Outcomes of infants born during the first 9 years of CF newborn screening in the United States: successes and the need for improvement

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Abstract:

Introduction: Newborn screening (NBS) for cystic fibrosis (CF) was implemented in all US states and DC by 2010. This hypothesis generating study was designed to form the basis of additional research and to plan quality improvement initiatives. The aims were to describe the outcomes of infants with CF born during the first 9 years of universal NBS.

Methods: We included participants in the CF Foundation Patient Registry born 2010-2018 with age at first CF event (first sweat test, clinic visit or hospitalization) by age 365 days. We assessed age of center-reported diagnosis, age at first CF event, demographics and outcomes for three consecutive 3-year cohorts born in 2010-2012, 2013-2015, and 2016-2018.

Results: In 6354 infants, median age at diagnosis was earlier than median age at first CF event, which decreased from 1st cohort to 3rd cohort. Weight-for-age (WFA) was < 10th percentile in about 40% of infants at the first CF Center visit. Median WFA z-score at 1-2 years was > 0 but height-for-age (HFA) z-score was < 0 through age 5-6 years. The second cohort had a higher HFA z-score than the first cohort at age 5-6 years. *Pseudomonas aeruginosa* infection rates decreased over time. About 1/3 of infants were hospitalized in the first year of life across cohorts.

Conclusion: Over 9 years of CF NBS, median age at first CF event decreased. CF NBS had positive health impacts but improving nutritional deficits and reducing infant hospitalizations remain targets for improvement.

Introduction:

In the United States, newborn screening (NBS) is implemented by states based on uniform recommendations from the Health Resources and Services Administration. Guidance includes what disorders should be included on the screening panel[1,2] and advises that screening results be reported to a health care provider by 7 days of life[3]. Newborn screening is implemented by state public health laboratories and follow-up programs that collaborate with health care providers for diagnosis and follow-up of infants with positive screening tests. Cystic fibrosis (CF) screening was implemented in some states[4] prior to the rigorous assessment of benefits compared to risks[5,6] conducted by a multidisciplinary group of clinicians, CF researchers, public health experts, and ethicists convened by the Cystic Fibrosis Foundation (CFF) and the Centers for Disease Control and Prevention. Based on this assessment, CF was added to the Recommended Uniform Screening Panel and guidelines for implementation were generated[7]. All states and Washington DC implemented CF NBS by December 2009. Prior reports have noted a temporal association between implementation of CF NBS, improved nutritional outcomes and reductions in *Pseudomonas aeruginosa* (PA) infections[8,9], but none have described outcomes of infants born after universal screening started throughout the US.

As CF NBS was implemented, many regions identified challenges and it was clear that a national quality improvement (QI) effort was needed. With the assistance of the CFF, a group of CF clinicians were organized as a NBS Quality Improvement Consortium (QIC). Annual QIC meetings have included review of process and outcomes data from the Cystic Fibrosis Foundation Patient Registry (CFFPR)[10] since 2011. We readily noted significant variations in approaches to CF NBS and age at diagnosis, similar to a report from Europe[11]. Variation in diagnostic testing and classification led to a comprehensive reassessment of criteria for the diagnosis of CF and related disorders, culminating in publication of a series of reports in the *Journal of Pediatrics* in 2017[12-16].

Here we report our evaluation of findings at diagnosis and clinical outcomes in infants diagnosed with CF seen at accredited CF Centers during the first 9 years of universal CF NBS in the US. The primary objective is to describe the presentation and clinical status of this cohort. While we expected that more experience in CF NBS at the level of both state newborn screening programs and CF Centers might lead to improvement in outcomes, the purpose of this work is for hypothesis generation and identification of targets for future QI activities.

Methods:

The CFFPR is a patient consented observational study[10], approved by local Institutional Review Boards. Parents or legal guardians provide written, informed consent for participation of infants and children. Established in 1966, the registry collects information on approximately 81-84% of people with CF in the US. The collected data include demographics, anthropometric measures, pulmonary function results, microbiology, prescribed medications, complications, comorbidities, socioeconomic status data and other details entered by the CF care teams. Most of the data reflects measurements, orders and observations made during the patients' clinic visits (encounters).

We included all participants enrolled in the CFFPR born between 2010-2018 and diagnosed during infancy, defined as age 0-365 days of age. The age range was chosen based on reports of median age at diagnosis prior to wide implementation of NBS, and to avoid inclusion of infants initially categorized as having CF-related metabolic syndrome/CF screen positive, inconclusive diagnosis (CRMS/CFSPID) who had a later diagnosis of CF. We compared demographic and clinical data, dates of key CF care events, and outcomes of 3 cohorts born in 2010-2012, 2013-2015, and 2016-2018. Age at diagnosis was defined as the date of diagnosis

entered in the CFFPR by CF Care Center personnel. Age at first CF event was a composite measure based on the earliest date of (1) a sweat test, (2) a clinical encounter at a CF Care Center (clinic visit), or (3) a care episode lasting >24 hours (hospitalization).

Clinical data included signs and symptoms reported at diagnosis, premature birth, CF transmembrane conductance regulator (CFTR) genotype class in accordance with the McKone classification[17], and use of pancreatic enzyme replacement therapy (PERT, a proxy for pancreatic insufficiency). Demographic data included median income by resident zip code, a marker of socioeconomic status, race and ethnicity. Nutritional outcomes were assessed for children who were documented as born at term (≥ 37 weeks) at pre-specified ages. We measured both categorical percentile ranges (< 10, 10-< 25, 25-< 50, ≥ 50) and median z-scores at the first clinic visit, age 1-2 years, 3-4 years, and 5-6 years. Except for measurements at birth and at the first clinic visit, WFA and HFA were calculated using the average of z-score for the entire age range, using World Health Organization (WHO) growth charts for age 0-2 years, and Center for Disease Control and Prevention (CDC) growth charts for age > 2 years[18]. Any breast feeding, supplemental feeding (enriched breast milk or formula to provide > 20kcal/oz) and tube feeding during the first year of life were evaluated to gain insight on feeding and the need for early life nutritional interventions. We also examined rates of PA infection, defined as at least one positive culture, and all-cause and pulmonary exacerbation hospitalizations, across the pre-specified age ranges.

Statistical analysis: All variables were summarized by descriptive statistics by cohort. Categorical and binary variables were summarized using counts and percentages, and continuous variables were summarized using the following descriptive statistics: number of observations (N), median, and interquartile range (IQR). To compare across cohorts, when the contingency table cell sizes were sufficiently large, the chi-square test was applied to

categorical and binary variables., If the expected frequency was <5 in at least 1 cell of the contingency table, Fisher's exact test was applied. The Kruskal-Wallis test was applied to continuous variables. No adjustments were made for multiple comparisons.

Results:

A total of 6354 infants born 2010-2018 reported to the CFFPR met inclusion criteria. Infants from all 50 United States and Washington DC were represented. The number in each cohort, demographics, and CFTR genetic mutation class are shown in **Table 1**. The proportion of infants of Black/African American Race was 6-7% in each time period and those of Hispanic ethnicity was 13%, slightly higher than the 4.8% and 9.4%, respectively, in the entire CF population reported to the CFFPR in 2019[19]. No changes in distribution of sex, race, ethnicity, or CFTR mutation class were noted between birth cohorts.

A summary of participant age at diagnosis, age at first CF event and clinical features at presentation are shown in **Table 2**. The distribution of age at first event for infants reported to have a positive NBS is shown in **Figure 1**. The age of center-reported diagnosis was younger than the age of first CF event, and not different between cohorts. The most common first CF event was a sweat test. Most infants were reported as having a positive NBS, and the percentage of infants with a positive screen increased over time. Clinical signs and symptoms were rarely reported at presentation. The most common was failure to thrive, ranging from 5-6% with no change over time. In contrast, 38-40% of infants with measurements recorded at the first encounter had WFA < 10th percentile ~~and 32-24% had HFA < 10th percentile,~~ with no difference between cohorts.

Infant feeding practices and nutritional outcomes are summarized in **Table 3**. There was a decrease in the proportion of infants prescribed PERT in the 2016-2018 birth cohort. The rate

of breast feeding increased over time and oral supplemental feeding during the first year decreased in the last cohort. Tube feeding was used in less than 10% of infants and did not change over time. Median WFA z-scores were close to 0 across all cohorts and ages. HFA z-scores were below 0 across all cohorts and ages. There was a statistically significant increase in median WFA and HFA at 5-6 years in infants born 2013-2015 compared to those born 2010-2012.

The proportion of infants hospitalized prior to 1 year of age for all causes (34-36%) did not change over time; most hospitalizations were for pulmonary exacerbation (**Table 4**). There was a decrease in the proportion of pulmonary exacerbation-related hospitalizations over time in infants less than 1 year of age. The proportion of children > 1 year old hospitalized for all causes and pulmonary exacerbations decreased in later cohorts. The proportion of positive cultures for PA decreased across cohorts and was temporally related to decreased age at first CF event as shown in **Figure 2**.

Discussion:

This is the first comprehensive study to evaluate outcomes in US children with CF born after universal implementation of NBS, describing findings over 9 years in more than 6000 infants. It is notable that 6-7% of infants were demographically characterized as being Black/ African American and that 13% were as being of Hispanic ethnicity, greater than the overall CFFPR population but consistent with trends in US births[20]. This observation is also consistent with the expectation that minority children with CF have been under diagnosed in the past[5], due in part to absence of their CF-causing mutations in CFTR panels among DNA-based NBS protocols[21]. Overall, expectations of NBS were met. Most infants were evaluated within the first month of

life and there were few preventable complications of CF reported at diagnosis, such as failure to thrive and electrolyte imbalance. Further, breast feeding increased, while oral supplemental feeding decreased, suggesting less nutritional intervention over time.

The decrease in median age at first CF event over time likely stems from the fact that states and therefore CF Centers implemented NBS over time, and processes improved based on both individual center and collective experience via the CF Foundation. The formation of the CFF NBS QIC, with nationwide representation, was coupled to a consensus-producing strategic planning process and CFF Screening Improvement Grants, has promoted sharing of strategies targeted at improving outcomes and processes in CF screening and care.

There remains need for further improvement, especially in nutritional outcomes. In spite of median age of diagnosis of about 2 weeks and median age of first CF event at 3-4 weeks, significant nutritional deficits were present in the population at the initial clinic visit that persisted across time periods. The median WFA z-score at that first visit was close to -1, and 40% of infants had WFA < 10th percentile. This is greater than the 11-15% who had birth WFA z-score < 10th percentile. There are limitations in birth weight data in CFFPR because these data are typically ascertained by parental recall or from medical records, and there were significant missing data. However, prior studies using healthcare system collected data have also shown that infants with CF had only slightly lower birth weights than the general population[22]. By 1-2 years, median WFA z-score was about 0 and remained close to 0 at 5-6 years of age. In contrast, median HFA z-score was -0.7 over time at the initial clinic visit and remained below 0 despite increasing slightly by 5-6 years. These data reinforce that nutritional deficits occurs very early in life in CF[8,23 24]. It is possible that earlier treatment could improve nutritional outcomes, including HFA, a strong predictor of childhood pulmonary function[23,25] and survival[26,27]. Impact of timeliness on nutritional outcomes and variation in AFE by state or CF

Care Center was not evaluated in this report. Nevertheless, prompt evaluation after a positive NBS and prompt implementation of PERT in infants with CF should be prioritized given the high prevalence of low WFA at initial CF encounter.

More than one third of infants were hospitalized in the first year of life, and this did not change between the cohorts. The most common cause of hospitalization was pulmonary exacerbation, consistent with reports of clinically relevant lung disease in infants with CF diagnosed through NBS[28,29,30]. Hospitalizations in older children decreased over time. PA infection decreased over time and in all age groups, similar to previously published reports[8,9]. This is an important observation with implications regarding the risk of lung disease in early childhood. The pivotal Centers for Disease Control report[5] emphasized that longitudinal studies of cohorts diagnosed through NBS in Wisconsin[31,32] and Australia[33] revealed nosocomial acquisition of PA in clinics that led to worsening lung disease and thus designated a "potential harm". Concurrently, the CFF recommended infection control practices to prevent patient-to-patient transmission[34]. Reorganization of CF clinics followed rapidly to ensure segregated care, especially for the emerging new population of infants diagnosed through NBS, an investment in QI that has paid dividends[35]. Although our observation of decreasing PA over time strengthens the hypothesis that early diagnosis through NBS coupled to early treatment can lead to reduced or delayed PA infections, the contribution of NBS *per se* is difficult to evaluate given the evolution of infection control standards and the era of routine eradication therapy for new PA infections[36,37].

There are a number of limitations to this study. The CFFPR has been an invaluable resource to describe the epidemiology and associations between care patterns and outcomes in CF. However, data entry was not designed for or significantly changed to evaluate the impact of NBS. Data entry for age at diagnosis can be before, on, or after the date of birth. Our decision

to exclude infants diagnosed at < 0 days of age was intended to separate NBS from prenatal diagnosis, but some prenatally diagnosed infants were included based on care centers noting the age of diagnosis at day of life 0 or later. There may be overlap in data entries for DNA analysis, prenatal diagnosis, and CFTR mutations diagnosed on NBS panels; this could not be evaluated. Significant missing data in birth weight and height limit the ability to evaluate correlations between these parameters and long-term nutritional outcomes. We evaluated age at first event at a CF Care Center, an imprecise proxy for initiation of CF care. Date of initial therapy, including PERT or salt supplementation, was not captured in the CFFPR during the time of this study. Thus, intervention may have began before age at first CF event based on presumptive diagnosis (two CFTR mutations or symptoms) or after the initial event. Further, it should be noted that the data entry to the registry may start only after obtaining signed informed consent from a family. Though retrospective data entry is allowed, a number of the first clinic encounters might be missing, affecting the date of the first CF event. We did not assess whether prescribed therapy changed over time during the study period. Interventions, including use of dornase alfa[38] and higher doses of PERT[39,40] are associated with improved nutrition in children with CF in observational studies and were not assessed in this study.

In conclusion, CF NBS has had successful implementation in the US. These results describe the demographic and clinical findings in infants born after universal adoption of CF NBS, showing trends over time as processes improve. The rapid onset of nutritional deficits in infants with CF and the lack of a decrease in hospitalizations during the first year of life are targets for further research and intervention. We hypothesize that further improvements in outcomes will require more efficient diagnosis, starting with improved timeliness of evaluation after a positive CF screening test, more effective infant nutritional management, and further development of preventive lung disease therapies.

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