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Comparison of Quantitative Sweat Chloride Methods after Positive Newborn Screen for Cystic Fibrosis

Theresa A. Laguna, MD MSCS⁽¹⁾, Nan Lin, BA⁽²⁾, Qi Wang, MS⁽³⁾, Bonnie Holme⁽¹⁾, John McNamara, MD⁽⁴⁾, and Warren E. Regelman, MD⁽¹⁾

⁽¹⁾Department of Pediatrics, University of Minnesota School of Medicine and The Amplatz Children's Hospital, Minneapolis, MN.

⁽²⁾University of Minnesota Medical School, Minneapolis, MN.

⁽³⁾Biostatistical Design and Analysis Center, Clinical and Translational Science Institute, University of Minnesota, Minneapolis, MN.

⁽⁴⁾Department of Pediatrics, Children's Hospitals and Clinics of Minnesota, Minneapolis, MN.

Summary

Objectives—Rapid and reliable confirmatory sweat testing following a positive newborn screen (NBS) for cystic fibrosis (CF) is preferred to allow for early diagnosis and to decrease parental anxiety. The Cystic Fibrosis Foundation (CFF) recently recommended a quantity not sufficient (QNS) rate of 10% in infants < 3 months of age referred for quantitative sweat chloride analysis. Two CFF-approved methods are available by which to quantitatively measure chloride concentration in sweat. Our objective was to compare the performance of the Macroduct® sweat collection system (MSCS) with the Gibson and Cooke technique (GCT) in the acquisition of samples for the determination of sweat chloride concentration in infants with a positive Minnesota State NBS for cystic fibrosis.

Methods—A retrospective database review of infants referred to the core Minnesota CF Center or its affiliate site for confirmatory sweat testing was performed to compare the QNS rates for the two techniques. Associations between birthweight, age at test, race and QNS rates were examined.

Results—568 infants were referred for 616 sweat tests from March 2006–January 2010. The mean age was 32.8 days at the initial sweat test. The GCT had a significantly higher QNS rate compared to the MSCS (15.4% vs. 2.1%, $p < 0.0001$). There was no association between age and the probability of QNS. The probability of QNS decreased as birthweight increased ($p = 0.02$). After adjusting for age, the odds of QNS using the GCT remained 8.34 (95% CI: 3.72–18.71) times that of the MSCS. Non-white infants had a significantly higher likelihood of QNS compared to non-Hispanic white infants ($p = 0.0025$).

Conclusions—Given the performance of the MSCS, the Minnesota CF Center has implemented the MSCS as its method of choice for diagnostic sweat testing in infants following a positive state NBS.

Corresponding Author/Reprint Request Author: Theresa A. Laguna, MD, MSCS Pediatric Pulmonary Medicine 420 Delaware St. SE MMC 742 Minneapolis, MN 55455 Phone: (612) 626-2916 Fax: (612) 626-0413 lagun005@umn.edu.

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Keywords

Macroduct; Gibson-Cooke; quantity-not-sufficient; immunoreactive trypsinogen; comparison; quality improvement

Introduction

The determination of sweat chloride concentration using pilocarpine iontophoresis with quantitative chloride [Cl^-] analysis remains the gold standard for the diagnosis of cystic fibrosis (CF) (1). Nationwide implementation of newborn screening (NBS) for CF has mandated the need for sensitive, specific and efficient sweat testing in infants as young as 2-4 weeks of age (2). Early diagnosis of CF and the initiation of therapy in symptom-free newborns are associated with improved growth and nutrition and possibly improved pulmonary outcomes (3-5). Alleviating parental anxiety by decreasing the time between a positive CF NBS and confirmatory sweat test is also important (6,7). Therefore, it is imperative to have a method with a minimal failure rate for sweat testing in a newborn infant.

The Cystic Fibrosis Foundation (CFF) publishes specific guidelines for sweat testing performed by laboratories in accredited CF Centers across the United States (1). Each CF Center must perform quantitative pilocarpine iontophoresis sweat chloride testing using either the Gibson and Cooke technique (GCT) or the Macroduct® sweat collection system (MSCS) (8). To minimize the variability of the chloride concentration measurement, the amount of sweat collected must reach a certain threshold (i.e. 75mg of sweat for the GCT and 15µl of sweat for the MSCS), or it is deemed quantity not sufficient (QNS) and a new sweat sample must then be obtained at a later date. Once collected, the sweat sample is then quantitatively analyzed for chloride concentration using a chloridometer, manual titration or a previously validated automated analyzer to obtain a result that meets clinical use standards (8).

The CFF requires that a CFF-approved Center maintain a QNS rate of 5% for individuals over 3 months of age undergoing sweat testing (9). For infants less than three months of age, the CFF recently recommended a QNS rate of 10% and encouraged centers to engage in quality improvement measures to improve their QNS rates in this population of NBS positive infants. Younger infants may have difficulty producing adequate amounts of sweat for analysis, thus presenting a diagnostic challenge to those who have a positive NBS for CF (2,10). The acquisition of a QNS sweat sample often requires parents to return to the CF Center for repeat testing, resulting in increased travel, time and anxiety while awaiting a definitive diagnosis. In addition, a QNS sample also may delay the initiation of therapy in the setting of a true CF diagnosis, making it useful to have a test with as low a QNS rate as possible.

The state of Minnesota (MN) started its CF NBS program in March 2006. Minnesota uses a two-tiered immunoreactive trypsinogen (IRT)/DNA based testing program on a dried blood spot obtained from a newborn heel-stick between 24 and 36 hours of life. Samples are sent to the Minnesota State Department of Health for daily analysis. Samples found to have an IRT level > 170ng/ml or those with an IRT in the top 4% of values calculated daily automatically trigger reflex cystic fibrosis transmembrane conductance regulator (CFTR) genetic mutation testing with a panel of 39 mutations. Patients with samples found to have at least one CFTR mutation are referred for confirmatory sweat testing by pilocarpine iontophoresis. Infants may also be referred for confirmatory sweat testing with an IRT > 170 ng/mL and no identified CFTR mutations. The core Minnesota CF Center, which is located

at the University of Minnesota Academic Health Center, uses the GCT to perform pilocarpine iontophoresis. Children's Hospitals and Clinics of Minnesota is a community affiliate site of the Minnesota CF Center and utilizes the MSCS technique for confirmatory sweat testing. The aim of our study was to compare the performance of the GCT with the MSCS in the determination of sweat chloride concentration in infants < 3 months of age with a positive Minnesota State NBS for CF.

Materials and Methods

Study Population

All infants referred to either the core Minnesota CF Center or its community affiliate, the Children's Hospital and Clinics of Minnesota, for confirmatory sweat testing following a positive Minnesota State NBS for CF from March 2006 – January 2010 were included.

Study Design

A retrospective database review at the core Minnesota CF Center site and its community affiliate was performed. Sex, race, birthweight, age at first sweat test, weight and/or height at first sweat test, method of sweat testing, QNS rates, chloride concentration, CF diagnosis, and CFTR mutations were collected on all infants who received at least one sweat test at either of the two sites. Only the core Minnesota CF Center site collected complete race data and infant weight at time of sweat test. Race was defined as American Indian/Alaskan, Asian, Black/African American, White or Mixed. The study was approved by the Institutional Review Board at both the University of Minnesota and the Children's Hospitals and Clinics of Minnesota.

Methods for Pilocarpine Iontophoresis

(1) Gibson and Cooke Technique (GCT): The GCT method was employed by the core Minnesota CF Center. The procedure was performed as per the standards of the National Committee for Clinical Laboratory Standards (CLSI) and CFF Guidelines (11). Two technicians were trained in the technique and performed the GCT in a dedicated sweat testing laboratory under the direction of the Division of Pediatric Pulmonology following the CLSI protocol. Chloride concentration was determined using a chloridometer. QNS was defined as a sample weight <75mg on 2 × 2 inch gauze pads from each of two collecting sites in a 30 minute period. If a sweat sample from one site was of adequate weight, the test was not considered to be QNS. **(2) Macroduct® Sweat Collection System (MSCS):** The MSCS method was used by the community affiliate, Children's Hospitals and Clinics of Minnesota. The procedure was performed as per the National Committee for Clinical Laboratory Standards and CFF Guidelines by nine technicians trained in the technique in the clinical laboratory of the main hospital (11). Chloride concentration was determined using a chloridometer. QNS was defined as a sample volume < 15µl in the coils from each of two collecting sites in a 30 minute period. If a sweat sample from one site was of adequate volume, the test was not considered to be QNS.

Diagnosis of CF

A sweat chloride concentration ≥ 60 mEq/L measured by GCT or MCS was considered diagnostic for CF. Sweat chloride concentrations between 30-59 mEq/L were considered intermediate and followed closely with a repeat sweat test. Any infant with a sweat chloride ≥ 30 mEq/L was referred to a CF Center for full evaluation by the CF healthcare team. It is the protocol of the Minnesota CF Center and its affiliate to repeat all QNS sweat tests until an acceptable quantity is obtained.

Statistical Analysis

Descriptive statistics were calculated using median and ranges for continuous variables and percentages for categorical variables. The chi-square test was used to examine the difference in QNS rates between the GCT and MCS and between white and non-white infants. For analysis purposes, non-white infants were defined as American Indian/Alaskan, Asian, African American or Hispanic. The Cochran-Armitage test for trend was used to examine the association between categorized age at test, birthweight and QNS rates. Logistic regression was used to model the probability of QNS with the two methods of sweat testing (GCT and MCS), adjusting for age at test. All analyses were performed using SAS 9.1.3 (Carey, NC).

Results

Patient Demographics

Demographic data from 568 infants who received 616 sweat tests from March 2006 – January 2010 is presented in Table 1. Complete race data was not available for those infants tested by MSCS at the Children's Hospitals and Clinics of Minnesota. Infants seen at the University of Minnesota CF Center had similar demographics but required more sweat tests than those seen at Children's Hospitals and Clinics of Minnesota (1.2 vs. 1.02, respectively; $p < 0.0001$).

Percent QNS in GCT vs. MSCS

Table 2 describes infants presenting with a positive CF NBS for an initial sweat test at each institution. Two infants tested by GCT and one infant tested by MSCS had an initial QNS sweat test and two confirmed CFTR mutations on NBS, resulting in a positive CF diagnosis at the time of their first test. Three infants had IRT levels $> 170\text{ng/mL}$ with no CFTR mutations identified, resulting in a referral for sweat testing that was subsequently negative for a diagnosis of CF. Infants sweat tested using the MSCS were significantly older at the time of their initial test than those tested using the GCT, 34.6 days vs. 29 days ($p = 0.02$). The likelihood of QNS using the GCT was significantly higher than that using the MSCS, 15.4% vs. 2.1% ($p < 0.0001$). Using only those infants tested by GCT, the likelihood of QNS was significantly higher in non-white infants vs non-Hispanic white infants, 32% vs. 12% ($p = 0.0025$).

Percent QNS in GCT vs. MSCS by Age at Test

Logistic regression analysis controlling for age at time of initial sweat test still showed a significant difference between the two techniques, with the GCT having a greater likelihood of QNS than the MSCS. After this adjustment for age at time of test, the odds of QNS using the GCT was estimated to be 8.34 times that of the MSCS (95% CI: 3.72 – 18.71). Although we did not find a significant relationship between QNS and age at test for either technique, the MSCS had a lower % QNS across all ages compared with the GCT (Figure 1).

Percent QNS in GCT vs. MSCS by Birthweight

We investigated the relationship between the proportion of first sweat tests with QNS and categorized birthweight (0-2500, 2500-3000, 3500-4000 or > 4000 grams) in all infants using the Cochran-Armitage test for trend (Figure 2). The probability of QNS decreased significantly as birthweight increased in both the GCT ($p = 0.023$) and MSCS methods ($p = 0.022$).

Percent QNS in GCT weight at Time of Sweat Test

We investigated whether there was a relationship between the proportion of first tests with QNS and categorized weight at time of test (< 7, 7-8, 8-9, 9-10 or > 10 pounds) using the Cochran-Armitage test for trend. Only the core Minnesota CF Center collected this weight data and, as such, analysis could only be done for the GCT. For these infants who had a sweat test by GCT, the probability of QNS decreased significantly as weight at time of test increased (Figure 3, $p < 0.001$).

Disposition of Infants with an Initial QNS Sweat Test

For both the core CF Center and its affiliate site, 14% (5/37) of those infants with an initial QNS sweat test ultimately received a diagnosis of CF. There was no significant difference in the number of infants with an initial QNS and those who had an initial diagnostic sweat test and a subsequent CF diagnosis. Of those infants with an initial QNS sweat test, 50% had a repeat sweat test performed within 25 days (range 0-715 days).

Percent QNS in MSCS at Minnesota CF Center Upon QI Study Completion

The Minnesota CF Center changed to the MSCS from the GCT upon reviewing the results of this QI project. Since implementation of the MSCS at the Core CF center, 30 sweat tests have been performed in infants > 3 months of age with one 1 QNS sample obtained (3% QNS rate).

Discussion

An accurate, precise and efficient sweat test is a mandatory component of any newborn screening algorithm for the diagnosis of CF. The CFF recommends either the GCT or MSCS method be utilized for quantitative pilocarpine iontophoresis to determine the chloride concentration in the sweat of newborn infants with a positive NBS for CF. We sought to compare the performance of the GCT versus that of the MSCS in a large population of newborn screened infants < 3 months of age born in the state of Minnesota with an elevated IRT and/or at least one identified CFTR mutation on a limited 39-mutation panel.

The determination of QNS rates for each method of sweat chloride testing is a vital part of maintaining CFF-accreditation as a CF Center. Routine, annual monitoring of the QNS rate for each center is mandated to decrease variability in sweat test practices and to provide the most rapid diagnosis in order to initiate early therapy in CF infants and maximize therapeutic outcomes. The CFF recently recommended that CF Centers aim for a QNS rate of 10% in infants < 3 months of age, and encouraged centers to engage in quality improvement initiatives to determine and obtain an acceptable QNS rate (9). Our CF Center and its community affiliate provided the unique opportunity to directly compare the performance of the GCT and MSCS methods of performing quantitative iontophoresis in a large number of infants in order to determine the more efficient method by which to confirm or refute a diagnosis of CF in our population in the state of Minnesota.

Our study is the largest to date to investigate and compare sweat testing techniques in infants < 3 months of age. We demonstrate an overall QNS rate for the Minnesota CF Center and its affiliate site of 6.5% in approximately 600 infants < 3 months of age referred for a confirmatory sweat test following a positive NBS for CF. This QNS rate falls below the recommended 10%, and is also below the mean QNS rate of 7.2% (± 7.6 ; range, 0-40%) determined by a comprehensive review of sweat test data from the state of Illinois and two national surveys of CF Centers (9). However, when analyzed individually, the MSCS method had a QNS rate of 2.1% for all infants referred to the affiliate site, Children's Hospitals and Clinics of Minnesota, while the QNS rate was 15.4% for the GCT at the core

Minnesota CF Center. Almost 15% of all infants sweat tested using the GCT needed to have a repeat sweat test in order to obtain an acceptable result. This was an unexpected finding, confirming the need for CF Centers to engage in quality improvement (QI) practices to ensure acceptable QNS rates for young infants.

The reason for such a high QNS rate with the GCT at the Minnesota CF center is unclear. It did not seem to be related to differences in patient demographics although patients who were sweat tested using the GCT were significantly younger which increases the likelihood of QNS. The Minnesota CF center had a validated GCT sweat testing protocol and had two personnel trained and dedicated to sweat testing, so technical error secondary to methodology or personnel seemed unlikely. Unfortunately, QNS rates of the two technicians were unavailable to allow for comparison of individual technique. A quality assurance review of the CLSI protocol did not reveal errors in either methodology or implementation of recommended sweat testing reagents. A possible contributing factor may be that prior to October 2009, the Minnesota CF Center did not have a written protocol identifying the patient criteria needed in order to optimize the likelihood of obtaining a sufficient quantity of sweat. Such a QNS Reduction Action Plan was implemented at that time that required patients to meet required criteria prior to sweat testing by GCT which included: hydration of at least 120ml/kg/day for 24 hours prior to the sweat test, age > 2 weeks, weight > 3 kilograms, no eczema present at potential site of sweat test, no current systemic steroid use and no current systemic illness. It is possible that the Minnesota CF Center was sweat testing patients that were at high risk of a QNS test to begin with. However, the QNS rate in older individuals > 3 months of age met performance standards (data not shown). Regardless, the calculated QNS rate using the GCT in these infants was well above the recommended percentage, and our CF Center has opted to adopt the MSCS for all sweat testing in our population moving forward with a subsequent drop in the QNS rate to 3%.

Previous studies comparing the performance of the GCT with the MSCS in various patient populations have revealed conflicting results in relatively small numbers of infants. Although comparable specificity and sensitivity were reported between the two techniques, Mastella et al. reported a 14.3% QNS rate for the MSCS (volume < 15 μ l) in 56 sweat tests performed in infants both with and without CF at 0 to 3 months of age (12). In a similar comparative study, Mattar et al. reported that 31% (23/75) of patients with CF had insufficient sweat collected by means of the GCT while only 4/75 (5.3%) provided an insufficient sweat sample using the MSCS (13). Similar percent QNS rates were obtained using both the GCT and MSCS in subjects without CF. Although Mattar et al. reported good correlation between the 52 patients with CF who had both sweat test methods performed, no demographic data was provided to allow for the identification of infants in the study. Hammond et al. also reported a 6.1% QNS with the MSCS compared to 0.7% with the GCT, with most failures of the GCT occurring in infants < 3 months of age (14). The recent report by LeGrys et al. reported no one sweat collection method was superior to the other (9). Our QNS rates for the GCT of 15.4% (29/188) and for the MSCS of 2.1% (8/380) in this population are similar to that of Mattar et al., although our study population included approximately 600 infants < 3 months of age. The Minnesota CF Center had continued to use the GCT for our CF newborn screening population given these previous published reports of comparability between the two techniques. However, through this quality improvement initiative, our own data have now provided evidence to adopt the MSCS technique for all future sweat testing at our core Minnesota CF Center and its affiliates.

The most challenging population in which to obtain an adequate sweat sample is an infant population (2). Given that most state newborn screening programs require confirmatory sweat testing at less than 3 months of age, the sweat testing method needs to be efficient in this at-risk population in order to diagnose CF as rapidly and accurately as possible.

Previous work has identified risk factors for obtaining a QNS sample in infants < 6 weeks of age including CF Care Center, African-American race, infant weight < 2000g, preterm birth and postmenstrual age < 36 weeks (10,15). Our study demonstrates that the % QNS rate did not change as age in weeks at the time of the sweat test increased. However, given that previous work has demonstrated a relationship between age and sweat testing, after adjusting for age at the time of the initial sweat test, the odds of QNS using the GCT was over 8 times that of the MCS. There was a significant relationship between greater birthweight and lower % QNS rate as well as greater weight at time of test and lower % QNS rate in the GCT. Specifically, weight at time of sweat test of 10 pounds in those infants utilizing the GCT was associated with a QNS rate of 0%. Our study also confirmed a higher % QNS rate in non-white infants, as previously reported by Eng et al (10).

Our study is not without limitation. The patient population was limited to infants born only in the state of Minnesota, utilizing our IRT/DNA based testing newborn screening program for CF. Therefore, we are only able to describe how this quality improvement project led to a change in practice at our CF Center. However, this allowed the opportunity for us to directly compare the performance of the two sweat testing methods, removing the variability introduced by differences in infant populations. This was also a retrospective, database review and not a prospective trial that directly compared the performance of the two sweat testing techniques in the same infants. It would be ideal to prospectively compare the GCS with the MSCS in the same population of newborn screened infants. However, our study incorporated the largest number of infants to date. The results we obtained were striking and have resulted in a change in the practice of our CF Center.

Our study demonstrates the superior performance of the MSCS, compared to the GCT, in obtaining an adequate sweat sample for analysis in infants < 3 months of age with a positive IRT/DNA (39 mutation) newborn screen for CF in the state of Minnesota. Given the overall observed 2.1% QNS rate of the MSCS in this young population, the Minnesota CF Center has opted to adopt the MSCS as its method of sweat testing infants to clarify the diagnosis of CF.

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List of Abbreviations

(MSCS)	Macroduct® sweat collection system
(GCT)	Gibson and Cooke technique
(NBS)	newborn screen
(CF)	cystic fibrosis
(CFF)	Cystic Fibrosis Foundation
(QNS)	quantity not sufficient
(MN)	Minnesota
(IRT)	immunoreactive trypsinogen
(CFTR)	cystic fibrosis transmembrane conductance regulator

(QI) quality improvement

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Figure 1.

QNS rates vs. Age at Initial Test for all infants presenting to the University of Minnesota CF Center and Children's Hospitals and Clinics of Minnesota for a sweat test following a positive CF NBS. The association between QNS for the GCT (**Panel A**)/MCS (**Panel B**) and age at initial test was not significant ($p = 1.0$ and $p = 0.28$, respectively). Error bars represent 95% confidence intervals (CI).

Figure 2.

QNS rates vs. Birthweight for all infants presenting to the University of Minnesota CF Center and Children's Hospitals and Clinics of Minnesota for a sweat test following a positive CF NBS. The probability of QNS decreases significantly as birthweight increases in both the GCT ($p = 0.023$) and MCS methods ($p = 0.022$). Error bars represent 95% CI.

Figure 3.

QNS rates vs. Weight at Test for infants presenting to the University of Minnesota CF Center for a sweat test (GCT) following a positive CF NBS. The probability of a QNS decreases significantly as weight at time of test increases ($p < 0.001$). Error bars represent 95% CI.

Table 1

Demographic data from infants with a positive CF NBS referred for sweat testing in Minnesota from March 2006 – January 2010. There are no significant demographic differences between the infants seen at the core University of Minnesota CF Center (UM) and those at our affiliate Children's Hospitals and Clinics of Minnesota (Children's). The mean number of tests per infant was significantly greater at UM (1.2) than Children's (1.02), $p < 0.0001$ by two-sample t-test.

	UM	Children's	Total
# Infants	188	380	568
Sex			
Female	94 (50%)	198 (52%)	292 (51.4%)
Male	94 (50%)	182 (48%)	276 (48.6%)
Race			
American Indian	2 (1.1%)	1 (0.3%)	3 (0.5%)
Asian	0	1 (0.3%)	1 (0.2%)
Black	9 (4.8%)	12 (3.2%)	21 (3.7%)
Caucasian	154 (81.9%)	239 (62.7%)	393 (69.2%)
Hispanic	7 (3.7%)	8 (2.1%)	15 (2.6%)
Mixed	14 (7.5%)	16 (4.2%)	30 (5.3%)
Not reported	2 (1.1%)	103 (27.1%)	105 (18%)
Birth weight (kg)			
Mean	3412.04	3356.1	3374.7
Median	3425	3402.5	3411
SD	509.85	599.4	571.4
Range	(1990-4490)	(460-5253)	(460-5253)
# Tests/infant			
1	155 (82.5%)	373 (98%)	528 (93%)
2	28 (14.9%)	7 (2%)	35 (6.2%)
3	4 (2.1%)		4 (0.7%)
6	1 (0.5%)		1 (0.2%)

Table 2

Descriptive statistics of infants at the initial sweat test. The overall % QNS rate for the Minnesota CF Center and its affiliate is 6.5%, below the CFF-recommended % QNS rate of 10%. Infants who received sweat testing by GCT were younger ($p = 0.02$), had a higher chloride concentration ($p = 0.004$) and had more positive/borderline CF diagnoses ($p < 0.0001$). The MCS was associated with significantly fewer QNS ($p < 0.0001$).

		Initial Sweat Test		
		GCT	MCS	Total
# Infants		188	380	568
Age at test (days)				
	Mean	29	34.6	32.8
	Median	22	30	29
	SD	27.5	26.5	27
	Range	7-264	6-285	6-285
Average Cl ⁻ concentration (mEq/L)				
	Mean	24	17.1	19.1
	Median	13.5	11.5	12.5
	SD	27.1	18.8	21.8
	Range	4.5-116.5	2.5-106.5	2.5-116.5
CF diagnosis				
	Positive	27 (14.4%)	35 (9.2%)	62 (10.9%)
	Borderline	10 (5.3%)	3 (0.8%)	13 (2.3%)
	Carrier	121 (64.4%)	335 (88.2%)	456 (80.3%)
	Negative	3 (1.6%)	0	3 (0.5%)
QNS				
	Yes	29 (15.4%)	8 (2.1%)	37 (6.5%)
	No	159 (84.6%)	372 (97.9%)	531 (93.5%)