Standards of care guidance for sweat testing; phase two of the ECFS quality improvement programme

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Abbreviations:

CV: Coefficient of variation

CFF: Cystic Fibrosis Foundation

CFTR: Cystic Fibrosis Transmembrane Conductance Regulator

CLSI: Clinical and Laboratory Standards Institute (American guideline)

DNWG: Diagnostic Network Working Group

ECFS: European Cystic Fibrosis Society

EQA: External Quality Assessment

LMIC: Low and middle income countries

NBS: Newborn screening

QC: Quality Control

QNS: Quantity Not Sufficient

POCT: Point Of Care Testing

SCC: Sweat chloride concentration

SoC: Standards of Care

Abstract

More than five decades after the introduction of the quantitative pilocarpine iontophoresis technique, surveys still highlight inconsistencies in the performance and reporting of sweat tests in Europe. The sweat test remains key for the Cystic Fibrosis (CF) diagnostic pathway for all age groups, as it reflects the basic pathophysiological defect in the sweat gland. It is also critical following newborn screening as a confirmatory diagnostic step. Despite its importance, sweat test quality is variable whether performed in the laboratory or as a point of care test. The ECFS DNWG aims to improve sweat test performance, taking into account the barriers and issues identified in the European survey; the previous step in the ECFS sweat test project. This manuscript proposes a grading of sweat test guidance from "acceptable" to "optimal", aiming to pragmatically improve quality while taking into account local situations, especially in resource-limited settings.

1. Background

Sweat testing is the cornerstone in the diagnostic process for cystic fibrosis (CF) for all ages, even with increasing availability of genetic testing. A sweat test should be done on every person being evaluated for CF, even outside of the newborn period. It is however particularly pertinent after newborn screening (NBS), when a positive test requires diagnostic assessment, which should always include a sweat test (ST).(1) The diagnosis of CF should be robust and include physiological confirmation of the basic defect. Even exhaustive *CFTR* gene analysis cannot replace a ST, due to the possible detection of variants of unknown clinical consequence, of two variants *in cis,* or even due to a sample processing error.

From the time consensus reports were published, guidelines were issued to refine and harmonize the different steps in the ST methodology.(2–4) Surveys on ST practices have however shown diverse and suboptimal practice. Quality improvement initiatives have been shown to improve the performance of laboratories/CF centres performing ST.(5–7)

The European ST survey showed variation with respect to sweat collection, analysis and interpretation of results. Cost was reported as a barrier to upgrading ST devices to approved commercial equipment as well as to implementation of recommended Quality Control (QC) procedures.(8)

Based on this evidence, the ECFS Diagnostic Working Group (DNWG) organized the first Sweat Test Training Workshops at the ECFS Conferences (Belgrade, 2018 and Liverpool, 2019) including

participants from Europe and other regions. Similar training events were replicated at national levels.

The present document builds on those initiatives and provides a tool to guide CF centres/labs in Europe to improve the performance of ST. For the first time, a grading of ST requirements is proposed from "acceptable" to "optimal", helping CF centres/laboratories to improve the ST performance, pragmatically taking into account local situations, especially in resource-limited settings. For ST best practice recommendations, we refer to the UK Guidelines 2nd Edition (2), the CLSI Guideline 4th Edition (4), and the Australasian Guidelines.(3) This document covers sweat chloride concentration (SCC) and conductivity measurements, excluding other non-standard sweat analysis methods.

2. Methods

A review of literature focusing on ST as a diagnostic tool was performed in Pubmed, using terms 'sweat test', 'sweat testing', 'sweat chloride'. Relevant papers were included, without publication date or language restrictions. Existing Guidelines and Consensus documents were reviewed and discussed within a core group during (6) online meetings. Results from the European Sweat Test survey were taken into account in order to identify barriers in performing optimal ST and to propose solutions applicable in real life.(8)

3. Sweat Test Recommendations

3.1 Institution and sweat test operators

A specialist CF centre, as referred to in this manuscript, has an appropriate level of expertise as stated in the ECFS Standard of Care (SoC) documents.(1,9) These documents have also outlined the minimal standards for laboratories performing ST as summarized in **Table 1** and **Appendix A**. (1,9,10)

All CF centres must have a clear policy for infection control and facilities must allow adequate patient segregation to prevent cross-infections, also for ST after positive NBS.

3.2 Written information for patients/parents/carers (**Appendix B**)

It is good clinical practice to provide written pre-test information to the patient, parents and caregivers. This should include at least "why" the test is being done, "how" it will be performed, "risks associated" with the test, what the subject will "experience", and "contact details" regarding the testing and final result.(2)

3.3 Subjects undergoing a sweat test: who and when?

A ST can be attempted in term infants from the 3rd day of life or even premature babies if clinically relevant, however with increased risk of collecting insufficient sweat volume (QNS). Yet, a recent study showed that more than 80% of infants younger than 2 weeks of age had adequate sweat volumes.(11) In order to reduce the amount of QNS samples, it is advisable to perform a ST in full term infants after 2 weeks of age, or when weight exceeds 2 kg in preterm infants. No upper age limit is defined for ST in adults, but the increasing sweat electrolyte concentration in adults needs to be considered.(12,13) While a sweat test is an essential diagnostic tool, treatment should not be delayed or withheld from an infant who has a positive NBS result and signs/ symptoms of CF, if the sweat collection is insufficient. These infants, with a presumptive diagnosis, should have a repeat sweat test after 2-4 weeks of therapy.

Situations that can lead to false positive or false negative results should be recognized and avoided if possible. (**Table 2**) (14,15) As long as the patient is stable, ST results are not affected by diuretics, antibiotics nor an intravenous line. High concentration oxygen therapy using open delivery systems including a headbox is a contra-indication to sweat testing due to the fire hazard, whereas nasal prongs or facemasks are considered safe.(2)

4. Sweat test procedure

A ST comprises three sequential steps: stimulation of sweat production, sweat collection and sweat analysis. **Table 1** lists the main requirements to perform a good quality ST and provides more details on each step described below.

4.1 Sweat stimulation

Site of stimulation

The preferred site is the distal flexor surface of either forearm, containing the highest concentration of exocrine sweat glands. Other sites may be considered.(2–4)

Bilateral collection is recommended by expert guidance (such as CLSI) as this may reduce QNS rates. (4) However, it does have resource, time and cost implications. Discordances between results from two collections taken on the same occasion are exceptional.(16) In case of low sweat rate on one site, contralateral collection is also insufficient in 2/3 of attempts, reducing the proportion of tests without results by only one third.(16) Earlier publication suggested however a decreased failure rate with bilateral ST.(2) Bilateral ST can be useful for QA and in situations in which an insufficient specimen is more likely to occur (e.g., in young infants (4) or an unsuccessful first

attempt).(16). Laboratories should monitor their QNS rates carefully, especially when initiating NBS programs resulting in larger numbers of young infants being tested.

Preparation before stimulation

The intact skin should be properly cleaned before iontophoresis.(2–4)

Iontophoresis device

The iontophoresis device must be battery powered, including a safety cut-out. At each use, a visual check of the power supply for damage or malfunction and monitoring of the current intensity is mandatory to guarantee safety throughout iontophoresis. Electrical safety of all power supplies must be annually checked by a technician and records kept.(2)

Electrodes for iontophoresis

Electrodes should be of appropriate size and curvature to comfortably fit the patient's limb. They should be firmly attached, however avoiding uncomfortable overtightening that might restrict circulation. Electrodes must be regularly cleaned and inspected, and discarded if they show pitting or irregularities. The positive (red) electrode needs to be placed the closest to the wrist, but avoiding too close contact with tendons or bone.(17) For safety reasons the negative (black) electrode must always be placed on the same limb as the positive electrode, so the current never crosses the trunk. Aqueous solutions on pad supports or gel discs containing pilocarpine nitrate should be placed in contact with the skin at both electrodes. Subsequently, iontophoresis is applied as described in **Table1**. The use of appropriate filter paper pads or hydrophilic pocket pads reduce the risk of burns. Manufacturer's instructions should be followed.

4.2 Sweat Collection

Two collection methods are in use: the capillary tube collection system and the gauze/filter paper method. The capillary tube system (e.g. Macroduct™) is approved and widely used.(2–4) Sweat is collected into a disposable capillary tube that contains a blue dye, facilitating visualization of the sweat progression. Alternatively, sweat can be collected onto a pre-weighed chloride-free filter paper or gauze of approximately equal size to the stimulated area (i.e. the pads used in iontophoresis). Filter paper or gauze will be sealed into position with impervious material and waterproof adhesive tape. During collection by any method, sweat must be protected from contamination and evaporation.

The same analytical balance should be used throughout the procedure. The minimal sweat volume collected over 30 minutes should correspond to a sweat secretion rate of at least $1g/m^2/min$, referring to the collection area. Sweat collections onto filter paper or gauze should be weighed and analysed immediately.(2–4) Collections below $1g/m^2/min$ should not be analysed nor pooled, but reported as QNS. A repeat ST can be performed on the same day, at another site. **Table 1** summarizes recommended maximal test failure rates (QNS) according to the age of the tested subjects.(2–4)

If sweat collection is performed at two sites, the test is reported as QNS only when both collections result in insufficient sweat volumes.(2,4) A high proportion of QNS is indicative of possible methodological shortcomings requiring action such as: training of personnel, re-evaluation of procedures and/or technical inspection of devices. Strategies to minimize QNS rates are outlined in **Appendix A.**(18)

4.3 Sweat storage and transport

Sweat may be collected at remote sites and transported to the laboratory for analysis as long as strict storage conditions can be adhered to. Every effort must be made to minimize evaporation and contamination of the sample during sweat collection, transport, storage (if needed) and analysis.(2–4) (see details in Table 1, section 3).

4.4 Sweat analysis

Chloride is the analyte of choice and not sweat sodium, potassium or osmolality. Accepted methods for quantitative analysis of sweat chloride are, in order of preference: coulometry, Ion Selective Electrode and colorimetry. Additional quantitative methods could be allowed (e.g., mass or gas spectrometry) only if validated on sweat. Duplicate readings of each sample are performed to report the average result.(4)

Sweat conductivity measurements using the Sweat-Check[TM] analyser have been demonstrated to be as effective as SCC in discriminating healthy children from those with CF (19-25) The American CF Foundation (CFF) recommends conductivity only as a screening test, (4) and a conductivity value <50 mmol/L is considered normal by the CFF, and a value ≥50 mmol/L should be referred to an accredited CF centre for a quantitative SCC measurement.(26) (**Table 3**)

A number of point of care testing (POCT) devices have been developed to provide a ST result at bedside. The most commonly used is the Nanoduct[TM], developed specifically for newborns, requiring only 3–5µl of sweat, which makes it possible to distinguish healthy children from those with CF. (27-31) Such a POCT device can aid early diagnosis when sweat collection with other

methods is insufficient, which may be especially relevant in newborns with a low weight and subsequently high risk of QNS samples. (27-30,32) Within NBS programmes, such a POCT approach may hasten the diagnosis, especially in low resources countries with wide geographical areas. In countries where conductivity is the only available method, the ECFS DNWG recommends creating at least one laboratory service for quantitative SCC measurement to confirm the diagnosis.

Preparing sweat collection for analysis

Sweat collected in the capillary tube system must be carefully expelled and homogenized prior to analysis but should not be diluted. When sweat is collected onto filter paper or gauze an elution step with deionized water is needed to extract the sweat from the paper or gauze, enabling measurement of SCC.(2,4)

Criteria to exclude a sample from analysis

Contamination of the sample with saline solutions, evaporation, and quantity not sufficient (QNS) are the main criteria to exclude a sample from analysis. An internal QC procedure (which differs from the calibration procedure) must be performed in the lab at two concentrations ("in house" or commercial) before each sweat analysis is performed, including concentrations appropriate for medical decisions with the QPIT method.(2,4) This means a SCC equal to and less than 29 mmol/L, between 30 to 59 mmol/L and equal or greater than 60 mmol/L. Results of the control samples must fall within these established ranges and should be reviewed periodically with a target imprecision indicated by a coefficient of variation (%CV). (2,4) (**Appendix A**)

4.5 Processing the sweat test result

All SCC results in the CF range must be repeated and/or confirmed with population adapted *CFTR* gene analysis. The diagnosis of CF should never be based on a single positive sweat test. (4,33) Reference values for ST interpretation are summarized in **Table 3**. Algorithms on how to assess the diagnosis of CF have been published.(33) A written ST report should be available after each test, including at least the information listed in **Table 4**.

Especially within a NBS programme, the ST should be analysed immediately, with the result being reported by a CF specialist to the family on the same day, even if negative.(10)

The results should be interpreted taking into account possible confounders.(14,15) (**Table 2**)

Individuals with SCC in the intermediate range should undergo a repeat ST. If results remain intermediate, further evaluation in a CF specialist centre, including a detailed clinical assessment

and extensive *CFTR* gene analysis are usually needed. In case of unclear diagnosis, further electrophysiological investigations like nasal potential difference (NPD) or intestinal short circuit current measurement (ICM) should be considered.(1,33,34)

5. Sweat testing and CF diagnosis in developing countries

Inequalities in CF diagnosis, care and outcomes are seen "both between and within countries, typically as a reflection of existing social inequities".(35) In the low- and middle-income countries (LMIC, World Bank classification, http://data.worldbank.org/about/country-classifications), CF is dramatically underdiagnosed as physicians have low awareness of CF, as well as insufficient ST equipment and trained staff. NBS programmes for CF often do not exist. Furthermore, these countries experience high prevalence of diseases with symptoms similar to CF, such as tuberculosis and non-CF bronchiectasis.(36)

Main barriers to sweat testing process in LMIC

Access to facilities offering ST is currently restricted in LMIC, hindering the ability to diagnose CF in individuals with suggestive symptoms. Public health systems are under-resourced and serve predominantly those who cannot afford private health insurance, while laboratory services for ST are mostly or exclusively available in private practice. Most private laboratory services are working with high standards (training staff, equipment, cut-off of sweat electrolyte concentration and QA procedures), in line with international norms but are not able to support the cost of ST for all poor people. Maintaining a high quality ST service with permanent trained staff remains a challenge. In addition, the cost of ST remains a major barrier for universal accessibility as commercially available kits come at high cost. Sweat testing using chloride measurement, the only accepted CF diagnostic electrolyte used in developed countries, is more labour intensive and less widely available than sweat conductivity that requires less expertise and is more affordable with all-in-one equipment. Current diagnostic algorithms, including SCC measurement, may not be feasible for use in many of these LMIC countries. An alternative pathway for CF diagnosis where ST is not feasible may be the use of molecular diagnosis that is becoming nowadays more available and affordable. However appropriate CFTR panels which depend on the prevalence of CFTR variants in these populations, still need to be developed and the cost is still high in these countries. The interpretation of the pathogenicity of uncommon detected variants remains very challenging, as not all are disease causing.

Interpretation of SCC should factor in the effect of malnutrition in non-screened population. In Rwanda, Mutesa et al. (37) have shown SCC values at or over 40 mmol/L in 80% of 60 children

with CF-like symptoms and malnutrition. In 62% these values even reached 60 mmol/L, with *CFTR* variants identified in only 13%, suggesting a high proportion of false positives, highlighting the potential flaws of universal algorithms in LMIC countries.

Solutions for mandatory steps in the sweat test process

To offer ST facilities for the whole population, CF should deserve the recognition as a "severe chronic disease" in LMIC and subsequently receive specific government funding. Implementation of ST laboratories in academic hospitals certified by the health ministry remains a major challenge. Although not accepted as a diagnostic tool for CF in developed countries, sweat conductivity, which is more affordable, more widely available and less labour intensive than SCC measurement, may represent a valuable option in LMIC countries for CF diagnosis.

Adopting a consistent and pragmatic approach for ST procedure according to the international guidelines is of utmost importance. Access to an online educational platform with pictures of each step in the ST procedure, an interactive tool explaining what happens could be a helpful opportunity.

Patient associations can help in supporting the cost of ST for families with insufficient financial resources or no health insurance. They should also reach out to health-care officials and policy makers to achieve partnerships and improve ST availabilities across the country.

International collaborative care efforts with appropriate training, skill development and creative initiatives, such as sweat test camps, is crucial.(35)

6. Conclusion

The sweat test remains the gold standard test to diagnose CF and should be undertaken promptly whenever this diagnosis is considered, especially in the context of NBS. The ST result should be assessed together with the clinical picture and information from *CFTR* gene variant analysis. To achieve high quality sweat testing is a challenge, requiring resources and well-trained staff. A European survey demonstrated variability in approach. This is particularly challenging in LMIC and countries with low prevalence of CF. In addition, most adult clinical services do not have regular access to sweat testing, unless they are directly affiliated with a CF centre. We have developed this guidance for CF centres and laboratories in Europe to provide a pragmatic approach to improve the quality of the performance of ST. It reflects the third step after the Sweat test survey and workshops to improve the sweat test practice in Europe. We feel it represents a more pragmatic real world

document to provide a guidance to established and emerging CF services, including LMIC. The ECFS DNWG created a subgroup of experts in ST that can be contacted for general info, training, documents, bibliography, and technical support (https://www.ecfs.eu/ecfs_dnwg/projects).

The next phase of the ECFS Sweat Test project will be an extensive collaboration with the ECFS Educational Platform (www.ecfs.eu/education), aiming to harmonize background knowledge and to reach learners from geographically dispersed locations to provide high quality sweat test services.

7. Acknowledgements

8. Conflict of interest statement

No conflict of interest is declared by the authors.

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