Newborn Screening
For
Sick or Preterm Newborns

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Newborn Screening and sick/premature newborns.
Newborn Screening is an important part of newborn health. Utah requires every newborn to be screened twice. The first sample is obtained in the hospital between 48 hours and 5 days of age, or as close to discharge as possible if discharged prior to 24 hours of age. The second sample is usually done by the medical home between 7 and 28 days of age.

However, like so many other programs designed primarily for the healthy term baby, screening of premature, low birth weight and ill newborns is not a simple or straightforward process. The neonate’s immaturity and the necessary therapeutic interventions can interfere with both the collection of samples and the interpretation of the newborn screening results. There are times when the collection of the first screening specimen prior to starting treatments is difficult or ill advised. Clinical judgment should prevail.

Why should sick/premature infants be screened differently?
Sick/premature newborns are more likely to have false positive results on the initial newborn screening due to the newborn’s immaturity or treatment received. The sick/premature screening protocol should minimize both the false positive and false negative results and at the same time, provide reliable results with the least number of specimens. Marking the demographic card as ‘Sick/Premature’ notifies the screening program to interpret the results with an understanding of the newborn’s status.

What if a transfusion is required?
If at all possible, collect the first specimen prior to a transfusion (whole blood, packed cells), even if this is before 24 hours of age. A pre-transfusion specimen is essential for detection of galactosemia, sickle cell disease and biotinidase deficiency. If the infant receives a blood transfusion before the first specimen is collected, collect the first specimen at the routine timing. Another screening specimen will need to be collected 120 days after the last transfusion given to validate all results, ensuring the baby’s blood is tested and not the donor blood. Results from a transfused specimen may not be valid and may represent a false result.

Is the testing done differently for the sick/premature newborn?
No. The laboratory testing is the same. Interpretation of the results is more focused. Clinicians will still be notified of abnormal results.
Utah sick/preterm newborns protocol.

First Specimen

a) Collect at 0-48 hours of age or before treatment or transfusion. (see Appendix C)

b) Clearly indicate on the screening collection card the pertinent clinical information (TPN, preterm/sick, transfusion).

c) Interpretation of an abnormal result and recommended follow up will be based on the clinical information noted on the card from the first specimen. If the results reflect a pattern of preterm or treatment (TPN, etc), the result will be reported as normal or with in normal limits with a note stating this is compatible with a sick/preterm newborn receiving TPN.

Second Specimen

a) Collect specimen at 8 days of age if still in the nursery/NICU.

b) Interpretation of an abnormal result and recommended follow up will be based on the clinical information noted on the cards from the first and second specimens.

c) If newborn is discharged before 8 days of age, the second specimen should to be collected by medical home at routine timing (7-28 days).

Are the screening result reports different for the sick/preterm newborn?

The report format is the same for all newborns, but the report on a sick/preterm newborn may have a different interpretation. Two specific changes are:

- If the initial screen for congenital adrenal hyperplasia (CAH) is abnormal, the report will include the second tier 17-OHP level and the Ratio [(17-OHP + androstendione)/cortisol]. A repeat specimen will be requested. The specimen needs to be drawn when the newborn is > 1500 gms.

- If the amino acid or acylcarnitine pattern is consistent with total parenteral nutrition (TPN) on the first specimen, no special action will be recommended; the report will state that the pattern is consistent with TPN. Another specimen is requested when TPN has been discontinued for at least 2 hours.
Specimen Collection

In Utah, the preferred method of collection is a heel stick.


The primary goal of this standard is to ensure the quality of blood spots collected from newborns. Poor quality specimens place an unnecessary burden on the screening facility, cause unnecessary trauma to the infant and anxiety to the infant's parents, potentially delay the detection and treatment of the affected infant and may contribute to missed or late diagnosed cases. When the Utah Newborn Screening Program receives an unacceptable (unsatisfactory) specimen, the program staff request another specimen.

Blood collected from the heel is the standard for newborn screening. The medial and lateral parts of the underfoot are preferred. Blood should never be collected from the arch of the foot, fingers, earlobe, a swollen or previously punctured site or IV lines containing other substances (TPN, blood, drugs, etc.). A puncturing depth beyond 2.0 mm might be excessive for some newborns and might cause trauma to the bone.

Although direct collection from a heel puncture is preferred for optimal laboratory results, it is acknowledged that an alternate collection method may be used if necessary. For sick/preterm newborns, blood has been collected from umbilical catheters. In order to avoid contamination from substances previously infused through the line, draw off 2-2.5 cc's before collecting the newborn screening specimen. Collect the blood in a syringe and apply it to the circles immediately to avoid blood clots that would make the specimen unsatisfactory. Apply the contents to the center of the circle on the screening card, allowing the blood to flow out and fill the circle before moving to the next circle.
## Maternal Conditions Affecting the Newborn Screening Results

<table>
<thead>
<tr>
<th>Maternal Condition</th>
<th>Analyte Affected</th>
<th>Results in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism treated with PTU</td>
<td>Low Thyroxine (T4), high thyroid stimulating hormone (TSH)</td>
<td>Transient hypothyroidism</td>
</tr>
<tr>
<td>131I (iodine) treatment during pregnancy: &lt; 8 weeks gestation</td>
<td>Low T4, high TSH</td>
<td>Transient hypothyroidism</td>
</tr>
<tr>
<td>131I (iodine) treatment during pregnancy: After ~8 weeks gestation (when fetal thyroid matures and traps iodine)</td>
<td>Low T4, high TSH</td>
<td>Permanent hypothyroidism</td>
</tr>
<tr>
<td>Hypothyroidism well controlled and treated</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Steroids: prednisone, betamethasone/dexamethasone</td>
<td>Low or normal 17-OHP</td>
<td>Suppresses fetal adrenal function and causes false-negative CAH</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia</td>
<td>Elevated 17-OHP</td>
<td>False-positive</td>
</tr>
<tr>
<td>Maternal PKU or moderate hyperphenylalaninemia - uncontrolled by diet or drugs</td>
<td>Elevated phenylalanine; ratio of Phe/Tyr should be normal; false-positive</td>
<td>Transient hyperphenylalaninemia</td>
</tr>
<tr>
<td>3-MCC deficiency</td>
<td>Low free carnitine, Elevated C5OH carnitine</td>
<td>False-positive</td>
</tr>
<tr>
<td>Primary Carnitine Deficiency</td>
<td>May have low free carnitine (C0)</td>
<td>False-positive</td>
</tr>
<tr>
<td>Glutaric Acidemia Type I</td>
<td>May have low free carnitine (C0)</td>
<td>False-positive</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>Elevated C3 (propionylcarnitine)</td>
<td>False-positive</td>
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## Conditions of the Newborn Affecting Newborn Screening

<table>
<thead>
<tr>
<th>Condition of Newborn</th>
<th>Effect on Screening</th>
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</thead>
</table>
| Immature hypothalamic-pituitary thyroid axis | Low T4, normal TSH  
Newborns with congenital hypothyroidism can be missed |  
Hypothyroxinemia of prematurity | Transient hypothyroidism, low T4; normal TSH followed by elevation |  
Liver enzyme immaturity | Transient elevations of tyrosine, methionine, and galactose, occasionally other amino acids |  
Iodine deficiency | Transient hypothyroidism, low T4, elevated TSH |  
Acute Illness | Transient hypothyroidism; low T4, elevated TSH  
Elevated immunoreactive trypsinogen (IRT) |  
Hypoxia | Elevated IRT |  
Liver disease | Elevated tyrosine, methionine, galactose |  
Renal immaturity | Elevated 17-OHP, amino acids |  
Hyperbilirubinemia | May cause elevated C3 carnitine |
## Treatments Used in the NICU and Effects on Newborn Screening Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect on Screening Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total parenteral nutrition (TPN)</td>
<td>Elevation of multiple amino acids</td>
</tr>
<tr>
<td>Carnitine supplementation</td>
<td>Elevations of free carnitine and several short chain acylcarnitines (C2, C3, C4)</td>
</tr>
<tr>
<td>Red cell transfusion and extracorporeal life support (ECLS) (pre- and postnatal transfusions)</td>
<td>Can mask the absence of enzymes and proteins intrinsic to the red blood cell (RBC), thereby negating results for hemoglobinopathies and galactosemia. ECLS invalidates all screening results.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>False-negative testing for CHYP, since levels of TSH are suppressed.</td>
</tr>
<tr>
<td>Steroids</td>
<td>Suppressed TSH and T4; possible false-negative for CHYP. May suppress 17-OHP resulting in false-negative of CAH.</td>
</tr>
<tr>
<td>Iodine exposure with providone/iodine preps</td>
<td>Transient hypothyroidism; low T4, elevated TSH.</td>
</tr>
<tr>
<td>Specimen collection early (&lt;12 or &lt;24 hours)</td>
<td>Unreliable testing of endocrinopathies (CHYP and CAH) due to the stress associated with birth and due to the immaturity of fetal thyroid. IRT may also be elevated.</td>
</tr>
<tr>
<td>Antibiotics; ampicillin, cefotaxime</td>
<td>May cause elevation of C5 carnitine, C16:1-OH carnitine and sometimes C14:1 carnitine</td>
</tr>
<tr>
<td>MCT oil supplementation</td>
<td>May cause elevation of medium chain acylcarnitine (C6-C10) and C5DC carnitine</td>
</tr>
<tr>
<td>Dextrose, IV</td>
<td>May cause elevation of C16-OH carnitine</td>
</tr>
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</table>
## Screening Panel Conditions and Factors Affecting Screening Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis (CF)</td>
<td>False-positive IRT result: hypoxia; respiratory or physiologic stress; low Apgar scores; organ damage; trisomies 13, 18, 21; renal dysfunction; hypoglycemia; contamination of filter paper; carrier status; and early specimen collection.</td>
</tr>
<tr>
<td></td>
<td>False-negative IRT result: infant with CF who is pancreatic sufficient; older affected infant with pancreatic insufficiency; meconium ileus. ECLS from volume replacement.</td>
</tr>
<tr>
<td>Congenital Hypothyroidism (CHYP)</td>
<td>False-positive T4/TSH results: prematurity; low birth weight; exposure to iodine, dopamine and/or steroid therapy; iodine deficiency; early specimen collection. False-negative results: prematurity with delayed rise of TSH; ECLS from volume replacement.</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia (CAH)</td>
<td>False-positive results: stress; prematurity, low birth weight; early specimen collection. False-negative results: prenatal maternal steroid treatment to prevent preterm labor.</td>
</tr>
<tr>
<td>Hemoglobinopathies (Hb)</td>
<td>False-negative result: red cell transfusion; ECLS</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>False-negative result: red cell transfusion; ECLS from volume replacement.</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>False-positive result: GALT enzyme destroyed by heat, humidity or time. False-negative result: red cell transfusion; ECLS.</td>
</tr>
<tr>
<td>Urea cycle, Amino Acid and Organic Acid disorders</td>
<td>False-positive result: TPN; liver disease, immature liver enzymes. False-negative result: early specimen collection or collection within a few hours after transfusion or ECLS.</td>
</tr>
<tr>
<td>Fatty Acid Oxidation disorders</td>
<td>False-positive result: carnitine supplementation. False-negative result: carnitine supplementation; well-fed state; ECLS from volume replacement.</td>
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</tbody>
</table>
NEWBORN HEARING SCREENING AND THE SICK/PRETERM

The Joint Committee on Infant Hearing (JCIH) endorses early detection of and intervention for infants with hearing loss. The goal of early hearing detection and intervention (EHDI) is to maximize linguistic competence and literacy development for children who are deaf or hard of hearing.

The hearing of all infants should be screened no later than 1 month of age. Those who do not pass screening should have a comprehensive audiological evaluation no later than 3 months of age. Infants with confirmed hearing loss should receive appropriate early intervention services (including amplification) no later than 6 months of age.

The following are highlights of the JCIH 2007 Position Statement and reflect changes specific to babies referred to a Newborn Intensive Care Unit:

**Definition of Hearing Loss.** The definition of targeted hearing loss has been expanded from congenital permanent bilateral, unilateral sensory or permanent conductive hearing loss to include neural hearing loss (e.g., auditory neuropathy / “dyssynchrony”) in infants admitted to the NICU.
Screening and Re-screening Protocols. Separate screening and re-screening protocols are recommended for NICU and well-baby nurseries.

Additional Medical Evaluations. Every infant with confirmed hearing loss should be referred for other evaluations - to determine the etiology of the hearing loss, identify related conditions and provide recommendations for treatment, specifically:

- an otolaryngologist with knowledge of pediatric hearing loss;
- an ophthalmologist experienced in evaluating infants.
- Since many genetic (and non-genetic) disorders associated with hearing loss manifest abnormalities in other parts of the body, genetic counseling should also be suggested to the family.

| Screening:                                      | NICU infants admitted for more than 5 days should have an auditory brainstem response (ABR) test included as part of their screening so that neural hearing loss will not be missed. |
|                                               | Infants who do not pass the ABR in the NICU should be referred directly to an audiologist. |
| Re-Screening:                                  | For re-screening, a complete screening on both ears is recommended, even if only one ear failed the initial screening. |
| Re-Admissions in first month of life (all infants) | When there are conditions associated with potential hearing loss (e.g., hyperbilirubinemia that requires exchange transfusion or culture-positive sepsis), a repeat hearing screening is recommended before discharge. |
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References:

