing meticulous attention to the delivery of O2 reduces ROP rates.
- Keys to this strategy are:
  - Checking that alarms are gestational age specific
  - Always using a blended O2 source
  - Do not just increase O2 when desaturation occurs
  - Address respiratory status (are they breathing, deep enough breaths)
  - If adjust O2 go in 2-5% increments and DO NOT LEAVE bedside until back to baseline

See [Oxygen Administration Procedure for oxygen parameters](#).

### Time Schedule for Fundus Examinations

<table>
<thead>
<tr>
<th>Gestational age at birth (weeks)</th>
<th>Postnatal Age at first exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>7</td>
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<td>25</td>
<td>6</td>
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<tr>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>27+</td>
<td>4</td>
</tr>
</tbody>
</table>

**Time of Follow-up Screening Exam**

- 1 Week or less: Zone I, stage 1 or 2 ROP
  - Zone II, stage 3 ROP
- 1 to 2 weeks: Zone I, no ROP
  - Zone I, regressing ROP
  - Zone II, stage 2 ROP
- 2 weeks: Zone II, stage 1 ROP
  - Zone II, regressing ROP
- 2 to 3 weeks: Zone II, no ROP
  - Zone III, stage 1 or 2 ROP
  - Zone III, regressing ROP

Follow up exam at 6 months in infants showing ROP of Grade II or worse at any time. Consider earlier exam if discharging infants before corrected age is reached and compliance with out-patient follow-up is question.

Make sure discharge information clearly spells out the need for follow up examinations if the retina is not mature at time of discharge. Specifically detail that failure to follow up on eye examinations may result in blindness (required for most ophthalmologist liability insurance.)

**Parental resources on ROP**

**Latest AAP statement on ROP**
Pharmacology

The Transfer of Drugs and Other Chemicals into Human Milk

Most drugs/medications taken by the mother reach her milk in some quantity. Depending on the chemical properties of the drug, the amount may be miniscule (and therefore the baby’s relative dose is tiny) or very large due to concentration into the breast milk. When the half life of the drug is short, maternal dosing after infant feeding will minimize the total dose the infant receives.

There are very few drugs that pass through to breast milk in such a way that breastfeeding or giving pumped milk is absolutely contraindicated.

The decision to use a drug while nursing or to continue to nurse while taking medication must be based on an individual assessment of risk and benefits. The following should be considered:

1. Is the drug therapy really necessary?
2. Use the safest drug. For example, acetaminophen is probably safer than aspirin.
3. If the drug poses a risk to the baby, consider measuring drug levels in the baby.
4. Minimize drug exposure to the baby by having the mother take the drug right after nursing or before the infant is due for a lengthy sleep period.

The most up to date lists are available in books such as:
Medications and Mothers’ Milk, Thomas Hale, PhD, the most current edition is 2009.

Briggs Drugs in Pregnancy and Lactation  link

Cloherty in the Medications section of the Manual of Neonatal Care gives a nice table of medications and the pregnancy risk category, AAP recommendation and those found in Hale’s Medications in Mother’s Milk.
Unless otherwise specified all doses are mg/kg per dose

When gestational grids are used gestation reflects corrected gestational age

Antibiotic Dosage Guidelines

Other sources of medication information are available on line
LEXICOMP LINK

**Antimicrobials**

**Acyclovir**
- **Individual Dose:** 20 mg/kg
- **Interval:** every 8 hours; every 12 h in infants <34 wks.
- **Route:** IV over 1 hour
- **Comments:** Hepatotoxicity, precipitation in kidneys,

**Amikacin**
- **Dose and Interval:**

<table>
<thead>
<tr>
<th>Gestational Age (weeks)</th>
<th>Postnatal Age (days)</th>
<th>Dose mg/kg</th>
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*or significant asphyxia with renal impairment
- **Route:** I.V. over 30 min.
- **Comments:** Reserve for multiply resistant organisms, particularly enterobacter. CSF penetration erratic. Measure peak and trough levels (Peak 20-30 mcg/ml, trough 5-10 mcg/ml.) Consultation with pharmacy is recommended before choosing this agent.

**Amphotericin Liposomal**
- **Dose:** Day 1 dose 1 mg/kg then 3-5 mg/kg
- **Interval:** every 24 hours
- **Route:** IV over 2 hours
- **Comments:** Protect from light. Available as 10 and 20 mg mixtures

**Amoxicillin (renal prophylaxis)**
- **Dose:** 25 mg/kg
- **Interval:** every 24 hours
- **Route:** oral
Ampicillin

- **Individual Dose:** 100 mg/kg for meningitis OR in first week until sepsis is ruled out or LP is reassuring
  50 mg/kg for sepsis treatment if no meningitis

- **Interval:**

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- **Route:** IV (preferred) over 15-30 min; IM if no IV access

- **Comments:** Do not use orally in newborn. Renal failure/shock 2° rapid IV. Ampicillin is not compatible with TPN line must be cleared with saline if given through a line with TPN running.

Cefazolin (Ancef, Kefzol)

- **Individual dose:** 25 mg/kg

- **Interval:**

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- **Route:** IV preferred over 15-30 minutes; IM.

- **Comments:** First generation

Cefotaxime (Claforan)

- **Individual dose:** 50 mg/kg

- **Interval:**

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- **Route:** IV over 30 minutes; IM

- **Comments:** Well tolerated in newborns. Good CSF penetration. Listeria and enterococcus are resistant.
Ceftazadime (Fortaz, Tazidem)
- **Individual Dose:** 50 mg/kg
- **Interval:**

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- **Route:** IV
- **Comments:** Only cephalosporin with significant anti-pseudomonal activity. Inactive against Listeria, enterococci. Synergistic with aminoglycosides.

Ceftriaxone (Rocephin)
- **Individual Dose:** 50-100 mg/kg
- **Interval:**

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- **Route:** IV, IM
- **Comments:** Not recommended for preterms or newborns with jaundice. Displaces bilirubin. Death has been reported when given with IV solutions that contained calcium. Third generation activity. Generally not used in NICU and must be over 4 weeks of age. Requires pharmacist consultation.

Clindamycin
- **Individual Dose:** 5-7.5 mg/kg
- **Interval:**

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- **Route:** IV, IM, oral
- **Comments:** Risk of pseudomembranous colitis. Poor CNS penetration. Higher doses may be needed for abscesses
Erythromycin

Oral dose
- For Pertussis and Chlamydia pneumonia: 12.5 mg/kg every 6 h oral
- For other infections and prophylaxis: 10 mg/kg every 6 h oral
- Intravenous dose: 5-10 mg/kg/dose every 6 h (reserve for serious infections). Monitor heart rate during administration. Hypotension and bradycardia reported with IV administration

- Comments: For treatment of chlamydia, mycoplasma and ureaplasma. Very irritating if given IV. May prolong half life of theophylline so monitor theophylline levels closely during therapy. Give with formula when using oral form to reduce side effects. Has been associated with hypertrophic pyloric outlet.

Fluconazole

- Individual Dose: 12 mg/kg loading then 6 mg/kg
- Interval:

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- Route: IV or po. IV over 30 minutes
- Comments: Used for fungal infections unresponsive to Amphotericin. Limited data in newborns. May prolong half life of methylxanthines

Fluconazole prophylaxis

- Individual Dose: 3 mg/kg
- Interval: < 29 wk 3 times a week (Tu-Th-Sat or Mo-Wed-Fr) ≥ 29 wk every 48hrs
- Route: IV over 30 minutes
- Comments: Used to prevent fungal infections when long term broad spectrum antibiotics are used.

5 Flucytosine (5-FC or Ancobon)

- Individual dose: 12.5-37.5 mg/kg
- Interval: every 6 hours
- Route: po
- Comments: Used in combination with amphotericin for systemic fungal infections. Good CSF penetration. Desired peak serum concentration 50-80 µ/ml. Reduce dose if renal function is impaired.

Ganciclovir

- Individual Dose: 6 mg/kg
- Interval: q 12 h
- Route: IV
- Comments: Treat for minimum of 6 weeks for congenital CMV. Limited data on efficacy
Gentamicin

- **Individual dose:** see below
- **Interval:**

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- **Route:** I.V. over 30 minutes; IM
- **Comments:** Increased potential for toxicity with administration beyond 7 to 10 days. Use lower doses and longer intervals in infants with poor renal function or asphyxia. **Dose must be adjusted with trough Gentamicin levels.** Ototoxicity and nephrotoxicity.

Therapeutic levels: Trough 1-2 mcg/mL; Peak 5-10 mcg/mL

Imipenem-Cilastin

- **Individual dose:** 20-25 mg/kg
- **Interval:** every 12 h
- **Route:** IV over 30 minutes
- **Comments:** A carbapenem. Treatment for enterobacteriacea and anaerobes resistant to other agents. **Requires consultation with pharmacist.**

Isoniazid (INH)

- **Dose and Interval:** Prophylaxis: 10 mg/kg/day as single dose or divided q 12
  Treatment: 10-20 mg/kg/day divided q 8 or 12.
- **Comments:** Check in Redbook for indications for use.

Methicillin see Nafcillin

Metronidazole (Flagyl)

- **Individual dose:** 7.5 mg/kg po or IV over 60 minutes.
- **Interval:**

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- **Route:** I.V., oral
Metronidazole (Flagyl) - continued

- **Comments:** For meningitis, ventriculitis and endocarditis caused by bacteroides fragilis and other penicillin-resistant anaerobes. Also used for anaerobic coverage for serious abdominal conditions (e.g. NEC) Poor coverage for other organisms. Good CNS penetration. Not FDA approved for neonates. Pharmacologic data limited but available in European literature.

---

**Mupirocin (Bactroban)**

- **Dose:** Apply small amount topically to affected area tid
- **Indication:** Topical use for skin infections from staph aureus including MRSA, S. epidermidis, S. saprophyticus and S. pyogenes.

---

**Nafcillin**

- **Individual dose:** 25 mg/kg for sepsis
  50 mg/kg for meningitis
- **Interval:**
  
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</table>
- **Route:** IV as 30 minute infusion
- **Comments:** Limited pharmacokinetic data in neonates. Use with caution in infants with compromised hepatic function. May cause phlebitis in PIV so central line the preferred route.

---

**Nystatin Oral Suspension (Mycostatin)**

- **Individual Dose:** 0.5-1.0 ml (100,000 units/ml)
- **Interval:** q 6 hr
- **Route:** Oral swab
- **Comments:** Consider using with broad spectrum antibiotics. Continue treatment for three days after symptoms subside.

---

**Nystatin Cream**

- **Dose:** apply ointment to affected area q 6 h
- **Comments:** Consider mixing with 0.5% hydrocortisone ointment if candidal rash is severe or inflamed.

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**Oseltamivir (Tamiflu)**

- **Individual Dose:** 3 mg/kg (max dose 12 mg)
- **Interval:** q 12 hr x 5 days
- **Route:** Oral
- **Comments:** No testing in neonates. FDA / CDC recommendations for use during pandemic influenza for treatment only not for prophylaxis. VLBW may need lower dose.
**Penicillin G**

- **Individual dose:**
  - 25,000 to 50,000 units/kg for sepsis.
  - 75,000 to 100,000 units/kg for meningitis.

- **Interval:**

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- **Route:** IV preferred; IM
- **Comments:** For treatment of documented Group B strep sepsis, use 200,000 u/kg/day; 400,000 units/kg/day for meningitis. May use 50,000 units/kg/day of procaine penicillin G IM or 50,000 unit/kg in schedule above for congenital syphilis. Rapid injection may cause seizures.

**Piperacillin**

- **Individual Dose:** 50-100 mg/kg (75 mg/kg usual for NEC)
- **Interval:**

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- **Route:** I.V. over 30 minutes; IM
- **Comments:** Good broad spectrum against gram negative bacteria. Inactivation by beta-lactamase producing bacteria. Good penetration to bone, CSF.
- **Monitoring:** Peak serum concentration: 150 µ/ml. Trough 15-50 µ/ml

**Piperacillin-Tazobactam (Zosyn)**

- **Individual Dose:**
  - 75 mg/kg for NEC
  - 50-100 mg/kg (dose calculated as piperacillin)
- **Interval:**

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- **Route:** I.V. over 30 minutes; IM
- **Comments:** Use for susceptible beta lactamase producing bacteria, including E coli, enterobacter, pseudomonas, Klebsiella, Haemophilus, Serratia and staph aureus. CNS penetration is modest (based on limited data.)
- **Monitoring:** Peak serum concentration: 150 µ/ml. Trough 15-50 µ/ml
Rifampin
- **Treatment Dose:** 10-20 mg/kg every 24 hours **ORAL** (may be with feeds)
  5-10 mg/kg every 12 hours **I.V.** over 30 minutes

- **Comments:** In combination treatment for persistent staphylococcal diseases. For prophylaxis against exposures to meningococcus or H flu see Red Book.

Septra (sulfamethoxazole/trimethoprim)
- **Treatment Dose:** 8-10 mg/kg/dose q 12 h based on the trimethoprim component
- **Route:** Oral

- **Comments:** Should not be used in neonates due to the sulfa component and displacement of bilirubin from albumin. Consider only in infants over 2 months of age with resolved jaundice.

Tobramycin
- **Individual dose:** SEE TABLE BELOW
- **Interval:**

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<td>&gt;7</td>
<td>5</td>
<td>24</td>
</tr>
</tbody>
</table>

- **Route:** IV as 30 minute infusion.
- **Comments:** Follow trough and peak levels. Use as first choice aminoglycoside for pseudomonas infections.

Vancomycin
- **Individual dose:** SEE TABLE BELOW (in neonate maximal dose is 60 mg/kg/day)
- **Interval:**

<table>
<thead>
<tr>
<th>Age (GA+PN wk)</th>
<th>Dose Mg/kg/dose</th>
<th>Interval (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤27 week</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>27-30</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>31-35</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>&gt;35</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>≥45</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

- **Route:** IV preferred over 60 minutes
- **Levels:** Trough 10-15 mcg/mL. In endocarditis and ventilator associated pneumonias may need a trough close to 20 mcg/mL. Levels greater than 50 are risky and greater than 80 are associated with ototoxicity. In rare instances a peak level is indicated (consultation with pharmacy is recommended.) Draw peak level 30 minutes after the infusion is complete and aim for peak 25-40 mcg/mL
Vancomycin - continued

- **Comments:** Indicated for staph epidermidis infections, or staph aureus resistant to mythically. Measure serum levels. Increased toxicity may occur when used with other drugs which alter renal function (indomethacin, gentamicin). Shock associated with rapid infusions.

Zidovudine (AZT, ZDV)

- **Dose and Administration:**
  - PO: 2 mg/kg
  - IV: 1.5 mg/kg over 60 minutes

<table>
<thead>
<tr>
<th>Gestational Age (Weeks)</th>
<th>Postnatal Age (Days)</th>
<th>Interval (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤29 weeks</td>
<td>0-28</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&gt;28</td>
<td>8</td>
</tr>
<tr>
<td>30-34</td>
<td>0-14</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&gt;14</td>
<td>8</td>
</tr>
<tr>
<td>≥35</td>
<td>ALL</td>
<td>6</td>
</tr>
</tbody>
</table>

- **Comments:** Treatment of infants of HIV positive mothers. Begin treatment within 6 to 12 h of birth and continue for 6 weeks. Monitor with weekly CBC for anemia and neutropenia.
## Medications (non antibiotic)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route &amp; Frequency</th>
<th>Caution and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC dophilus (probiotic)</td>
<td>&lt;1000 gram: ¼ teaspoon 1000-1500 g ½ teaspoon</td>
<td>Oral once a day – may divide q 12 h Dissolved in milk or sterile water</td>
<td>Combination of S thermophilus, B infantis, B bifidum</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>5-25 mg/kg/dose</td>
<td>IV or oral q 6 hours. Increase as tolerated to maximum dose</td>
<td>For hydrocephalus. Causes metabolic acidosis which may be severe in preterms.</td>
</tr>
<tr>
<td>Acetominophen</td>
<td>10-15 mg/kg/dose</td>
<td>Oral, rectal q 6-8 h Rectal dose may be increased to 20-30 mg/kg/dose</td>
<td>Extensively metabolized by liver. Limited data in babies</td>
</tr>
<tr>
<td>Actigal (Ursodiol)</td>
<td>10-15 mg/kg/dose Maximum 30 mg/day</td>
<td>Oral q 6-12 h</td>
<td>Treatment for cholestasis</td>
</tr>
<tr>
<td>Adenosine</td>
<td>50 microgram/kg (0.05 mg/kg)</td>
<td>Rapid IV push</td>
<td>Used for supraventricular tachycardia. Increase dose by 50 microgram/kg to max 4000 microgram/kg q 2 minutes. Do not refrigerate</td>
</tr>
<tr>
<td>Albumin</td>
<td>1 gm/kg/dose (use 5% solution)</td>
<td>IV slowly</td>
<td>Do not use for routine volume expansion</td>
</tr>
<tr>
<td>Albuterol</td>
<td>0.1-0.5 mg/kg/dose. Use 0.5% solution and dilute with 2 ml NS Alternative Dose: 0.5 ml of 0.5% solution (2.5 mg) per dose Preferred route: MDI with spacer 1-2 puffs (each puff is approximately 0.1 mg)</td>
<td>Aerosol q 2-6 h ET tube See respiratory section re administration methods</td>
<td>Dosages poorly defined in neonates. Discontinue administration if Heart Rate &gt;200 bpm</td>
</tr>
<tr>
<td>Alteplase t-PA</td>
<td>For central catheter: 0.5 mg/ml, instill 110% of catheter lumen volume Maximum 2 mg For intravascular thrombi: 200 microgram/kg/hour for 6-24 h</td>
<td>IV instillation or IV drip</td>
<td>For catheter: may repeat x 1 if not patent in 2 hours. For intravascular thrombi: follow coag studies. Risk of bleeding. See hospital protocol</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td>Route &amp; Frequency</td>
<td>Caution and Comments</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------------------</td>
<td>-------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Loading dose: 5 mg/kg over 30 minutes IV or oral</td>
<td>IV or oral q 8-12 h in preterm or infants &lt;2months. q 6-8 h in older infants.</td>
<td>In older infants, maintenance dose may need to be increased to 25 mg/kg/day divided q 6-8 h. Therapeutic levels: apnea 7-12µ/ml bronchospasm – 10-20µ/ml</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Loading dose: 5 mg/kg</td>
<td>IV over 60 minutes</td>
<td>For refractory SVT and other arrhythmia. Central vein preferred route. SE: bradycardia, abnormal LFT. Follow thyroid panel.</td>
</tr>
<tr>
<td>Ammonium Chloride</td>
<td>meq of chloride (as ammonium) = chloride deficit (meq/L) x 0.2 x wt (kg). Give 1/2 dose and recheck lytes</td>
<td>IV q 12 hour</td>
<td>Use for severe hypochloremia</td>
</tr>
</tbody>
</table>
| Arginine Chloride 10% (0.475 meq/ml or 100 mg/ml) | To treat hypochloremic alkalosis:  
# meq = 0.2 x wt in kg x (130 - serum chloride in meq/L)  
or  
0.3 x wt in kg x base excess in meq/L  
For metabolic disorder: Load 600 mg/kg in 25ml D10W IV over 90 mins, then 200-600 mg/kg/day infusion | IV over > 30mins | Avoid use in patient with renal and hepatic impairment (or if on spironolactone in hepatic impairment) due to hyperkalemia. Can cause hypoglycemia with high dose |
| Atropine              | 0.01 mg/kg/dose                           | IV slowly ; may repeat q 10-15 min to max 0.04 mg/kg SC  
ET: give 2-3 X IV dose; follow with 1 ml normal saline. | For vagal bradycardia. Not routinely indicated for neonatal resuscitation. For reversal of muscle paralysis: Give 0.1-0.2 mg/kg 30 seconds before edrophonium |
<p>| Bicarbonate (sodium bicarbonate) | 1-2 mEq/kg                                 | IV over at least 30 minutes | Evidence suggests limited clinical benefit for use – consult neonatologist before administration |
| Biotin                | 5-20 mg                                   | Oral once daily   | For metabolic disorders                                                              |
| Bumetanide            | 0.015-0.05 mg/kg                          | IV, IM, or oral q 24 hrs. | For edema refractory to furosemide or with renal insufficiency. Hyponatremia common |
| Caffeine Citrate      | Loading: 20 mg/kg                          | IV or oral once daily | Therapeutic levels for apnea: 10-20 µg/ml. Toxic levels &gt;50 µg/ml. (caffeine base is half the amount) |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route &amp; Frequency</th>
<th>Caution and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Chloride</td>
<td>0.2 ml/kg/dose of 10% solution</td>
<td>IV slowly</td>
<td>1 ml 10% = 27 mg elemental Ca/ml Use as last resort in neonatal resuscitation</td>
</tr>
</tbody>
</table>
| Calcium glubionate (NeoCalglucon) | Treatment: 500 mg/kg/day  
Supplement: 150 mg/kg/day | Divide q 3-4 hours in feedings         | Syrup has 360 mg cal glub./ml =23.6 mg elemental Ca/ml. High osmotic load             |
| Calcium Gluconate          | 100 mg/kg dose as slow push; then 200-700 mg/kg/day as continuous infusion | IV slowly boluses q 6-8 h  
Do not use conc >200 mg/100 ml in peripheral IV’s. Give as slow push if needing higher concentrations | 1 ml contains 9 mg elemental Ca/ml. Can cause sloughs if infiltrated into sq tissue.  
May precipitate if given in line with bicarbonate or balanced TPN solution containing Ca and Phos |
| Captopril                  | 0.01-0.05 mg/kg/dose                     | oral q 8-12 hours                       | Begin with low dose and increase with each dose to achieve desired effect on blood pressure. Administer 1 hour before feeding. For hypertension and for afterload reduction in CHF |
| Carnitine                  | Load: 100 mg/kg load  
Maintenance: 200 mg/kg/day | IV over 2-3 minutes in acute metabolic emergency  
Continuous infusion in metabolic emergency  
In carnitine deficiency may give daily dose divided q 8 hours by IV or oral route | For myocardopathy with carnitine deficiency  
For acute metabolic emergencies, after consultation with metabolic specialist, carnitine can be used to aid excretion of metabolites and facilitate long chain fatty acid entry into mitochondria. |
| Chlorothiazide (Diuril)    | 10-20 mg/kg/dose (oral)  
1-4 mg/kg/dose (IV) | Oral or IV q 12 hrs                     | Do not use with significant renal or hepatic dysfunction                              |
| Clonidine                  | 1 microgram/kg/dose                     | Oral every 6-12 h                       | For treatment of severe withdrawal symptoms to reduce adrenergic symptoms. Can cause hypotension.  
- see Neonatal drug abstinence policy                                      |
| Copper sulfate             | oral: 200-600 µ/day; IV 20µ/kg/day        | oral divide q 4-6 h; IV as continuous infusion | For copper deficiency.  
Use 1% solution                                                              |
<p>| Cyclomydril (Cyclopentolate/phenylephrine) | One drop each eye, repeat dose in 5 minute | Dilation for eye exam, may cause hypertension |                                                                 |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route &amp; Frequency</th>
<th>Caution and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>For BPD: 0.05-0.1 mg/kg/dose</td>
<td>IV or oral q 12 h</td>
<td>Higher doses have been associated with cerebral palsy when used for BPD. Hydrocortisone is preferred drug for stress and physiologic replacement. Weaning schedule may need to be altered by response to weaning and needs to be discussed with attending. Consider H2 blocker during use.</td>
</tr>
<tr>
<td></td>
<td>Initial dose for 3 days, then reduce by</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% for 3 days, then reduce by 50% for</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 days then off (may wean faster is</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rapid improvement seen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Seizures, sedations: 0.1-0.3 mg/kg/dose</td>
<td>Seizures: IV or oral q 12 h</td>
<td>Causes apnea. Displaces bilirubin. Half life of oral drugs extremely long (&gt;12 h) Rarely used as first line drug in neonatal seizures-lorazepam preferred.</td>
</tr>
<tr>
<td></td>
<td>(Status: 0.5-1 mg/kg/dose X 3 q 15-30</td>
<td>Drug withdrawal: Begin at</td>
<td></td>
</tr>
<tr>
<td></td>
<td>min)</td>
<td>low dose q 8 h and increase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug withdrawal: 0.35-1 mg/kg/dose (oral)</td>
<td>to max of 1 mg/kg q 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>as needed</td>
<td></td>
</tr>
<tr>
<td>Diazoxide</td>
<td>2-5 mg/kg/dose</td>
<td>Oral q 8 h</td>
<td>For treatment of refractory hypoglycemia due to hyperinsulinemia. Fluid retention is common.</td>
</tr>
<tr>
<td>Digiband or DigiFab</td>
<td>mg of Digiband: ([serum dig conc x 5.6</td>
<td>IV over 30 minutes with 0.22</td>
<td>Each vial Digiband contains 38 mg Each vial DigiFab contains 40 mg</td>
</tr>
<tr>
<td>(digoxin immune Fab)</td>
<td>x wgt in kg)/1000] x 76 OR serum dig conc</td>
<td>micron filter</td>
<td>Brand varies by availability Consult pharmacist</td>
</tr>
<tr>
<td></td>
<td>x 0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin (Lanoxin)</td>
<td>Digitalizing load: Preterm: 10 to</td>
<td>Digitalizing: divided into</td>
<td>Double check calculations, solutions used and strength. Write order as mg/dose and as microgram/dose. Check with another M.D. Oral Solution: 0.05 mg=50 microgram/ml Parenteral solution: 0.1 mg=100 microgram/ml</td>
</tr>
<tr>
<td></td>
<td>20 microgram/kg/day</td>
<td>3 doses =&gt; ½</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Term: 30 microgram/kg/day</td>
<td>¼ ¼ ¼ at 8 h intervals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance: &lt;1.5 kg: 4 microgram/kg/day</td>
<td>Maintenance: Begin 12 -24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5-2.5 kg: 8 microgram/kg/day</td>
<td>after last digitalizing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Term: 10 microgram/kg/day</td>
<td>dose. A single daily dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>is used in preterms until 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>month of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>oral dose is 20-25% higher</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>than IV dose due to bioavailability of drug orally</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td>Route &amp; Frequency</td>
<td>Caution and Comments</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2-25 microgram/kg/minute</td>
<td>IV infusion</td>
<td>Volume load prior to using for hypotension. Large or central vein preferred</td>
</tr>
<tr>
<td>Dopamine</td>
<td>3-20 microgram/kg/minute</td>
<td>IV infusion</td>
<td>May cause tissue slough. Large or central vein preferred</td>
</tr>
<tr>
<td>Doxapram</td>
<td>1-1.5 mg/kg/hr</td>
<td>IV infusion</td>
<td>Therapeutic level: &lt;5 µg/ml When control of apnea achieved, wean infusion. Contains benzyl alcohol. Use with caution in VLBW infants. Causes hypertension at higher doses</td>
</tr>
<tr>
<td>DTaP vaccine (diphtheria, tetanus, acellular pertussis)</td>
<td>0.5 ml</td>
<td>IM</td>
<td>At 2 months of age, may be given in combination vaccine (Pediarix includes DTaP, IPV and Hep B)</td>
</tr>
<tr>
<td>Elamax cream (lidocaine)</td>
<td>0.5-2 gram under occlusive dressing</td>
<td>Topical 15-60 minutes before procedure</td>
<td>No safety data on recurrent usage in preterm infants</td>
</tr>
<tr>
<td>Enalaprilat / Enalapril</td>
<td>Enalaprilat: Begin with 5-10 microgram/kg/dose (0.005 to 0.010 mg/kg/dose) Enalapril: Begin with 40 microgram/kg/dose, increase to max of 150 microgram/kg/dose</td>
<td>Enalapril: IV over 5-10 minutes q 24 h Enalapril: oral q 24 h, increase to as often as q 6 as needed for effect.</td>
<td>Treatment of moderate to severe hypertension. Also used as afterload reducer in CHF. For both drugs, may need to increase dose every few days.</td>
</tr>
<tr>
<td>Epinephrine(1:10,000)</td>
<td>0.1-0.3 ml/kg/dose = 10-30 microgram/kg; Continuous infusion: Start with 0.1 microgram/kg/minute and increase to max of 1 microgram/kg/min</td>
<td>IV, Intratracheal, intracardiac For ET administration give 2-3 times IV dose followed by 0.5-1.0 ml normal saline.</td>
<td>Tachycardia, local ischemia if extravasated; not compatible with NaHCO₃</td>
</tr>
<tr>
<td>Epoetin alfa (Epogen)</td>
<td>250 units/kg/dose Total dose = 750-1400 unit/kg/week</td>
<td>SC every other day for 3 days/wk (eg MWF)</td>
<td>CBC to check for neutropenia Reticulocyte count at 1 wk Give with iron and Vit E</td>
</tr>
<tr>
<td>Esmolol</td>
<td>For SVT: 100 microgram/kg/minute increase by 50-100 microgram/kg/minute q 5 minutes For postop hypertension: 50 microgram/kg/minute. Increase by 25-50 microgram/kg/minute q 5 minute</td>
<td>Continuous IV infusion</td>
<td>May cause hypotension in high doses. Monitor IV site for extravasation. Very short half life. Maximal dose is 200 microgram/kg/min</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td>Route &amp; Frequency</td>
<td>Caution and Comments</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------</td>
<td>------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Famotidine</td>
<td>0.5 mg/kg/dose</td>
<td>IV intermittent or oral q 12 h</td>
<td>May adjust if gastric pH remains &lt;4 for ≥2 h. Tolerance develops on prolonged IV use. Ideally if needed should be added to parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg/day in TPN</td>
<td>Continuous infusion if added to TPN</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Anesthesia: 10-20 microgram/dose</td>
<td>IV bolus q 2-4 h Continuous infusion: 0.5 - 4 microgram/kg/hour</td>
<td>Tolerance develops rapidly with continuous infusion. Chest wall rigidity may occur with rapid bolus. May cause hypotension when given with midazolam or lorazepam. Reversal with Narcan</td>
</tr>
<tr>
<td></td>
<td>Analgesia: 1-4 microgram/kg/dose</td>
<td>oral (may be divided into 2 doses)</td>
<td></td>
</tr>
<tr>
<td>Ferrous Sulfate</td>
<td>Prevention of anemia: 2-4 mg/kg/day</td>
<td>oral (may be divided into 2 doses)</td>
<td>Infant iron drops vary in concentration: 15 mg/0.6ml (at CPMC). Supplements not required when iron containing formula used in term infants.</td>
</tr>
<tr>
<td></td>
<td>Treatment or if using with EPO: 6 mg/kg/day</td>
<td>IV over 15 seconds. May repeat q 45 seconds to max of 50 microgram/kg</td>
<td>For reversal of sedation respiratory distress from benzodiazepams</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>5-10 microgram/kg/dose</td>
<td>IV over 15 seconds. May repeat q 45 seconds to max of 50 microgram/kg</td>
<td>For reversal of sedation respiratory distress from benzodiazepams</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>Load: 15-20 mg phenytoin equivalent/kg</td>
<td>IV or IM over 10 minutes Maintenance q 24 h</td>
<td>Used for seizures refractory to phenobarbitol. Maximum rate of infusion 1.5 mg phenytoin equivalent/minute</td>
</tr>
<tr>
<td></td>
<td>Maintenance: 4-8 phenytoin equivalent/kg</td>
<td>IV or IM over 10 minutes Maintenance q 24 h</td>
<td>Used for seizures refractory to phenobarbitol. Maximum rate of infusion 1.5 mg phenytoin equivalent/minute</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>1-2 mg/kg/dose to max of 6 mg/kg/dose</td>
<td>IV q 8-12 h oral q 8-12 h may also be given IM</td>
<td>Hypokalemia, hyponatremia and hypochloremia; displacement of bilirubin from albumin; hypercalciuria; bone demineralization and renal stones with chronic use. Ototoxic and nephrotoxic</td>
</tr>
<tr>
<td>Glucagon</td>
<td>0.03 to 0.3 mg/kg/dose</td>
<td>IV, IM, SC. May repeat in 20 minutes prn</td>
<td>For IDM’s: begin with 0.3 mg/kg (maximum dose=1 mg)</td>
</tr>
<tr>
<td>Glucose (10%)</td>
<td>2-4 ml/kg/dose</td>
<td>IV push slowly. Follow with infusion of 6-8 mg/kg/minute</td>
<td>IV push slowly</td>
</tr>
<tr>
<td>Hemophilus B vaccine (Hhib)</td>
<td>0.5 ml</td>
<td>IM</td>
<td>At 2 months of age</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td>Route &amp; Frequency</td>
<td>Caution and Comments</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>-------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Heparin</td>
<td>For central line patency: 1 unit/ml of infusate. For flush solution: use premixed syringes of 1 unit per ml saline For systemic anticoagulation: 50-75 unit/kg bolus over 1 minute followed by 20-25 unit/kg/hr. Adjust according to clotting studies</td>
<td>IV</td>
<td>Adjust dose to maintain PTT at 1.5 to 2X normal. May cause thrombocytopenia. Do not use if platelets &lt;50,000. Use protamine sulfate to reverse overdose: give 1 mg for each 100 units of heparin given in last 3-4 hr (max of 50 mg)</td>
</tr>
<tr>
<td>Hepatitis B Immune Globulin (HBIG)</td>
<td>0.5 ml</td>
<td>IM only</td>
<td>For perinatal hepatitis B exposure, give within 12 hours of birth</td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>0.5 ml</td>
<td>IM</td>
<td>Engerix-B is 10 microgram dose = Recombivax HB is 5 microgram</td>
</tr>
<tr>
<td>Hyaluronidase (Wydase, Vitrase)</td>
<td>dose is 20-25 units injected into infiltrate site (0.1 ml of solution)</td>
<td>Injected in small aliquots into extravasation site per protocol: 20 units = 0.1 ml hyaluronidase diluted with normal saline to 1 ml volume. Inject 5 0.2 ml aliquots along edges of infiltrate</td>
<td>Not to be used with vaso-active medication infiltrates (e.g. dopamine) see phentolamine Protocol for use is in NICU IV Protocol</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>IV: 0.1 to 0.5 mg/kg/dose Oral: 0.25-1 mg/kg/dose (2 times the IV dose)</td>
<td>oral, IV 6-8 h Max. dose: 2 mg/kg/day</td>
<td>Begin with low dose and increase until clinical response (bounding pulses, increasing pulse pressure and decreasing diastolic blood pressure) is seen. Consider adding beta blocker to enhance antihypertensive effect and decrease reflex tachycardia</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td>Route &amp; Frequency</td>
<td>Caution and Comments</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>-------------------</td>
<td>---------------------</td>
</tr>
</tbody>
</table>
| Hydrocortisone | Physiologic:  
oral = 8-10 mg/meter$^2$/day  
IV = 6-8 mg/meter$^2$/day  
(a term newborn is about 0.2 meter$^2$)  
Stress doses or for CLD:  
1 mg/kg/dose  
Initial dose for 3 days, then reduce by 50% for 3 days, then reduce by 50% for 3 days then off  
Stress dose 25-50 mg/meter$^2$/day  
Hypoglycemia – use stress dose | IV or oral **divided** q 8-12 h  
IV q 8 h | Weaning schedule may need to be altered by response to weaning and needs to be discussed with attending  
Consider H2 blocker during use  
Avoid abrupt discontinuation if have been giving >3 days |
| Ibuprofen (Neoprofen) | Initial dose: 10 mg/kg  
2$^{nd}$ and 3$^{rd}$ dose: 5 mg/kg | IV once every 24 hours | For PDA closure  
NPO not necessary in all cases |
| Indomethacin | Infants <28 wk gestation  
Initial dose: 0.2 mg/kg  
2$^{nd}$ and 3$^{rd}$ dose: 0.1 mg/kg  
Infants 28 weeks and greater  
0.2 mg/kg for all 3 doses  
**See Management of PDA** | IV every 12 hours | Compatible only with D5 and NS  
[CPMC Protocol on Indocin](#) |
| Insulin (regular) | Hyperglycemia: Initial 0.1 unit/kg/dose IV over 15-20 minutes.  
**Hyperkalemia:** 0.05-0.1 unit/kg/hour with dextrose 5 mg/kg/min | IV continuous infusion: 0.01 to 0.1 unit/kg/hr | Hyperglycemia  
Hyperkalemia  
[CPMC NICU Insulin Protocol](#) |
| Intravenous Gamma Globulin, Intravenous (IVIG) | Hemolytic jaundice (rH, ABO)  
0.5-1 gram/kg/dose  
Gram negative sepsis:  
0.4 gram/kg | IV slowly (see infusion protocol)  
Jaundice – may repeat once after 12 h if needed  
Sepsis – dose once | Jaundice due to hemolysis with concern will reach double volume exchange transfusion levels  
For septic shock. Give as one time dose. Conflicting reports of efficacy. |
| Ipratropium | 75-175 microgram/dose by nebulizer;  
36-72 microgram/dose by MDI. May be combined with albuterol  
Nebulizer q 6-8 h  
MDI with spacer | | Derivative of atropine. Synergistic with $\beta$-agonists |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route &amp; Frequency</th>
<th>Caution and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayexalate</td>
<td>1 gm/kg/dose</td>
<td>oral or as retention enema q 6 hours, retain enema for at least 30 minutes</td>
<td>For hyperkalemia. Avoid oral use in VLBW infants. Mix 3.5 gm of kayexalate in 10 ml of 20% sorbital = 0.33 gm/ml = 3 ml/dose. May mix in saline for VLBW infants.</td>
</tr>
<tr>
<td>Labetalol</td>
<td>0.25 mg/kg; 1.0 mg/kg max bolus dose. Total dose 4 mg/kg</td>
<td>Give IV bolus over 2 minutes. May repeat q 4 hours</td>
<td>Powerful antihypertensive for acutely lowering blood pressure. Causes smoother pressure drop than diazoxide and nitroprusside.</td>
</tr>
<tr>
<td>Lanoprazole (Prevacid)</td>
<td>1-2 mg/kg</td>
<td>oral, q 24 hr</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>Levetiracetim (Keppra)</td>
<td>Load: 10-20 mg/kg/dose</td>
<td>IV or oral over 30-60 minutes</td>
<td>No drug levels available</td>
</tr>
<tr>
<td></td>
<td>Maintenance: 10-20 mg/kg/dose</td>
<td>IV or oral q 12 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum dose 60 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Levothyroxine (T4, Synthroid)</td>
<td>Oral dose:10-15 microgram/kg/dose</td>
<td>q 24 hours.</td>
<td>After 4 wks, T4 should be in high normal range (10-16 µ/dL). TSH should have declined.</td>
</tr>
<tr>
<td></td>
<td>IV dose: 5-8 microgram/kg/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine HCl (1%) (10 mg/ml)</td>
<td>Bolus: 0.5 to -1 mg/kg Infusion: 10 to 30 microgram/kg/min. (Lowest dose for preterms)</td>
<td>IV bolus slowly. May repeat in 10 minutes as necessary for arrhythmia. Total bolus dose not to exceed 5 mg/kg</td>
<td>For ventricular tachycardia or fibrillation</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>0.05 -0.1mg/kg/dose</td>
<td>IV: May repeat dose in 15 minutes. For sedation give 0.05 mg/kg/dose q 8-12 h in infants &lt;2000 gm (33 weeks gestational age), q 6-8 h in infants ≥2000 gm. Levels cumulative in LBW infants. Oral</td>
<td>Use for seizures not responding to phenobarbital or Dilantin. Half life is ~ 8 hours. May cause apnea, hypotension and paradoxical CNS stimulation. Hypotension more common when used with narcotics</td>
</tr>
<tr>
<td>Magnesium Sulfate</td>
<td>0.2-0.4 meq/kg (25-50 mg/kg/dose)</td>
<td>Infuse IV over 2-4 hours (max 1 meq/h) Max 200 mg/kg/day = 1.6 meq/kg/day</td>
<td>Minimum volume 100 mg/ml in normal saline or D5</td>
</tr>
<tr>
<td>MCT oil</td>
<td>1-8 ml in a /24 hr period</td>
<td>oral divided in feedings</td>
<td>Each ml contains 7.6 cal Does not include essential fatty acids</td>
</tr>
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</tr>
<tr>
<td>Metaproterenol (Alupent)</td>
<td>Oral:1.5-3.0 mg/kg/day</td>
<td>oral q 8 h</td>
<td>For bronchospasm in BPD</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.05-0.2 mg/kg/dose (use 1 mg/ml concentration)</td>
<td>Oral with feeds every 6-8 h based on withdrawal scores</td>
<td>See Neonatal drug abstinence policy for titration based on infant withdrawal scores. Used for post-natal opiate exposure withdrawal</td>
</tr>
<tr>
<td>Metoclopramide (Reglan)</td>
<td>0.03 to 0.1 mg/kg/dose</td>
<td>Oral or IV q 8 hr</td>
<td>To facilitate gastric emptying. Lethargy, extrapyramidal signs, and diarrhea may occur. USE WITH CAUTION – long term side effects may include movement disorders</td>
</tr>
<tr>
<td>Midazolam (Versed)</td>
<td>0.05 -0.1mg/kg Continuous infusion: &lt;33 wks gestation: 60 microgram/kg/h x 24 h, then 30 microgram/kg/h ≥33 wks: 60 microgram/kg/h</td>
<td>IV over 5 minutes q 4-6 h</td>
<td>Little data in neonates. Do not give bolus to infants &lt;28 wk gestations. For procedural sedation. Reversal agent: flumazenil (5-10 microgram/kg IV)</td>
</tr>
<tr>
<td>Morphine for oral usage in drug withdrawal</td>
<td>0.05-0.15 mg/kg/dose (use the 2 mg/ml preparation)</td>
<td>Oral every 4 hours based on withdrawal scores</td>
<td>See Neonatal drug abstinence policy for titration based on infant withdrawal scores</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>0.05-0.2 mg/kg/dose Continuous drip 0.01-0.03 mg/kg/hour</td>
<td>IV every 4-6 h if bolus</td>
<td>Adjust for gestational age as may accumulate in very preterm infants. Reversal with Narcan</td>
</tr>
<tr>
<td>Naloxone (Narcan)</td>
<td>0.1 mg/kg/dose (0.4 mg/mL=0.25 ml/kg/dose)</td>
<td>IV, SC or IM. May repeat in 3-5 minutes if no effect. May need to repeat dose in 4 hours</td>
<td>Confirm dilution strength. Do not use in infants of drug using mothers</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Pavulon reversal: 0.05 to 0.1 mg/kg/dose Myaesthenia test: 0.02-0.04 mg/kg/dose</td>
<td>IV</td>
<td>Give atropine (0.02 mg/kg) immediately before IV dose or 30 minutes before IM dose</td>
</tr>
<tr>
<td>Nitric oxide for inhalation</td>
<td>2-20 ppm</td>
<td>Inhaled in line with respiratory circuit</td>
<td>Possible methemoglobinemia</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Start 0.1-1 microgram kg/min</td>
<td>Continuous infusion Increase 1 microgram/kg/min every 30-60 minutes to max 10 microgram/kg/min</td>
<td>For congestive cardiomyopathy. Little newborn data available.</td>
</tr>
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</tr>
<tr>
<td>Nitroglycerine paste</td>
<td>2-4 mm/kg of paste to affected area</td>
<td>To area of vasospasm</td>
<td>Protocol for use is in NICU IV Protocol</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.25-0.5 microgram/kg/min</td>
<td>IV continuous infusion</td>
<td>Can cause severe hypotension. High dose (over &gt; 5 microgram/kg/min) results in cyanide accumulation. Little data in newborns</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.01-1 microgram/kg/min</td>
<td>Continuous infusion</td>
<td>Anxiety, tachycardia, bradycardia</td>
</tr>
</tbody>
</table>
| Opium Tincture (10%)       | Add 1 ml to 25 ml water = 0.4 mg morphine/ml  
Dose = 0.2-0.3 ml/kg/dose  | oral q 3-4 h               | For narcotic withdrawal. Not a first line drug choice at CPMC. See morphine oral and methadone. Do not confuse with paregoric |
| Palivizumab (Synagis)      | 15 mg/kg/dose                             | IM                         | Recommendations change yearly and should adhere to AAP guidelines published in current Redbook |
| Pancuronium (Pavulon)      | 0.1 mg/kg/dose (initial)  
0.03 to 0.1 mg/kg/dose maintenance | IV q 1-4 h prn             | Hypotension and or transient hypertension. Levels accumulate over time. Remember to order eye lubrication. With prolonged paralysis may see acidosis, hypothermia, hypermagnesemia, hyperkalemia |
| Pentobarbital (Nembutal)   | 2-6 mg/kg/dose                           | IV, oral q 4-6 hr          | May accumulate; Poorly metabolized by tiny babies  
Serum concentration for sedation: 0.5-3 µg/ml                                              |
| Phenobarbital              | Loading: 20 mg/kg/dose. Additional doses of 5-10 mg/kg have been given to total dose of 40 mg/kg  
Maintenance: 3-5 mg/kg/day  | IV, IM, oral.              | Apnea at levels > 50 µg/ml. Therapeutic level usually 15-30µg/ml.                     |
| Phentolamine (Regitine)    | 0.5 mg/ml solution use 1-5 ml depending on size of infiltrate | Subcutaneous injection in area of extravasation | For vasopressor infiltrates Protocol for use is in NICU IV Protocol |

CPMC NICU Manual v7
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<tr>
<td>Phenylephrine (Neosynephrine)</td>
<td>5-20 microgram/kg/dose</td>
<td>IV every 10-15 minutes</td>
<td>For “Tet” spells</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Loading: 10-20 mg/kg Maintenance: 2-4 mg/kg/dose</td>
<td>Load: IV slowly in saline. Maximum infusion rate = 1 mg/kg/min Maintenance IV or oral q 12 h</td>
<td>Difficult to achieve therapeutic levels with oral solution. Therapeutic levels are 10-20 mcg/ml. Start maintenance 12-24 hours after the loading dose</td>
</tr>
<tr>
<td>Phosphate (as potassium or sodium salts)</td>
<td>0.1-0.4 mmol/kg</td>
<td>IV infusion over 4-6 h Maximum 0.06 mmol/kg/h Oral replacement divided into feeds maximal concentrations in NS or D5 PIV: 0.03 mmol/ml CVL 0.12 mmol/ml</td>
<td>1 mmol phos contains 1.5 meq K 1 mmol phos contains 1.3 meq Na IV access in PCIS PICU pathway</td>
</tr>
<tr>
<td>Pneumococcal 7-valent vaccine (Prevnar)</td>
<td>0.5 ml</td>
<td>IM</td>
<td>At 2 months of age</td>
</tr>
<tr>
<td>Polio vaccine (inactivated)</td>
<td>0.5 ml</td>
<td>IM</td>
<td>At 2 months of age, may be given in combination vaccine (Pediarix includes DTaP, IPV and Hep B)</td>
</tr>
<tr>
<td>Potassium (as chloride or acetate)</td>
<td>0.5-1 meq/kg</td>
<td>Infuse over 1-2 h Maximum 0.5 meq/kg/h Maximal concentrations (in NS or D5) PIV: 0.04 meq/ml CVL 0.2 meq/ml</td>
<td>IV route access via PICU pathway</td>
</tr>
<tr>
<td>Predforte eye drops</td>
<td>1-2 drops in affected eye</td>
<td>Interval varies, drops in eyes as directed by ophthalmology</td>
<td>Used in ROP at threshold or post laser</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.5 to 2 mg/kg/day</td>
<td>oral divided q 12 h</td>
<td>Hypokalemia, cushingoid syndrome. Adrenal suppression. Use 1 mg/ml liquid or crushed tablet. Avoid 5 mg/ml solution due to high alcohol content.</td>
</tr>
<tr>
<td>Propanalol</td>
<td>Oral dose: 0.25 mg/kg/dose to max of 3.5 mg/kg/dose IV dose: 0.01 mg/kg. to max of 0.15 mg/kg/dose</td>
<td>Oral: q 6 h IV: q 6 h over 10 minutes</td>
<td>Treatment of tachyarrhythmias and hypertension. Palliation of tetralogy of Fallot and obstructive cardiomyopathy. Can cause bradycardia, bronchospasm and hypoglycemia</td>
</tr>
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</tr>
<tr>
<td>Prostaglandin E (Alprosdatil)</td>
<td>Initial dose: 0.05-0.1 microgram/kg/min by continuous infusion</td>
<td>IV, UAC*, UVC</td>
<td>Be prepared to intubate/ventilate as apnea is very common. Other side effects include fever, cutaneous flushing and bradycardia. Long term use (&gt;120 h) may lead to gastric outlet obstruction and long bone cortical proliferation</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: may be as low as 0.01 microgram/kg/min</td>
<td>*if use UAC should have line as close to ductus as possible</td>
<td></td>
</tr>
<tr>
<td>Protamine</td>
<td>1 mg/100 units of heparin given in last 30 minutes (see NeoFax for sliding scale down for dosing for heparin given over 30 minutes ago) Max dose 50 mg</td>
<td>IV slow push, do not exceed 5 mg/min</td>
<td>Reverses heparin. Excessive doses can cause bleeding</td>
</tr>
<tr>
<td>Pyridoxine (Vit B6)</td>
<td>Diagnostic dose 50 mg/dose (note NOT per kg)</td>
<td>IV, single dose, may also be given IM (note this is not per kg) Oral q 24 h</td>
<td>Used to diagnose pyridoxine dependent seizures and treat metabolic disorders</td>
</tr>
<tr>
<td></td>
<td>Treatment / Maintenance: 50-100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>Oral : 2 mg/kg/dose IV in term infant: 1.5 mg/kg/dose IV in preterm infant: 0.5 mg/kg/dose Continuous: 0.1 mg/kg/hr</td>
<td>oral q 8 h IV for term infant q 6-8 h IV for preterm infant q 12 h</td>
<td>H₂ receptor antagonist. reduces gastric acid. Fewer side effects than cimetidine</td>
</tr>
<tr>
<td>Racemic epinephrine (Vaponephrine 2%)</td>
<td>0.25 ml/dose diluted to 3 ml with saline</td>
<td>By aerosol q 4 h</td>
<td>For postextubation stridor</td>
</tr>
<tr>
<td>Saline (3%) (Hypertonic saline)</td>
<td>4 ml/kg (0.513 meq/ml)</td>
<td>IV over 10 min</td>
<td>Use for hyponatremia seizures. Has an osmolality of 1030 mosm/L</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>0.3-1 mg/kg/dose</td>
<td>Gavage (oral) q 6-12 hr</td>
<td>For pulmonary hypertension</td>
</tr>
<tr>
<td>Silver Sulfadiazine (1%) (Silvadene)</td>
<td>Apply cream approximately 1/16 inch thick over area</td>
<td>q 12 h</td>
<td>Contains sulfa – avoid if jaundiced</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>0.5-1 meq/kg/dose</td>
<td>oral q 6-12 h</td>
<td>Oral is 1 ml = 4 meq NaCl</td>
</tr>
<tr>
<td>Spironolactone (Aldactone)</td>
<td>1-2 mg/kg/dose</td>
<td>oral q 12 h</td>
<td>Potassium sparing diuretic Poor diuretic in infants</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>50 U/kg/hr (Doses as high as 2000 unit/kg as loading dose have been described)</td>
<td>IV or intraarterial close to thrombus until clot lysis (mean=4 days)</td>
<td>For thrombolysis in major arteries or veins. Very little info in neonates</td>
</tr>
<tr>
<td>Sucrose solution (SweetEase)</td>
<td>Dipped pacifier – 0.5 ml of 24% solution</td>
<td>Oral</td>
<td>0.5 ml = 0.12 gram sucrose</td>
</tr>
<tr>
<td>Drug</td>
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</tr>
<tr>
<td>Survanta</td>
<td>4 ml/kg</td>
<td>ET as soon after birth as possible with up to 24 additional doses as needed</td>
<td>See package insert for method of administration</td>
</tr>
<tr>
<td>THAM acetate (0.3 M solution)</td>
<td>1-2 mmol kg/dose (3.3 – 6.6 ml/kg/dose)</td>
<td>IV over at least 30 minutes</td>
<td>Do not use if anuric or uremic. Can cause hypoglycemia and hyperkalemia with repeated dosing</td>
</tr>
<tr>
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</tr>
<tr>
<td>Theophylline – see aminophylline</td>
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</tr>
<tr>
<td>Vecuronium</td>
<td>0.1 mg/kg/dose</td>
<td>q 1-2 h</td>
<td>For muscle paralysis</td>
</tr>
<tr>
<td>Vitamin D (D2 ergocalciferol)</td>
<td>400 int. units (0.05 ml of oral liquid)</td>
<td>oral daily</td>
<td>Daily dose – may need increased dose for rickets. Can cause hypercalcemia. <strong>CAUTION</strong> – stock solution is 8000 units/ml</td>
</tr>
<tr>
<td>Vitamin B1 (thiamine)</td>
<td>50-150 mg</td>
<td>IV or oral once daily</td>
<td>For metabolic disorders</td>
</tr>
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<td>50-150 mg</td>
<td>IV or oral once daily</td>
<td>For metabolic disorders</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>1-2 mg</td>
<td>IM once daily</td>
<td>For metabolic disorders</td>
</tr>
<tr>
<td>Vitamin B6 (see pyridoxine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E (tocopherol acetate)</td>
<td>15 units per day</td>
<td>Oral once a day</td>
<td>Used in conjunction of erythropoietin</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>&lt;1 kg 0.5 mg</td>
<td>IM</td>
<td>Activates factors II, VII, IX, X</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>&gt;1 kg 1 mg</td>
<td>IM</td>
<td>Activates factors II, VII, IX, X</td>
</tr>
<tr>
<td>Vitamins, multi-</td>
<td>0.5 – 1 ml daily</td>
<td>Oral once a day</td>
<td>Vitamin D is 400 units per 1 ml Iron is 9-10 mg elemental iron per ml</td>
</tr>
<tr>
<td>VZIG</td>
<td>1 vial (125 mg)/10 kg wt</td>
<td>IM x 1</td>
<td>For varicella exposure</td>
</tr>
</tbody>
</table>