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Newborn Screening for Preterm, Low Birth Weight, and Sick Newborns; Approved Guideline

This guideline outlines the recommended protocols for screening preterm, sick, or low birth weight infants for hearing loss and disorders detectable through dried blood spot testing.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.



Newborn Screening for Preterm, Low Birth Weight, and Sick Newborns; Approved Guideline

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Abstract

Clinical and Laboratory Standards Institute document I/LA31-A—*Newborn Screening for Preterm, Low Birth Weight, and Sick Newborns; Approved Guideline* addresses newborn screening of preterm, low birth weight (LBW), and sick newborns worldwide to detect treatable conditions before physical damage can occur to the infant. In developed countries, advances in the treatment they receive have improved survival rates, making the early detection of conditions detected by newborn screening even more important. The physiological states associated with preterm, LBW, and sick newborns, and the treatments they receive, directly affect the reliability of results for many conditions screened in public health dried blood spot and newborn hearing screening systems. This guideline describes the effects of maternal and infant conditions, as well as treatments given to newborns. It also provides the rationale for the recommended intervals for screening designed to minimize the risk of missing or delaying a diagnosis in an affected newborn. It is intended for use by those involved in any aspect of newborn screening specimen collection or hearing screening testing and follow-up, including health care providers, parents, public health professionals, and others concerned with the health and welfare of newborns.

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Foreword

There are approximately 127 million births per year worldwide.¹ In the United States, in 2005 4.1 million infants were born, and 8.2% of those infants were low birth weight, 12.7% were preterm (< 37 weeks' gestation), and 3% were born with birth defects.² In developed and developing countries, these infants are usually cared for in specially equipped wards or units such as special care baby units (SCBUs) sometimes referred to as neonatal intensive care units (NICUs). For the purpose of this document, SCBU is used to represent these levels of nursery care.

Preterm birth is defined as a gestational age of less than 37 completed weeks and low birth weight (LBW) as less than 2500 g. In some countries, approximately 25% of infants are less than this weight and may or may not be considered candidates in need of the specialized care. Tremendous advances in the care of preterm infants have resulted in improved survivability for increasingly smaller and more preterm infants. Today in developed countries, infants of 28 weeks' gestation or older have a > 96% chance of survival, with the lower limits of viability at about 22 weeks, with only 2% of these infants surviving.²

Newborn screening (NBS) systems and laboratory technology have evolved as well, with the addition of isoelectric focusing and high-performance liquid chromatography for hemoglobinopathies, enzyme assays for biotinidase deficiency and galactosemia, DNA analysis for cystic fibrosis and hemoglobinopathy screening, and tandem mass spectrometry (MS/MS) for metabolic disorders and other multiplex screening tests. It is now possible to screen for a large number of conditions. As of 2008, more than 50 conditions are included in blood spot screening panels in some NBS programs.³ In addition, most infants are now screened for hearing loss before discharge from the birth facility. Including hearing screening, the collective incidence of disorders for which NBS is available is 1:250 infants compared with 1:3000 only 10 years ago.⁴ New tests for additional conditions are under development, undergoing pilot testing, or both in many parts of the world. With the pace of technologic and therapeutic advances, it is certain that more conditions will be added to NBS panels in the future.

As more conditions are added, it becomes increasingly difficult to advise practitioners about the ideal time to collect an NBS specimen. Each condition has its own best 'screening window' when there is the greatest chance of diagnosing and treating the disorder in question before symptoms or permanent damage occurs. Some conditions, such as maple syrup urine disease (MSUD), galactosemia, and congenital adrenal hyperplasia, have very short screening windows, with abnormal analytes present in the first day or so of life, illness beginning by the end of the first week, and death in the second week if not diagnosed. Therefore, the best time to collect specimens for those disorders that necessitate early treatment is in the first 24 to 48 hours, and specimens collected after four days may be too late to prevent death or damage. Other conditions, such as homocystinuria, are difficult to detect on a specimen collected in the first 24 to 48 hours of life because the analyte currently used in many programs, methionine, rises very slowly in affected infants and may not be elevated for several days to a week. Likewise, in some infants with congenital hypothyroidism, the decline in thyroid hormone (thyroxine – T4) and rise in thyroid-stimulating hormone (thyrotropin – TSH), analytes commonly used to detect the condition, may not occur for several days (or longer) if the infant has a large ectopic gland producing sufficient T4 to suppress TSH production at birth. Because maturation of the hypothalamic-pituitary axis at birth is insufficient to produce TSH in very low birth weight (VLBW) infants, these infants with hypothyroidism often have low or normal TSH levels at birth and may not be identified on a screening specimen collected at less than one week of age.⁵ Specimen collection timing varies around the world; in Europe and Australia-Asia, most specimens are collected at 48 to 72 hours of age; in the United States, before 48 hours of age; and in Great Britain, infants are not screened until the fifth to eighth day of life.⁶ No published data on age at collection were found for the Latin American or Middle East/South African regions.

Unfortunately, SCBU infants are at greater risk for missed or incomplete NBS than normal newborns owing to the focus on the critical activities surrounding their care, their pre- and postnatal environments,

the treatments given to them, and the unique genetic and biochemical nature of the infants themselves. These factors can negatively affect both the quality and validity of the screening results for many of the disorders included in NBS panels. As a result, SCBU infants are much more likely to have false-positive or false-negative results after NBS and thus, they account for a disproportionate follow-up effort, compared with normal newborns. Preterm, LBW, or sick term infants often have multiple NBSs and diagnostic specimens collected in an attempt to clarify the significance of an out-of-range result. At the other extreme, collection of NBS specimens can be overlooked in the complexity of activities that occur in the SCBU. These factors increase the chance that a newborn requiring SCBU care will not have a condition detectable by NBS identified in a timely manner, with potentially catastrophic results.⁷⁻⁹ Although a few case reports have documented the presence of this problem, studies assessing its magnitude have not been performed.

During the development of this guideline, experts in neonatology, NBS, endocrinology, metabolism, hematology, hearing loss, genetics, and cystic fibrosis worked collectively to outline factors that interfere with the reliability of NBS, review the significance and duration of the interference, and provide recommendations for NBS specimen collection, including information on timing and number of specimens. This guideline is in agreement with existing consensus guidelines, including those from CLSI (see CLSI documents I/LA27¹⁰ and LA04¹¹) and various neonatology organizations.¹²⁻¹⁴ This guideline provides reference for NBS programs and SCBUs to develop and provide screening, testing and follow-up protocols. The goal is to complete NBS for every SCBU infant in the shortest period of time, with the highest degree of reliability and using the fewest number of specimens. It is hoped that individual NBS programs will adopt this guideline to standardize procedures for intensive care practitioners, and most important, to improve the quality of NBS and follow-up for all infants in their jurisdictions.

Key Words

Best practices, congenital anomalies, low birth weight, newborn hearing screening, newborn screening, preterm birth, sick infants, special care baby unit

Newborn Screening for Preterm, Low Birth Weight, and Sick Newborns; Approved Guideline

1 Scope

This guideline addresses best practices for SCBU personnel, as well as primary health care providers, laboratory, and follow-up personnel to provide all preterm, LBW, and sick infants with valid newborn blood spot and hearing screening. Best practices are defined with consideration of the conditions screened for and timing of screening events. Special circumstances include the condition of the infant, treatments given, maternal conditions/therapies, and other factors. This document does not intend to dictate SCBU care practices.

Goals of this guideline are to

- 1) Ensure rapid, consistent, and complete blood spot and hearing screening, including appropriate follow-up to ensure early diagnosis and treatment for preterm, LBW, or sick newborns affected with a screened condition.
- 2) Minimize the risk of a missed or delayed diagnosis and treatment for all screened conditions.
- 3) Optimize the timing and minimize the number of blood spot specimen collections and hearing screening events.
- 4) Define essential elements of quality assurance relevant to this guideline.
- 5) Provide education on the effects of SCBU treatments on newborn blood spot and hearing screening.
- 6) Identify areas needing further research.

2 Introduction

This guideline is a part of a series produced by CLSI over the last several years that includes related CLSI documents LA04¹¹ and I/LA27.¹⁰ These documents provide more detail regarding the structure and function of specific elements of NBS systems, and this information is not duplicated here, except for a discussion of proposed reporting and follow-up algorithms. This document focuses on treatments and practices within the SCBU and neonatal conditions that are either known or suspected to interfere with valid NBS, the consequences of the interference, and recommendations for avoiding or counteracting these problems.

Care and treatment of preterm, LBW, and sick infants and improvements to NBS programs have made great advancements, but little is known as to the impact of one on the other. The effects of preterm birth and its associated treatment are partially understood for certain disorders on NBS panels, for example, endocrine disorders, hemoglobinopathies, enzymopathies such as galactosemia, and cystic fibrosis (CF). However, very little is known about most metabolic disorders. Simple questions such as how long parenteral nutrition (PN) affects results on amino acid tests are unknown at this time, and this document reflects areas where no data exist. Further research is urgently needed. Because no test has been proven to produce results consistently with 100% sensitivity and specificity, including those used in NBS, practitioners should be reminded to remain vigilant for signs and symptoms associated with screened conditions, even in the presence of normal NBS results.

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The approach is based on the model presented in the most current edition of CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*. The quality management system approach applies a core set of “quality system essentials” (QSEs), basic to any organization, to all operations in any health care service’s path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager’s guide. The QSEs are

Documents and Records Organization	Equipment Purchasing and Inventory Process Control	Information Management Occurrence Management Assessment—External and Internal	Process Improvement Customer Service Facilities and Safety
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I/LA31-A addresses the QSEs indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Documents and Records	Organization	Personnel	Equipment	Purchasing and Inventory	Process Control	Information Management	Occurrence Management	Assessment—External and Internal	Process Improvement	Customer Service	Facilities and Safety
					X I/LA27 LA04 M29						M29

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, CLSI/NCCLS document GP26—*Application of a Quality Management System Model for Laboratory Services* defines a clinical laboratory path of workflow, which consists of three sequential processes: preexamination, examination, and postexamination. All clinical laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

I/LA31-A addresses the clinical laboratory path of workflow steps indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Preexamination				Examination			Postexamination	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
LA04	LA04	LA04	LA04	LA04				LA04

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Related CLSI Reference Materials*

- I/LA27-A** **Newborn Screening Follow-up; Approved Guideline (2006).** This guideline describes the basic principles, scope, and range of follow-up activities within the newborn screening system.
- LA04-A5** **Blood Collection on Filter Paper for Newborn Screening Programs; Approved Standard—Fifth Edition (2007).** This document addresses the issues associated with specimen collection, the filter paper collection device, and the application of blood to filter paper, and provides uniform techniques for collecting the best possible specimen for use in newborn screening programs.
- M29-A3** **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

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