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4th Edition

C34

Sweat Testing: Specimen Collection and Quantitative Chloride Analysis

This guideline describes methods for all aspects of sweat testing, including collection and analysis, results evaluation and reporting, and quality control.

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

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Sweat Testing: Specimen Collection and Quantitative Chloride Analysis

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Abstract

Clinical and Laboratory Standards Institute guideline C34—*Sweat Testing: Specimen Collection and Quantitative Chloride Analysis* describes methods for performing sweat testing for cystic fibrosis diagnosis. Sweat stimulation, collection, and quantitative measurement of sweat chloride are described, along with results evaluation and reporting, quality assurance, and method validation.

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Foreword

The quantitative measurement of chloride in sweat (commonly called the "sweat test") is used to confirm cystic fibrosis (CF) diagnosis, and sweat chloride levels are used as a biomarker for evaluation of response to mutation-specific drugs used to treat the disorder. With an approximate incidence of 1:3000, CF is the most common life-shortening genetic disease in Caucasians. CF is an autosomal recessive disorder characterized by viscous secretions that affect the exocrine glands, primarily in the lungs and pancreas. Patients with CF have increased sodium, chloride, and potassium concentrations in their sweat.

Two sets of criteria are evaluated to confirm a CF diagnosis. First, a CF diagnosis involves the presence of one of the following[1,2]:

- One or more characteristic phenotypic features
- CF history in a sibling
- A positive newborn screening test result (see CLSI document NBS05[3])
- Prenatal testing performed due to carrier status in both parents, showing two CF-causing mutations

Second, in addition to one of the criteria above, a CF diagnosis involves the presence of one of the following[1]:

- An increased sweat chloride concentration by pilocarpine iontophoresis
  - This must occur on two or more occasions in the absence of a positive newborn screening test or prenatal testing that identifies two CF-causing mutations.
- Identification of two CF-causing mutations
- Demonstration of abnormal nasal epithelial or intestinal mucosal ion transport

Newborn screening has been implemented throughout the United States and in many other regions and countries. It is essential to note that a positive newborn screening test cannot be used to confirm a CF diagnosis, which requires confirmatory sweat chloride testing or demonstration of two CF-causing mutations in a specimen not obtained prenatally or through newborn screening. Furthermore, false-negative results occur with newborn screening, and sweat testing should always be performed when symptoms suggestive of CF occur, regardless of the newborn screening result.

The sweat test has been reported to have unacceptably high false-positive (up to 15%) and false-negative (up to 12%) rates, attributable to inaccurate methodology, technical error, and varying patient physiology.[2-7] Therefore, comprehensive[2,4-7] guidelines for sweat collection and quantitative chloride measurement in sweat are needed. Performance improvement of such tests can only occur when laboratorians and clinicians are aware of appropriate methods for patient selection, specimen collection, analysis, results evaluation, and quality control. This guideline describes, in detail, the quantitative pilocarpine iontophoresis test for sweat chloride determination, including techniques to minimize the potential for false-positive and false-negative test results. Sweat conductivity screening methods are also mentioned.[2,4-7]

For diagnosis, CF care center accreditors require that sweating be stimulated by pilocarpine iontophoresis and collected in either gauze or filter paper or in coiled tubing collectors, followed by quantitative chloride[8] measurement. At alternative sites, as a screening procedure, conductivity may be measured (see Subchapter 2.4.4). Patients with a sweat conductivity value of 50 millimoles per liter (mmol/L) (equivalent NaCl) or above should have a quantitative sweat chloride measurement.[8]

Overview of Changes

This guideline replaces the previous edition of the approved guideline, C34-A3, published in 2009. Several changes were made in this edition, including:

- Moved procedures for gauze or filter paper collection and analysis to Appendix A because many of these systems are no longer manufactured
- Moved the procedure for sweat chloride analysis using a chloridometer with individual titration vials and the coiled tubing collector to Appendix B because that chloridometer is no longer manufactured
- Expanded discussion of sweat testing in infants following a positive newborn screening test
- Updated reference intervals for sweat chloride concentration

NOTE: The content of this guideline is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

Key Words

Chloridometer, cystic fibrosis, iontophoresis, sweat chloride, sweat testing

Sweat Testing: Specimen Collection and Quantitative Chloride Analysis

Chapter 1: Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Standard precautions information
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline

1.1 Scope

This guideline provides recommendations for sweat stimulation by pilocarpine iontophoresis (specific precautions are noted), sweat collection in filter paper or gauze (see Appendix A) or in a commercial sweat collector using coiled tubing (see Appendix B), and quantitative chloride measurement. The procedure for sweat chloride (chloride ion [Cl^-]) determination using coulometric titration is described. Sweat conductivity screening methods are also mentioned. Sweat chloride test results evaluation, including reference intervals and diagnostic criteria, is described, with an emphasis on sweat chloride testing for newborn cystic fibrosis (CF) screening. Validation studies and QA techniques are discussed, along with analytical and biological error sources.

The intended users of this guideline are laboratory and clinical personnel responsible for collecting sweat specimens, measuring sweat chloride, and evaluating and reporting sweat test results.

Procedures for gauze or filter paper collection and analysis are located in Appendix A because many of these systems are no longer manufactured. Other methods for measuring sweat electrolytes after pilocarpine iontophoresis exist but are not included in this guideline. Some of these methods have significant documented analytical problems, as well as limited diagnostic application.[2,4-7]

1.2 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of bloodborne pathogens. Published guidelines are available that discuss the daily operations of diagnostic medicine in humans and animals while encouraging a culture of safety in the laboratory.[9] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.[10]