CLSI Announces New Sweat Testing Guideline for the Diagnosis of Cystic Fibrosis

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Cystic fibrosis (CF) is a debilitating, chronic, inherited disease—the most common life-threatening genetic disease in the white population. With CF, a defective gene causes the body to produce thick, sticky mucus that coats the lungs, causing infections, and obstructs the pancreas and stops natural enzymes from helping the body to break down and absorb food. Newborns screened for CF can benefit from early diagnosis and treatment, which can lead to much better outcomes and a longer life expectancy. If a newborn has a positive CF screen, a doctor may order a sweat test, which measures the amount of chloride in sweat. A high chloride level indicates CF.

Although it has been considered the best test for CF for 50 years, the sweat test has been reported to have very high false-positive and false-negative rates. This can be due to inaccurate methodology, technical error, and patient physiology. Therefore, guidelines for conducting and evaluating sweat tests are needed. Clinical and Laboratory Standards Institute (CLSI) recently released a new document, *Sweat Testing: Sample Collection and Quantitative Chloride Analysis; Approved Guideline—Third Edition* (C34-A3), which describes appropriate methods of collection and analysis, quality control, and evaluation of results in sweat testing.[1]

Vicky A. LeGrys, DrA, MT(ASCP), University of North Carolina School of Medicine, and chairholder of the CLSI committee that developed the document, says, "This updated version of C34 is very timely because now all 50 states have mandatory newborn screening for CF. The new material included in the revised guideline will be a valuable resource for laboratory professionals performing sweat chloride testing for the confirmation of CF."

Because of the increased number of newborn screenings, laboratories will see an increase in the number of sweat tests they perform. Laboratories performing sweat tests will want to have the C34-A3 guideline because sweat testing accreditation checklist items used by the College of American Pathologists are based on the CLSI guideline. In addition, the Cystic Fibrosis Foundation accredits its approximately 115 care centers in the United States using standards adopted from C34-A3, LeGrys explains.

Vijay Laxmi Grey, PhD, FCACB, a Pediatric Clinical Chemist at Hamilton Health Sciences, describes the usefulness of C34-A3, saying, "This document is an excellent resource to update protocols in laboratories that are already doing the sweat tests, and provides a framework for setting up correct protocols in laboratories that have never done the test before."

Grey notes that this new version of the guideline includes updated information about newborn screening, and reflects the increased knowledge in CF since the discovery of the CF transmembrane conductance regulator (CFTR) gene. Early detection and treatment can help with the management of this terrible disease and can produce improved outcomes. Patients with CF, on average, are living longer, from an average of 10 years before 1980 to 30 years in the United States now and 40 years in Canada, Grey explains.

The following items are new in this edition of the guideline:

- Microvolume procedure for sweat chloride analysis
- Method validation for sweat chloride
- Quality assurance (QA) for sweat collection
- Reference ranges for infants and beyond infancy[1]

A sweat test is conducted in 2 parts. In the first part, a chemical pilocarpine causing sweating is put on a small area on an arm or a leg. An electrode is then put over that spot, allowing the technician apply a weak electrical current to the area to cause sweating. The second part of the test consists of cleaning the area and collecting the sweat on a piece of filter paper, gauze, or in a plastic coil. Thirty minutes later, the collected sweat is sent to a hospital laboratory to measure the chloride in the sweat.[2]

Stanley F. Lo, PhD, DABCC, FACB, Children's Hospital of Wisconsin, and a member of the CLSI subcommittee that produced the document, believes the most useful aspect of C34-A3 is that it is "one-stop shopping" for sweat chloride testing - providing many of the elements involved in one reference. "There are many details that a laboratory must be familiar with to perform sweat testing properly, and information on how to perform the test can be hard to find. This document is the best resource available to assist laboratories in performing this test," he says.

Topics covered in the guideline include:

- The stimulation and collection of sweat and the quantitative measurement of chloride; sweat stimulation by pilocarpine iontophoresis (specific precautions are noted); and sweat collection on filter paper, gauze, and microbore tubing
- Sweat chloride (Cl^-) determination using coulometric titration
- Screening methods based on sweat conductivity
- Verification studies and QA techniques
- Analytical and biological sources of error
- Evaluation of sweat chloride test results to include reference intervals and diagnostic criteria[1]

C34-A3 emphasizes the application of sweat chloride testing to newborn screening for CF. Dr. Lo explains the collection process for the sweat test in infants is difficult owing to the physical size of the arms of newborns and the need to use large (relative to a newborn arm) electrodes.

LeGrys notes, "False sweat test results can be attributed to unreliable methods, lack of competency of personnel performing the test, and incorrect interpretation of the results by clinicians. C34-A3 addresses all of these concerns."

LeGrys explains that sweat testing in infants brings on unique challenges, especially with collecting sufficient amounts of sweat. Individuals with an initial insufficient sweat specimen must return for retesting, which delays the confirmation of diagnosis and initiation of treatment. A highly insufficient rate after a positive CF newborn screening test can be clinically, psychologically, and economically significant. The CLSI guideline will aid laboratories in collecting a sufficient amount of sweat and in accurately performing the test.

CLSI will expand its library of documents related to CF screening. CLSI is developing a document discussing newborn screening for CF using dried blood specimens. *Newborn Screening for Cystic Fibrosis; Proposed Guideline* (I/LA35-P), expected to be released in 2011, will explore the various approaches to newborn screening for CF and discuss the advantages and disadvantages of each. The document will cover all the components of newborn screening for CF from education of professionals and parents, to the screening itself, including confirmatory testing and follow-up of unsatisfactory results, medical management, and QA. Because newborn screening for CF is now required in all 50 states, I/LA35-P will be an indispensible resource for laboratories striving to provide the highest quality of care to the tiniest of patients.

The Experts

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1. CLSI. Sweat Testing: Sample Collection and Quantitative Chloride Analysis; Approved Guideline—Third Edition. CLSI document C34-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.
2. Cystic Fibrosis Foundation. Available at www.cff.org/AboutCF/Testing/SweatTest/. Accessed March 31, 2010.

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