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The Need for Quality Improvement in Sweat Testing Infants Following Newborn Screening for Cystic Fibrosis

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Abstract

The proportion of insufficient sweat tests after positive newborn screening for CF was determined. Infants 3 months old had a mean ($\pm$ sd) rate of 7.2% ($\pm$ 7.6) (range 0–40%). Collection methods did not impact the rates. The high and variable rates indicate a need for quality improvement.

Nationwide newborn screening (NBS) for cystic fibrosis (CF) has led to sweat chloride testing for infants as young as 2–4 weeks of age (1,2). A diagnostic sweat test requires sweat stimulation by pilocarpine iontophoresis, collection of sweat onto pads or into Macroduct® coils and quantitative analysis of chloride concentration (3,4). The minimum acceptable sweat volume or weight required for an accurate test corresponds to 75 mg of sweat collected on 2×2 inch pads and 15 uL of sweat collected in Macroduct® coils (3); lower sweat weights or volumes cannot be analyzed and are referred to as a “quantity not sufficient” (QNS) specimens. Individuals with an initial QNS specimen must be retested, delaying confirmation of diagnosis and initiation of treatment. A high QNS rate after a positive CF NBS test is clinically, psychologically, and economically significant.

For individuals over three months of age, it is recommended that the QNS rate be 5% (3,4). Neonates do not produce as much sweat as older, larger infants, leading to a higher proportion of QNS test outcomes in patients less than 6 weeks of age (1,5). There are no current metrics for establishing a target range for QNS rate in infants 3 months of age. A

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Conflict of interest:

project based on the results from a national survey, the consensus of clinical leaders involved in NBS for CF, and prospective data from a single state, addressed this concern.

Methods

Three sets of data concerning QNS rates were collected and analyzed in 2009 and 2010: a national survey to 110 pediatric CFF accredited care centers (“CFF Annual Application”); a national survey to 48 state leaders involved in newborn screening for CF (NBS Special Interest Group (“NBS-SIG”)); and a review of sweat test data prospectively collected by the Illinois Department of Public Health NBS program, which includes 13 Illinois and 2 Missouri sites performing sweat testing for Illinois infants with a positive CF NBS result. QNS was defined as the percentage of sweat tests where an adequate sweat sample was not obtained; when bilateral testing is performed, the test is QNS only if an adequate sweat sample is not obtained from either site. The NBS-SIG and the national survey assessed sweat testing practices in the respondents’ local CF center. Response rates were 100% and 89.5% for the CFF annual application and the NBS-SIG questionnaire, respectively.

We used t-tests for normally, or Mann-Whitney U-tests for skewed distributed continuous data, and Fisher’s exact test for categorical sparse data.

Results

We found that QNS rates were often high and generally variable in the national survey (Table 1). T-tests were performed comparing the QNS rate with regard to collection method of pad (gauze or filter paper) versus Macroduct® coil according to age. For infants ≤ 3 months, $t=1$; $p=0.321$ with a 95% CI of 1.46–4.38. For individuals > 3 months of age, $t=1.75$; $p=0.086$ with a 95% CI of -0.15 – 2.3 . It can be inferred that with regard to QNS rates, no one collection method is superior to another.

Age at sweat testing and number of QNS sweat tests were reviewed in Illinois between January 1 and October 27, 2009. Sweat tests for 469 infants with positive CF NBS were performed at 15 sites; 47 (10%) unique infants had an initial QNS test. The median age (25%, 75% quartile) at the first sweat test in infants with QNS tests was earlier than that in those with sufficient tests (17(15, 31) vs. 22 (17, 32) days, $p=0.04$, (two-tailed Mann Whitney U test). There was variability in the number (11–112) and the percentage of QNS (0–40%) sweat tests among sites. Eight of 11 (73%) sites accredited by the CFF as centers or affiliate programs had QNS rates of $\leq 10\%$, whereas only 1 of 4 (25%) sites achieved that rate; this difference was not statistically significant ($p=0.24$, two tailed Fisher’s exact test).

Discussion

Determining QNS rates is important because a very high rate signifies a problem in sweat collection. Routine monitoring of the QNS rate should trigger evaluation of the sweat testing protocol. The CFF annual application and the NBS-SIG data reveal that young infants can be successfully sweat tested. On average, 92.8% of individuals yielded sufficient sweat for analysis. The CFF annual application, the NBS-SIG data, and the Illinois data all support the QNS metric for infants 3 months of age and younger of $\leq 10\%$ as the means were 7.2% for

CFF annual application and 8% for the NBS-SIG and 10% for the first sweat test after a positive CF NBS for the Illinois program.

In Illinois, the trend towards higher QNS rates in sites not accredited by the CFF was concerning. The variation in Illinois can only be attributable to differences in performance of the sweat collection technique, pointing to a need for quality improvement efforts.

All data sources revealed a large amount of variation in the percentage of QNS results, ranging from 0 to 40%. In the survey instruments, this may be due to respondents not calculating QNS results correctly or uniformly; skewing from repeatedly testing and failing to collect sufficient sweat in one or two difficult to sweat infants; and operator variability in sweat collection. Techniques to improve sweat collection are listed in Table 2 (1).

Improving sweat test practices at individual sites will reduce QNS rates and provide more reliable results. Given the great variability reported in both surveys and in the Illinois data, system-level quality improvement appears necessary. The CFF accredits qualified CF Centers in the United States. The accreditation process includes annual written review of sweat test procedures, and periodic on-site program evaluation, including a review of sweat testing. For geographic and other reasons, many state programs refer infants with positive newborn screens for CF to laboratories outside of the CFF system. States should consider using only CFF accredited programs or institute proficiency assessment procedures similar to those performed by CFF.

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Dr. LeGrys is a consultant regarding sweat testing performance and receives honoraria for this activity. Dr. McColley is an advisor and speaker's bureau member for Genentech and has received honoraria for these activities. She is a member of the Illinois Department of Public Health Genetic and Metabolic Diseases Advisory Committee. Dr. Farrell is the CFF National Facilitator for Newborn Screening and receives honoraria for that work.

List of Abbreviations:

CAP	College of American Pathologist
CF	Cystic Fibrosis
CFF	Cystic Fibrosis Foundation
CLSI	Clinical and Laboratory Standards Institute
QNS	Quantity not Sufficient
NBS	Newborn Screening

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Table 1:

Comparison of QNS Rates. Units are percent

	N	Mean	Median	Std Dev	Range
CFF Annual application: 3mo; all methods	110	7.2	4	7.6	0–40
NBS-SIG: All methods	42	8	7	6.3	0–25
CFF Annual application: 3 mo; gauze/filter paper	56	6.5	3	6.6	0–23
CFF Annual application: 3 mo; Macroduct®	54	7.9	5	8.6	0–40
NBS-SIG: Gauze/filter paper	25	7.6	6	6.5	0–25
NBS-SIG: Macroduct®	12	7.5	6	5.2	0–17
CFF Annual application: > 3mo; all methods	110	4.3	4	3.3	0–19
CFF Annual application: > 3 mo; gauze/filter paper	56	3.7	3	3.0	0–14
CFF Annual application: > 3 mo; Macroduct®	54	4.8	4	3.5	0–19

Table 2:**Recommendations for Quality Improvement in Sweat Collection (3).**

Follow the CLSI-34 A3 guidelines exactly.

Calculate QNS rate correctly. The QNS rate is the percentage of sweat tests where an adequate sweat sample was not obtained upon initial testing. When bilateral testing is performed on two sites, the test is QNS only if an adequate sweat sample is not obtained from either site.

Limit the number of personnel performing sweat collection to few well trained individuals. Each technician should perform at least 1 collection per week to maintain competency. Routinely perform competency testing on all personnel performing sweat testing to include direct observation of performance.

Perform bilateral testing (i.e. collect and analyze sweat from two sites). While samples from separate sites may not be pooled for analysis, testing bilaterally increases the likelihood of collecting a sufficient sample from at least one site.

Ensure that the patient is well hydrated, not acutely ill; and asymptomatic infants weigh at least 2 kg and are at least 2 weeks of age.

Periodically evaluate the iontophoresis equipment for voltage leak and current control.

Use pilocarpine nitrate, not pilocarpine hydrochloride for iontophoresis.

Use 1 ½ inch × 1 ½ inch electrodes over 2 × 2 inch gauze or filter paper for stimulation regardless of patient age or size.

Ensure the stimulation and collection area are the same size.

Place the positive electrode on the inner volar surface of the lower arm where there is a higher density of sweat glands.

Place the collection device or material directly over the area stimulated by the positive electrode.

Wrap the collection area with a stretch bandage for security.

Thermal warming of the collection site does not appear to increase the sweat yield.

Blot back the condensate formed into the pad when collecting onto gauze or filter paper.

Do not store or transport sweat in the Macroduct® coil as evaporation can occur.

Accurately determine the amount of sweat collected either gravimetrically or volumetrically.

Develop a continuous quality improvement program by periodically monitoring the:

Training and competency testing of collection and analysis personnel

Performance on external inspections like CAP and CFF

Percent QNS rate associated with each collection personnel