



Newborn Screening in the Neonatal Intensive Care Unit

Over the past 40 years, state mandated newborn screening has proven effective in detecting infants at risk for serious metabolic, endocrine and hemoglobin disorders, and thus enabling the early diagnosis and treatment of affected infants. In spite of past successes, no screening program can be considered to be 100% effective in detecting all infants affected with a particular disorder. State newborn screening programs publicly recognize the limitations of newborn screening methodologies, and advise physicians and parents that any infant with a family history of a newborn screening disorder, symptoms of a disorder, or otherwise known to be at risk for a disorder requires prompt evaluation by a medical specialist and diagnostic testing, regardless of the infant's newborn screening test results.

State newborn screening programs and the neonatal community recognize that while newborn screening is necessary for all infants, there are difficulties associated with screening of infants who, due to prematurity or serious underlying medical problems, require admission to highly specialized neonatal intensive care units (NICU's). The support therapies required by these infants, including blood transfusions, total parenteral nutrition (TPN), ventilation, intravenous medications and, in some circumstances, surgical procedures complicate newborn specimen collection, testing and interpretation of results. NICU infants are not the "normal" newborns for which this type of screening was first envisioned and developed by Dr. Robert Guthrie. Special guidelines addressing newborn screening practices for NICU infants is needed.

Even though NICU's provide continuous monitoring of infants on both a physical and biochemical level, newborn screening is a valuable tool for alerting neonatologists to infants at risk for certain metabolic, endocrine and hemoglobin disorders. However, the unique medical circumstances of the NICU infant result in an increased possibility of false positive and false negative newborn screening results.

These false positive and false negative newborn screens may be the result of known factors including:

- Delayed or suppressed thyroid stimulating hormone (TSH) surge associated with very low-birth weight and/or certain congenital anomalies
- Physiological elevations of alpha 17-hydroxy progesterone (17-OHP) due to prematurity and/or co-existing illness
- Effects of pre-natal and/or post-natal steroid administration
- Blood transfusions in which transfused red-blood cells negate enzyme activity assays and/or hemoglobin genotyping
- Lack of milk and/or protein feedings
- TPN, medium chain triglyceride (MCT) and carnitine supplementation and certain medications that may complicate tandem mass spectrometry screening
- Early or delayed specimen collection due to the infants' unstable medical condition
- Surgical procedures that may further complicate specimen collection and interpretation



State newborn screening programs and the neonatology community have acknowledged many difficulties in applying standard newborn screening procedures to the NICU infant. The complexities of NICU care can affect how and when newborn screening specimens are collected, and physiological and treatment factors can affect the validity of screening results. Within the Region 4 Short Term Follow-up Workgroup, several states have undertaken steps to address these concerns and develop guidelines for newborn screening for NICU infants.

Several Region 4 states have developed protocols for scheduled re-screening of some, or all infants admitted to the NICU for extended care. Some states have developed newborn screening protocols for NICU infants in partnership with NICU staff. These partnerships between the state program and the medical communities have encouraged better integration of newborn screening into the neonatologists' clinical management of these infants, and lead to more open lines of communication between the state program and the neonatal community.

The Region 4 states involved in this workgroup hope to share these NICU re-screening protocols with the Advisory Group as a model practice initiative that is worthy of review and may benefit other state programs faced with the difficulties of newborn screening in the NICU.

Neonatal Intensive Care Unit Babies Specimen Collection Procedures

A review of the NICU testing procedures in Region 4 can be divided into two approaches:

- 1) Routine Re-Testing at Specified Intervals; and
- 2) Result Specific Repeat Testing

Both approaches have inherent advantages and disadvantages. Determining the approach that works best for a state newborn screening program or even for an individual hospital needs to take into account the accuracy of screening results, labor involved and cost of testing.

The starting point for both approaches is the same:

A newborn screen specimen should be drawn prior to specific medical intervention – especially transfusion – regardless of the infant's age.



In the Routine Re-Testing approach:

Repeat screens are drawn at set intervals (e.g. 2 weeks, 30 days, 60 days), and continue for every 30 days until discharge.

In the Result Specific Repeat Testing approach:

The need for repeat screening is determined by the analyte test results of the initial newborn screen. Clinical judgment is used to determine whether to repeat screen or proceed to diagnostic testing for follow-up. The following lists those issues that need to be addressed for each of these two testing approaches.

NICU Specific Test Guidelines

Following are issues that should be considered when establishing a specific test (abnormal, TPN, Transfusions, etc.) repeat testing schedule for babies in neonatal intensive care units. The repeat testing may include confirmatory testing in place of subsequent filter paper specimens.

A Repeat specimens based upon transfusions

1. The initial specimen collected pre-transfusion
 - i. Collect a second specimen if initial was collected prior to early discharge definition
2. The initial specimen collected post-transfusion
 - i. Collect initial specimen 24 to 48 hours after transfusion
 - ii. Collect a second specimen about 30 days after transfusion
 - a. Questions to be addressed
 - aa. Retest all disorders on newborn screening panel?
 - bb. Retest a subset of disorders on newborn screening panel (Hemoglobin and enzyme tests)?
 - iii. Collect a third specimen about 60 days after transfusions
 - a. Questions to be addressed
 - aa. Retest all disorders on newborn screening panel?
 - bb. Retest a subset of disorders on newborn screening panel (Hemoglobin and enzyme tests)?
 - iv. Alternative to newborn screening (dried blood) testing
 - v. Quantitative hemoglobin, biotinidase and/or GALT on whole blood or plasma

B. Repeat testing based upon Total Parenteral Nutrition (TPN)

1. Collect initial specimen 24 to 48 hours after TPN has been administered
2. Post TPN testing
 - i. Collect a second specimen 24 to 48 hours after TPN is discontinued
 - ii. Alternative to newborn screening (dried blood) testing
 - a. Quantitative amino acid profile on serum/plasma

C. Abnormal test results on initial specimen

1. Results classified as needing special attention

- i. Confirmatory/Diagnostic testing as outlined in the NBS programs' established reporting procedure (serum testing, urine testing, mutation analysis, etc.)

2. Results classified as borderline

- i. Follow established repeat testing recommendations as outlined in the programs reporting policy.

D. Other re-testing options

1. Quantitative testing at discharge (e.g., plasma T4/TSH)

E. Advantages and disadvantages of a specific test guideline

1. Advantages

- a. The number of repeat newborn screening specimen collections will be minimized

2. Disadvantages

- a. Disorder specific re-testing recommendations can be confusing to NICU staff (nurses and neonatologist) or to the primary care providers especially if there are several different re-testing recommendations from multiple abnormal reports

For example: Multiple reports on the same baby with different retesting recommendations: Transfused – repeat in 30 days, TPN – repeat 48 hrs after TPN discontinued. Galactosemia – repeat immediately

- b. Babies with disorders may escape detection unless there is repeat testing at discharge. Application of repeat testing (serum or blood spot) upon discharge can detect any potential disorder but the delay between the initial (normal) newborn screen and discharge can be weeks or months. This delay in detecting the disorder may compromise the benefits of earlier treatment
- c. A serum testing recommendation may not be practical due to the blood volume in very low birth weight babies

NICU Routine Re-Testing Guidelines

Following are issues that should be considered when establishing a routine repeat testing schedule for babies in neonatal intensive care units (or a subset of NICU babies).

- A. Define target - To whom should the guidelines apply?
 - 1. To all babies in a NICU?
 - 2. To a subset of NICU babies?
 - i. Low birth weight
 - a. Need to define weight cutoff
 - ii. Very low birth weight
 - a. Need to define weight cutoff
- B. Guideline should include a repeat testing sequence
 - 1. Establish a repeat testing time line
 - i. List the number of days/weeks after initial specimen collection
 - 2. Establish when the routine repeat testing will be completed
 - i. When babies reach a specific age
 - ii. Should specimen be taken at discharge
- C. Recommendations based on specific medical interventions
 - 1. Repeat testing based on transfusions
 - i. If the 1st specimen was collected prior to a transfusion
 - a. Follow the established repeat testing guidelines (B above)
 - b. Establish a last specimen collection if beyond repeat testing guidelines (B.2.ii above).
 - ii. If the 1st specimen was collected post transfusion
 - a. Collect a 1st specimen 24 to 48 hours after transfusion
 - b. Follow the established repeat testing guidelines (B above)
 - c. Establish a last specimen collection if beyond repeat testing guidelines (B.3.ii.)

2. Repeat testing based upon Total Parenteral Nutrition (TPN)
 - i. Repeat specimen collection 24 – 48 hrs after TPN has been discontinued.
 - ii. Follow established repeat testing guidelines (B above)
- D. Abnormal test results on any of the repeat specimen collections
 1. Results classified as needing special attention
 - i. Confirmatory/Diagnostic testing as outlined in the NBS programs' established reporting procedure.
 - a. Consult Specialist for diagnostic testing (serum testing, urine testing, mutation analysis, etc)
 2. Results classified as borderline as outlined in the NBS programs' established reporting procedure
 - i. Follow established repeat testing guidelines (B above).
- E. Advantages and disadvantages of a routine repeat testing guideline
 1. Advantages
 - i. The detection of disorders when the initial newborn screen was normal
 - a. Wisconsin has reported detecting 20 hypothyroid (2002 – 2005) cases on the 2nd or subsequent screens
 - ii. The retesting recommendations are significantly simplified since it applies to the results of all disorders and medical interventions. The exception is those abnormal results needing immediate intervention
 - iii. Retesting of premature babies is likely to provide specimens that can more accurately be compared to the screening population as a whole
 2. Disadvantages
 - a. The implementation of a routine repeat testing guideline will *likely* increase the number of specimens submitted for testing. The actual number will depend upon the subset of NICU babies targeted for re-screening and the number of repeat collections requested, in contrast to repeats already obtained on NICU babies