Year in Review 2020: Multisystemic Impact of Cystic Fibrosis

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Abstract

Clinical care in cystic fibrosis (CF) has continued to advance over the last several years, particularly with the widespread eligibility and use of highly effective modulator therapy. Awareness of the multisystem concerns that face persons with CF (PwCF) has also continued to be recognized as an important aspect of the burden of the disease. This review will cover a broad array of topics, from diagnosis to multisystem effects related to mental health, endocrine, palliative care, reproductive health, otolaryngology, and cardiac issues. Additionally, an understanding of worldwide care delivery will be reviewed, demonstrating variation in outcomes based on resources and populations served, ranging from the advances in care in the United States (US) to the challenges of disease recognition and diagnosis in low-and-middle-income countries (LMIC). This review is the third in a three-part CF Year in Review 2020 series, focusing on the multi-system effects of CF. Part one focused on the literature related to CFTR (cystic fibrosis transmembrane conductance regulator protein) modulators, while part two focused on pulmonary outcomes, radiographic and physiologic assessments, as well as infection and inflammation. Part three has been split into two individual parts, Part 3A presented here, and Part 3B related to CF specific nutrition and gastrointestinal publications will also be published this year. This review focuses on articles from Pediatric Pulmonology but also includes articles published in 2020 from other journals that are of particular interest to clinicians.

Introduction:

The year 2019 brought a sense of hope and excitement to the Cystic Fibrosis (CF) community with the approval of elexacaftor, tezacaftor, ivacaftor (ETI) by the Food and Drug Administration (FDA) for patients with at least one copy of F508del. The excitement was interrupted by the world-wide challenge of the COVID-19 pandemic. For the CF community the rules of masking and 6-feet apart were not novel or unusual, however, the strain of the pandemic was still felt within our CF community. Clinics shifted to telehealth, the North American CF Conference gathered virtually, and usual care for research conduct was challenged. Despite these difficulties, many papers were published throughout the year, continuing to accelerate CF research.

CF is a multisystem disease which impacts multiple organ systems. This review will cover research articles and case reports that were published during the last year pertaining to diagnosis, mental health, endocrinology, palliative care, epidemiology, delivery of clinical care, women's health, and more. It was humbling to review the great work that has been done during this extraordinary year.

DIAGNOSIS

Diagnosis of CF is based on a positive newborn screen (NBS), family history or clinical signs/symptoms and evidence of CF transmembrane regulatory conductance (CFTR) dysfunction through abnormal sweat chloride test or two disease causing mutations[1]. Despite these guidelines, there are often complexities in diagnosis where research published this year has allowed for some additional clarity.

One less anticipated area of concern relates to the identification of carriers for CF due to NBS. Farrell et al.[2] conducted interviews, following a structured script, of 288 parents of infants who were found to be carriers for CF, to determine the communication and understanding related to the NBS result. Miscommunication was observed, as 2.4% of parents had no recollection of being informed of the NBS results, 13% of those who recalled an explanation characterized it as negative, and 7.8% felt their child may still get the disease. Although overall anxiety levels were low at the time of the interview, parents recalled higher anxiety at the time of reported NBS results. At the time of the interviews, more than half (56.1%) were planning a future pregnancy, with 84% planning on testing for themselves and 74.3% for their partner. Using the same parents, Farrell et al.[3] also measured parental perceptions of child vulnerability, using the Vulnerable Baby Scale. Parental perceptions of their child's vulnerability were worse than expected compared to parents screened at a well-baby visit in an urban/suburban clinic. The results of these studies emphasize the need for continued understanding of the adverse effects of NBS identification of carrier status and how to mitigate these effects.

Interestingly, more information about the clinical effects for CF carriers has also been reported. Colak et al.[4] genotyped over 100,000 Danish individuals from the Copenhagen General Population Study for the F508del mutation. These patients also completed a questionnaire and underwent an examination (including pulmonary function test). In the 2,858 carriers, compared to the general population, there was a 1.3-fold increased risk of chronic bronchitis, a 1.9-fold risk of bronchiectasis, and a 1.5-fold risk of lung cancer. No differences in mortality, airflow limitation or other pulmonary, gastrointestinal, or reproductive complications were seen. In a separate study from claims data, using a retrospective population based matched cohort method, Miller et al.[5] also sought to determine if CF carriers are at risk for a range of CF-related conditions. Each of the 19,802 CF carriers were matched with 5 controls. A higher prevalence of all 59 CF-related conditions examined were identified in CF carriers compared to controls. Risk for certain CF-related conditions was significantly increased in carriers including pancreatitis, male infertility, and bronchiectasis. The authors concluded that despite the individual risk being low, population level morbidity related to carrier status is still high, therefore identification of carrier status can lead to prevention, diagnosis and treatment for these patients. In an editorial referencing the Colak and Miller research, Martin and Burgel[6] discussed an evolving dogma that for a CF carrier there may be modifiable risk factors such as smoke exposure, infections that can improve health. Additionally, they indicate that possible CFTR modulator use for non-CF pulmonary disease may show clinical benefit. Therefore, it may no longer be appropriate to counsel carriers of a CF mutation (parents or infants identified via NSB) that they are at no risk of disease and that there is no potential treatment.

In infants who were diagnosed with CF via NBS, Schluter et al.[7] evaluated improvements in clinical outcomes and the impact of NBS on reducing social inequities. Using the United Kingdom CF registry, from 2000 to 2015, outcomes prior to and after NBS implementation in 2007 showed improvements in weight, lung function and chronic *Pseudomonas aeruginosa* in those diagnosed by NBS. Despite these improvements, using the Index of Multiple Deprivation based on postal code, no impact on social inequalities was seen in their population, as the children who lived in the most deprived areas continued to have worse nutritional and lung function status, despite diagnosis via NBS.

Another diagnostic conundrum for clinicians is sweat chloride testing in infants, as there can be difficulties obtaining enough sweat based on current testing modality. Durc and colleagues[8] assessed the performance of a newly developed skin wipe test (SWT) for diagnosis of CF, designed to be simpler, noninvasive, less expensive, not reliant on pilocarpine iontophoresis, and more likely to obtain results in very young patients compared to traditional macroduct testing. The test analyzes multiple ions collected on spontaneously generated sweat,obtained by a cotton swab moistened with deionized water. Simultaneously collected SWT and macroduct tests were compared in 114 patients with CF, 76 CF carriers, and 58 controls. The authors explored several ion ratios. Sensitivity was found to be 93.9% for chloride to potassium ratio and 99.1% for chloride plus sodium to potassium ratio compared to 98.3% for macroduct analysis. This preliminary data is of interest as a potential diagnostic testing in resource limited countries.

The timing of the sweat test is also crucial to ensure the early benefits of NBS and ensure adequate diagnosis.

Unfortunately, inability to obtain a sufficient quantity of sweat, leading to a quantity not sufficient (QNS), can delay diagnosis. McColley and colleagues[9] used the CF Foundation Patient Registry (CFFPR), from 2010-2018, to examine sweat testing. They compared 3 different spans of time (2010-2012, 2013-2015, and 2016-2018) to evaluate impact of NBS on first attempt to sweat testing, finding the median age for obtaining a sweat decreased from 32 days of age in 2010-2012 to 29 days in 2016-2018. Sadly, however, 23.8% of infants still did not have a sweat test by 60 days of age. Younger age led to higher QNS rates: a decrease in QNS rate was seen with every increasing 10-day increment of age, whereby at 0 to <10 days of life the QNS rate was 16.4% while at 50 to 60 days of life it was 4.1%. Additionally, preterm infants (<37-weeks gestation) were more likely to have higher rates of QNS compared to term infants (19.5% versus 6.6%, $p<0.001$). Despite the risk factors for QNS tests in young infants and preterm infants, McColley and colleagues showed that sweat testing is successful 83.6% of the time in infants as young as 0 to <10 days of age. Therefore, this important diagnostic test should not be delayed in infants with a positive NBS test for CF for fear of a QNS result.

The final complexity in the diagnosis of CF explored in this year's published research relates to the many unanswered questions related to CF-related metabolic syndrome (CRMS)/CF screen positive inconclusive diagnosis (CFSPID). What is the progression to CF in this population? How often and when should additional sweat testing be completed? How long should they be followed in a specialized CF center? Munck et al.[10] sought to characterize the phenotypic expression of children with CRMS/CFSPID and define the presence of disease and prognosis. In a prospective, longitudinal multicenter study from 2002-2015, 63 patients with CRMS/CFSPID were matched to 63 patients with CF. The patients were followed clinically through age 6-7 years. They found that the CRMS/CFSPID cohort, overall, had lower immunoreactive trypsinogen, sweat chloride values, delayed visits, less symptoms and better nutritional status. When seen in follow-up at age 6-7 years, they had fewer overall CF-related morbidities and lower chest radiograph scores, higher pulmonary function test and improved nutrition leading to reduced treatment burden, reduced hospitalizations and less*Pseudomonas* and MRSA identification. Progression to a diagnosis of CF occurred in 44% (28/63) due to an elevation in sweat chloride (16/28) or identification of a second mutation (20/28) or both (n=8). Based on this data, the authors highlight the recommendation that monitoring of CRMS/CFSPID infants should continue in a CF center until the age of at least 6 years, at which time if no progression to CF by genetics, sweat or clinical findings, discharge from care with vigilance by primary physician could occur.

There is ambiguity in the diagnosis and care plan for children identified through newborn screening who have less common mutations or variations. In a letter to the editor, Rock[11] argues that patients do not "convert", but were born with CF, and additional diagnostic information should be obtained (such as more comprehensive genetic analysis or expansion of the CF-causing mutation list). He urges the CF community to come together to develop new guidelines regarding the progression from CRMS/CFSPID to CF.

Exploring this further, Terlizzi et al.[12] examined the role of repeated sweat chloride testing in patients with mutations of varying clinical consequences (MVCC) (with diagnosis of CF, CRMS/CFSPID or CFTR related disorder). In an evaluation of 39 patients with MVCC, after 4 years with sweat testing done every 6 months, 54.5% (18/33) progressed to a diagnosis of CF, with 14 due to an elevation in sweat chloride. Specifically, in the 18 CRMS/CFSPID patients, 14 (42.4%) had sweat tests that became elevated after a mean follow up time of 3.1 years. The authors highlighted the need to continue to monitor sweat chloride in the presence of one CF causing mutation located in trans with an MVCC as there is risk of progression to CF diagnosis by elevation of sweat chloride.

The research on CRMS/CFSPID that has emerged this year emphasizes the challenge of this uncertain diagnosis. What seems to be clear from all of the researchers, is that CRMS/CFSPID patients need to be monitored for the development of morbidities associated with this diagnosis. Further study of this patient population of CRMS/CFSPID is warranted to better understand the pathophysiology and potential progression to CF. Only then will we be able to have evidence-based guidelines on how to monitor and manage patients with this CRMS/CFSPID.

MENTAL HEALTH

There is no physical health without mental health and wellness. Early recognition of mental health concerns has been a priority of the US CF Foundation (CFF) over the last several years. Establishing routine screening is the first step in ensuring adequate mental health services are provided to all persons with CF (PwCF) and their caregivers. Several publications from this year describe the experience of mental health screening (MHS) as it becomes more universally applied throughout CF care centers worldwide. There were also publications examining the impact of mental health on executive functioning and alcohol use. In addition, several studies explored mechanisms to improve wellness through the use of electronic applications on reducing social isolation, building resilience, and even providing mental health services on a virtual platform.

Mental health screening (MHS) is an important aspect of CF care. In recent years, adoption of guidelines[13] to integrate MHS into CF care has significantly increased. Caregivers at Seattle Children's Hospital used quality improvement methods to improve their MHS in eligible adolescent patients[14]. Their social worker(s) performed a preclinical review of eligible patients, administered screening on an electronic tablet and reviewed results with the patient and family. This identification process led to 90% of eligible patients receiving a MHS within the first year of implementation of the MHS guidelines, creating a process that has been successfully sustained in subsequent years. Quittner et al.[15] evaluated 84 programs across the United States who received CFF grant funding to support the role of a mental health coordinator (MHC). Using an internet-based survey (88% response rate), 41% of MHC were new to the team, with most being social workers (54.1%) or psychologists (41.9%). MHS occurred in over 5000 PwCF and over 1000 caregivers in the first year of implementation of MHC grant. Collectively, these two articles highlight the possibility of incorporating MHS into a busy, specialized clinic. MHS was facilitated by universal uptake of screening tools, improved awareness and detection, reduced stigma and positive feedback from patients and families. Overall barriers were similar across both studies[14,15], including limited resources (such as staff, time, space and logistics). One additional challenge highlighted by Quittner et al.[15], was screening for caregivers, as parents are not the "identified patient". This has brought up ethical concerns about a CF center's responsibility for documentation of abnormal MHS in caregivers and oversight of appropriate referrals, limiting caregiver screening in many pediatric CF centers.

Another area related to mental health is executive function (EF). EF can be defined as a set of skills that allow for successful engagement in goal-oriented behavior. Borschuk et al.[16] had 19 children (6-18 years of age) with CF and their caregivers complete several different questionnaires including the Barkley Deficits in Executive Functioning scale, CF Questionnaire–Revised (CFQ-R), and Treatment Adherence Rating Scale. Overall, children with CF did not have a higher level of EF impairment compared to the general population. However, a strong association was observed between poor family communication/cohesion and worse EF in the children with CF. Outpatient records revealed that those children with CF who had worse EF demonstrated higher treatment burden, worse lung function, and poorer adherence.

A risk factor for mood disorders is excessive alcohol use (EAU), which is an unhealthy pattern of drinking including chronic heavy use and binge drinking. Heavy alcohol use is defined as 8 or more drinks per week (14 in men) and binge drinking is defined as 5 or more drinks on a day or 4 drinks in a 2-hour period (5 in males). Lowery and colleagues[17] sought to understand alcohol use in adults with CF. In an anonymous survey, 952 PwCF (>18 years), 77% of respondents use alcohol currently. Compared to the general population, rates of heavy drinking (24% versus 6%) and binge drinking (49% versus 25%) were higher in PwCF. Self-reported clinical findings revealed that despite comorbidities, such as advanced lung disease, transplant, CFLD, CFRD, and increased number of hospitalizations, EAU still occurred. PwCF who were more likely to develop EAU were younger, started drinking at a younger age, male, had a high school or lower education, and were not married. The authors conclude with a call to action to teams to increase awareness, use of screening tools and interventions to work toward reduction in alcohol consumption in this at-risk population.

Promotion of resilience is one mechanism to enhance well-being. Toprak and colleagues[18] sought to test the acceptability and feasibility of the program, Promoting Resilience in Stress Management (PRISM). PRISM is a skills-based intervention targeting stress management, goal setting, cognitive reframing, and meaning

making, which is completed over 4 sessions. In 10 patients (12-21 years of age) admitted to the hospital, PRISM was employed as a means to mitigate the negative effects of hospitalization. Resilience, distress and disease specific CFQ-R scores did not change after PRISM intervention; however, it was found to be both feasible and acceptable. Participants felt there would be increased benefit in a younger CF population. This insight by the participants is poignant as Amerio et al.[19] highlights, in a letter to the editor, an assertation that more attention needs to be paid to risk factors for developing anxiety and depression. Use of PRISM at a younger age may allow for primary prevention of mental health disorders and improvement in the development of resilience that can positively impact medical outcomes later in life.

PwCF are not alone in their need for enhanced well-being. Hente et al.[20] describes 24 CF health professionals who completed 6 training sessions incorporating mindfulness, cognitive therapy, and experiential exercises for processing feelings related to stress and burnout. Significant improvements were seen for empathy, perceived stress, depersonalization, anxiety, perspective taking, resilience, and negative affect one month post training, compared to baseline. Although improvements were seen for depressive symptoms, fatigue, emotional exhaustion and positive affect, none were statistically significant. Sleep was the only parameter with no improvement. At 15 months follow up, positive effects were sustained for empathy, perspective taking and depressive symptoms and 35% of participants reported continued use of mindfulness skills. The authors a call to health system management to encourage, incentivize, and have available for these types of training as part of routine responsibilities.

3.0 ENDOCRINE

3.1 Cystic Fibrosis Related Diabetes

The diagnosis of CF Related Diabetes (CFRD) is challenging for PwCF and caregivers. As clinicians it is important to understand the epidemiology of CFRD, mechanisms to screen, diagnose and upcoming novel treatment options. The prevalence and risk factors for CFRD have changed over years due in part to overall advances in care. In order to understand a more recent cohort, the European CF Patient Registry was examined between 2008 and 2015[21]. The overall prevalence of CFRD (defined as daily insulin use) was 9.7% in those 10-19 year of age, 24.1% in 20-29 years, and 32.7% in PwCF 30 years. Females were found to have a higher

prevalence at all ages under 30 years (11.6% females versus 8.1% males for 10–19 year old; 27.8 versus 21.2% for 20–29 year old, $p < 0.0001$). CFRD was more likely in those with severe CF mutations (defined as both mutations being class I-III) (OR = 3.11, 95% CI: 2.77–3.48), PI (OR = 1.46, 95% CI: 1.39–1.53), lung function FEV1 percent predicted <40% (OR = 1.82, 95% CI: 1.70–1.94), BMI z-score of [?] -2 (OR = 1.24, 95% CI: 1.15–1.34) and higher rate of chronic infection with *Pseudomonas aeruginosa* , *Burkholderia cepacia* or *Stenotrophomonas maltophilia.*

In a pilot study of 11 children with CF <10 years of age (median age at study entry of 3.8 (±2.5) years), Prentice et al.[22] used continuous glucose monitoring (CGM) over 3 days, with repeated CGM after 12 and 24 months. Normal glucose at all time points was only seen in 27% (n=3). Impaired glucose levels (defined as [?]104 mg/dL/7.8mmol/L for >4.5% of the time) were seen in 73% (n=8) compared to 2% in children without CF. Of those 8 patients, 5 had impaired values at more than one test and two had impaired glucose at all time points. Peak glucoses ([?]200mg/dL/11.1 mmol/L) were seen in 64% (n=7) at any time point, while this is not reported in children without CF. The authors conclude this variation could be based on alteration in dietary intake during CGM monitoring, evolving exacerbation, or variable insulin resistance. The study provides further support that glucose abnormalities begin early in life for patients with CF and suggests that CGM may be the appropriate test to detect glucose abnormalities in this age. In an editorial, Chan[23] emphasized the challenge of screening and the need to consider other methods, acknowledging that CGM has limitations and is not ready to replace or even compliment OGTT yet.

Another outcome of screening for CFRD, can be the appearance of post-prandial or OGTT-related hypoglycemia. While the mechanism remains unclear, it is speculated to be related to derangement in glucose homeostasis involving both insulin and glucagon[24,25]. Kilberg et al.[24] used a mixed meal tolerance test

(MMTT) in 34 nondiabetic adolescents and young adults with pancreatic insufficiency, finding 26% (9/34) with hypoglycemia. Those with hypoglycemia, had a higher peak glucose (215 +- 21 versus 168 +-33 mg/dL, p<0.01) and had a later peak phase of insulin, defined by peak after 60 minutes, (89% versus 48%, p=0.03). The authors concluded that a delayed but overly robust insulin secretion led to hypoglycemia.

Further study of hypoglycemia was done by Armaghanian et al.[25] using a 3-hour glucose tolerance test in 24 patients (7 normal glucose tolerance, 12 abnormal glucose tolerance and 5 CFRD). None of the patients with CFRD had hypoglycemia, while 79% (15/19) of the remaining subjects showed hypoglycemia at the 3-hour time point, with 5 being symptomatic (sweaty, clammy hands and dizzy). Similar to the study by Kilberg et al.[24], those with hypoglycemia had a higher peak glucose and delayed and higher insulin release[25]. Incretins, hormones produced by the intestines that signal insulin secretion after eating, were not different between groups, and there was no change in the counter regulatory glucagon response. Together the two articles help to better outline the potential mechanisms for post prandial/post OGTT hypoglycemia.

Beyond accurate diagnosis, partnership with an endocrinologist can be helpful as treatment modalities broaden. A small study by Sherwood et al.[26] looked at use of a bionic pancreas (BP) in management of CFRD. A bionic pancreas can have two different mechanisms, a bihormonal BP (BHBP) providing both insulin and glucagon or an insulin only BP (IOBP). In a three-arm crossover pilot study of BHBP, IOBP and usual care, with one week study periods, 3 females with CFRD were assessed. CGM monitoring revealed nominally lower glucose levels with BP (BHBP 139 +- 15 mg/dL, IOBP 149 +- 10 mg/dL versus usual care at 159 +- 35 mg/dL). Other measures of glucose control were also improved/shown to be equivalent to usual care. BP is an interesting new technology that deserves additional exploration for CFRD.

3.2 Bone Disease

Multiple factors can contribute to low bone mineral density (BMD) in patients with CF. A prospective, single center study evaluated 40 patients (>age 7 years) with CF to help determine clinical factors likely to contribute to BMD[27]. Osteopenia was seen in 37.5% (15/40) and 27.5% (11/40) had osteoporosis, with no differences seen between PS or PI patients. BMD did however correlate with FVC, FEV1, lean arm mass, fat free mass, hand grip strength, modified Shwachman-Kulczycki (SK) score (composite of general activity, physical findings, and nutritional status) and quality of life. The SK score was found to be the highest predictor of BMD. The authors conclude that use of the SK score, which can be easily obtained, may help with early identification of patients in need of further evaluation.

4.0 PALLIATIVE CARE

While life expectancy has improved in CF over the last several decades, CF continues to plague patients with significant morbidity and mortality, making palliative care an essential aspect of the services provided to PwCF and their caregivers/families. Palliative care is a comprehensive and holistic approach to care of patients and families aimed at improving the quality of life and reducing the emotional toll of illness. Traditionally palliative care is used at the end of life, but more recently, utilized in the setting of major life and death treatment decisions, such as transplant. A survey completed by 164 adult patients at one center identified that 78% of participants reported at least one unmet palliative care need[28]. Specifically, one or more unmet needs were seen in the following domains: physical such as symptom burden (72%), psychological needs such as anxiety surrounding worsening disease (66%), health system and information (41%), patient care and support (30%) and sexuality (20%). When looking at specific needs, more than half of respondents indicated unmet needs due to "lack of energy/tiredness" (65%), "feeling unwell a lot of the time" (52%) and "fears about my CF getting worse" (50%). While lower FEV1 values were found to correlate with increased treatment and symptom burden, there was not a correlation seen between lower FEV1 and more unmet needs. The authors conclude that identification of this large unmet need justifies the use of palliative care services and underscores the importance of systematic screening using patient reported outcomes versus clinical factors such as FEV1 since not strongly associated with these unmet needs.

Trandel et al.[29] also surveyed clinicians (n=350), adults with CF (n=70) and CF caregivers (n=100) to understand perceptions of palliative care. The majority of adults with CF (64%) and caregivers (74%) were

unaware if their center had palliative care programs, while only 14% of adult and 23% of pediatric clinicians were unaware. Clinicians perceived confidence in their ability to provide both primary (basic symptom management and initial discussion of prognosis and goals) and advanced palliative care skills (advanced symptom management provided by fellowship trained palliative care physicians). Patients and caregivers reported their CF clinicians as "very good" in the basic assessment of pain and "good" at discussing prognostic uncertainties, both important skills of primary palliative care, but did not rate clinicians as highly regarding advanced palliative care including specifically transplant, hospice care, and end-of-life care. The results for this survey call to attention the need for increased awareness and knowledge regarding palliative care. In fact, as Waldman and Quinn[30] note in their editorial, there need to be opportunities for improving palliative care skills among CF clinicians, and improving partnering and integration with existing palliative care specialty services.

5.0 POPULATION

As part of the Lancet Respiratory Medicine Commission on the future of cystic fibrosis care, Bell et al.[31] beautifully summarized the understanding of CF pathophysiology, diagnosis, care model, and therapeutic advancements in their very thorough article, "The future of CF: a global perspective". While discussing the amazing advancements that have been made over the last 6 decades, the article also takes a real look at the changing epidemiology of CF disease within non-European descents across the globe and challenges specific to low-income and middle-income countries (LMIC). The Commission focused on five key areas, 1) the changing epidemiology of CF, 2) future challenges of clinical care and its delivery, 3) the building of CF care globally, 4) novel therapeutics, and 5) patient engagement. The article delves into each key area providing historical perspective, current state of affairs, and a look into how to improve the future of CF care. Bell's article is a must read, especially for those new to the field of CF, including medical students and residents.

Several publications from this year expanded on themes presented in Bell's executive summary, describing the experience with CF in specific ethnic populations to create a better understanding of the similarities/differences and struggles across the globe. Dogru et al.[32] described the data of the CF registry in Turkey from 2017. As a LMIC, the authors conclude there are still gaps in knowledge leading to low diagnosis, thus low inclusion in the registry (only ˜30% of the total Turkish CF population is included). Significant advances were made when NBS started in 2015, such that 81.9% of those under 3 years of age were diagnosed via NBS. Sweat testing and genetic testing occurred in the majority, however, 19.7% only had one mutation identified and 25.2% had no mutations identified. Additionally, the heterogeneity of the population is reflected in the most common mutation being F508del, however, only at an allelic frequency of 28%. Based on the 2017 registry data, 8.8% of the population was homozygous F508del and 12.9% were heterozygous. Clinical care differs due to availability of resources, with dornase alpha and pancreatic enzymes/vitamin supplements being commonly used (86.7%) but very low percentages of patients using other medications/therapies and no access to modulators. Outcomes were poor; as an example, FEV1pp was 82 ±28.7% between 15-19 years of age and all patients having Z scores for weight, height and BMI less than zero. Mortality was at a young age with median age at death of 13.5± 9.9 years. Complication rates varied with only 20.9% having chronic *Pseudomonas* , although culture frequency was not included. The most common complication reported was Pseudo-Bartter syndrome (PBS) (acute exacerbation of hyponatremic, hypochloremia dehydration with metabolic alkalosis without kidney pathology) seen in 10.2% despite recommendations for routine salt supplementation. This snapshot of care in Turkey is enlightening to provide perspectives regarding care in other countries.

Shi et al.[33] provided insight into the demographics and common clinical characteristics for PwCF in China. Of the 113 patients included, 78 were diagnosed within the last five years showing an increase in knowledge and awareness amongst providers. The median age of diagnosis was 8.7 years, with the majority (68%) diagnosed in the first year of life (not including 5 diagnosed in the neonatal period). Only 8% of infants were found to have meconium ileus (MI). Sweat tests were only reported in 79 patients and genetic testing revealed the most common mutation to be c.2909G>A (9.15%). Only one patient in China has been reported to have

a mutation in F508del. Outcomes presented included normal FEV1pp in 13.3% however the authors do not mention nutritional outcomes. Median age of death was not provided, but 20/113 patients died, between the ages of 3 months and 24 years of age. Complications included pancreatic disease (defined by authors as pancreatitis or PI) in 12.4% and 8.8% with PBS.

Both studies[33,34] from Turkey and China report on the complication of PBS, which was further characterized in two additional studies. Shen et al.[35] described 12 cases of PBS at Beijing's Children's Hospital over the last 10 years. The median age of PBS diagnoses was 4 ±1.7 months and subsequent diagnosis of CF occurred at median age of 28.6 ±37.5 months. The patients had comorbidities at time of PBS diagnosis that included recurrent or persistent pneumonias (91.7%), pancreatitis (83.3%), vomiting/diarrhea (66.7%), liver disease (58.3%) and severe failure to thrive (58.3%). In comparison, the Turkish registry from 2017 was used to evaluate patients with CF with or without PBS[36]. Those with PBS were younger, more likely to have been diagnosed at an earlier age, but less likely via NBS, and had lower second sweat chloride test values. Compared to age and gender matched patients with CF, there were no differences found in any parameters. Both authors conclude that PBS is a common complication in warmer countries and reinforce the importance of recognition of PBS as an early clue for diagnosis[35,36].

In an exploration of racial disparities in CF in South Africa, 34 black patients with CF (defined as at least two sweat conductivity tests >80mmol/L in the presence of phenotypic manifestation compatible with CF) were compared to 34 Caucasian homozygous F508del patients[37]. The most common mutation in the Black African patients with CF was the 3120+1G>A and none had a F508del mutation. The 3120+1G>A mutation had an allele frequency of 81%, 23 (67.6%) were homozygous and 6 (17.6%) were heterozygous. Median age at diagnosis was similar (5.0 (2.0-15.0) months for cases, 6.0 (3.0-15.0) months for controls), as was percent with pancreatic insufficiency (88.2% for cases, 85.3% for controls). Black African children were found to be more malnourished at diagnosis and less likely to be diagnosed with neonatal bowel obstruction (5.9% versus 31.3%, p = 0.03). By three years of age, no differences were seen in nutritional status between the two groups. No significant differences were seen in regard to change in FEV1 over time (at 6, 10 and 14 years of age), age of first *Pseudomonas* infection, or prevalence of *Pseudomonas* . Three Black patients died early (8.8% compared to only one Caucasian patient [2.9%]). The authors conclude that despite differences in presentation and genetics, there were comparable outcomes regardless of race, and encourage a high index of suspicion should be maintained for black African infants who present with symptoms consistent with CF.

Fitzgerald et al.[38] evaluated the effect on clinical outcomes after establishment of NBS in Ireland comparing pre-NBS (2008-2011) to post-NBS (2011-2016). Not surprisingly, NBS infants were diagnosed earlier (0.69 months versus 10.22 months, p=0.001). Children diagnosed by NBS were more likely to be on prophylactic antibiotics and less likely to have other siblings with CF or a mother whose nationality was Irish. Those diagnosed clinically had an odds ratio of 2.80 (95% CI 1.24-6.29) of hospitalization for pulmonary exacerbation in the first 3 years of life. Time from diagnosis to age of first acquisition of*Pseudomonas* was longer in the NBS cohort. Nutritional outcomes of weight and length/height were better in the NBS cohort at ages 6 and 12 months. This study highlights the importance of NBS in improving outcomes for patients through earlier diagnosis and treatment.

Greenland, as part of the Danish Kingdom, started NBS in 2016. The first known case in an infant of Inuit (defined as being born in Greenland) origin diagnosed via NBS was published (F508/c.3000_3014del, sweat chloride 116 mmol/L, fecal elastase <15 mcg/g)[39]. Interestingly, the infant's ancestry was traced to Danish descent, which has one of the highest frequencies of the classic F508del mutation with approximately 96% of patients with CF having the mutation on at least one allele. The authors concluded that although a population may not have genetic predisposition to a particular disease, it can be introduced by ancestors, thus further expanding the rationale for universal NBS.

Pasterkamp et al.[40] used the Canadian CF Registry to describe a population of 92 Hutterite Brethren, a communal group of Anabaptists (which also included the Mennonites and Amish), who live in Western Canada, to Canadian homozygous F508del controls. The Hutterites have a high incidence of CF (1:467) and almost exclusively carry the F508 and M1101K mutations (due to founder effect). The Hutterite group

had no difference in age at diagnosis compared to the Canadian homozygous F508del patients. As the M1101K mutation is associated with PS, diagnosis consisted of less gastrointestinal presentation and better nutritional outcomes in the Hutterites. Lung function was lower in Hutterite children, with no difference found later on in adulthood. The only microbiological difference of statistical significance was the Hutterites had an increased incidence of *Staphylococcus aureus* . The Hutterites also had socio economic instability and minimal exposure to SHSe due to communal practices of the population. Hutterites had a lower median age of death (17.5 $\pm$ 11.5 versus 28.2 $\pm$ 10.8 years, p $<$0.0001) compared to the Canadian homozygous F508del controls.

In Poland, Zybert et al.[41] studied 13 infants with CF born between September 2006 and May 2019 (11 diagnosed via NBS and 2 with symptoms and subsequent diagnosis), who had at least one allele with a rare or mutation of unknown consequence. All infants had elevated sweat chloride tests ($>$60 mmol/L) and at least 2 CFTR mutations detected and compared clinical information for the infants to partner with their genetics. The authors identified three novel pathogenic mutations (A1217E, E33X, and dup16,17A). Given their experience, they encouraged clinicians to ensure adequate attentive follow up of any infants with rare/novel mutations in order to elucidate the clinical effect.

6.0 PARTNERSHIPS IN CARE

In 2018 and 2019, the James Lind Alliance Priority Setting Partnership in CF and the CF Foundation, respectively, queried the CF community regarding research priorities, including burden of care for CF[42,43]. A follow-up survey was developed by Davies et al.[44] to better understand the size and diversity of the treatment burden in PwCF. A summary of the 941 responses (20% PwCF, 48% relatives/friends of PwCF, 32% health professionals) from 21 countries, described the most important and burdensome treatment areas. There was confirmation of the high burden and concordance between lay and professional perceptions. The top 5 most important treatments were identified as pancreatic enzyme, airway clearance, CFTR modulators, exercise and physical activity, and long-term nebulized antibiotics and the top 2 burdensome treatments were identified as airway clearance and long-term nebulized antibiotics. Themes related to simplifying treatment burden were prioritized as research questions including the development of interventions that engage both patients and caregivers in shared decision-making and goal setting to continue to improve the quality of life for PwCF.

The relationship between PwCF, caregivers and CF care teams allows for productive shared decision-making, however, communication barriers can lead to difficulties. Therefore, Cooley et al.[45]evaluated communication skills at 5 US CF Centers through observation of clinical visits, 1:1 interview, and focus groups with CF team members, PwCF, and caregivers. Four main themes emerged 1) eliciting psychosocial concerns, 2) addressing childhood development and transition, 3) negotiating agendas and sharing decision-making and 4) educating to enhance CF conversations. All participants including PwCF, caregivers and CF clinicians who participated in the study expressed the desire for additional resources to facilitate improved conversations. Development of advanced communications skills including open communication, trust-building and active listening will allow all care team members, PwCF, caregivers and CF clinicians to better partner in shared decision-making and goal setting.

The ties between PwCF and their care teams often blur the lines of primary care and specialty care. As adults with CF are living longer, they are in need of routine health screening. Haywood et al.[46] evaluated 92 charts of adult CF patients, at the University of North Carolina at Chapel Hill and found no identified primary care provider in 59%. Routine preventive care was poorly documented for non-CF priorities such as mammography (22%), cervical cancer screening (12%), and sexually transmitted infection (STI) screening (20%). In contrast, higher rates were seen for CF priorities including colorectal cancer screening (48%), osteoporosis (66%), diabetes (96%), and mental health issues (92%). The authors concluded that pulmonologists should encourage adults with CF to seek appropriate primary care. If the pulmonologist chooses to serve as the primary care physician, then they must stay up to date on general preventive adult care.

Douglas et al.[47] evaluated the impact of participating in AREST-CF (Australian Respiratory Early Surveil-

lance Team for CF), a longitudinal study (over two decades) looking at key drivers of lung disease in early life. Specifically, the impact of additional intensive early diagnostic testing embedded in clinical care on families in terms of providing reassurance about their children's health or creating anxiety was studied. This study brings attention to the hidden cost of doing research, adding to the stress that families with children with CF experience in "monitoring" disease progression even when children are seemingly doing well[79]. Several themes emerged: 1) a degree of uncertainty regarding what to expect, which became easier with time, 2) optimism (via control due to increased knowledge regarding disease progression leading to a sense of power and gratitude), 3) pessimism (through anticipation of disease progression and reduced life expectancy) and 4) feelings of helplessness and lack of control (a feeling of "studying for an exam"). The results of the intensive additional testing led to disparate impact. If results were positive, parents had increased confidence and self-esteem in their role as caregiver, however negative results led to feelings of accountability and self-blame. Similarly, emotional ambivalence was seen when contrasting the best interest of the child with the risk and discomfort involved. The authors concluded their research supports the inclusion of psychosocial support when using sensitive measures of lung disease. The same approach should be extrapolated to other studies of monitoring progression of other challenging comorbidities of CF.

Oates et al.[48] set out to understand how to partner with caregivers and CF care teams to limit exposure of SHSe for children with CF by using the PRECEDE model to identify predisposing, reinforcing and enabling factors. Semi-structured interviews of 8 caregivers who were current or former smokers and 9 clinical team members focused on how to facilitate discussion between caregivers and clinicians focused on smoking cessation, not limiting exposure. The authors concluded the need for a multi-level intervention including professional cessation counselor support, nonjudgmental support from CF team and support from families partnered with nicotine replacement. The lack of CF specific resources focusing on the specifics of how smoke impacts the lungs of children with CF was identified. The authors concluded that the study identified a need for a family-centered and health system interaction to develop a program that includes family education emphasizing harms to children with CF, screening for smoking with biochemical confirmation, access to tobacco cessation counselors, access to free and low-cost pharmacotherapy, and outpatient follow-up.

Medication access is a challenging and frustrating issue for PwCF, caregivers and clinicians alike. Zobell et al.[49]studied the impact of adding both a specialty pharmacy (SP) technician and a clinic-based pharmacy (CB) technician at Intermountain Primary Children's Hospital in Salt Lake City, Utah. The SP technician works within the hospital special pharmacy on behalf of CF patients, while the CB technician works in the CF clinic verifying medications, obtaining insurance coverage and is an active part of the CF quality improvement (QI) team. Addition of the SP technician led to faster delivery of dornase alpha, decreasing from 8 days to 3 days ($p<0.00001$). Addition of the CB technician reduced the need for multiple pharmacies, increasing use of only one pharmacy from 8% to 38% ($p=0.005$) and reducing use of three pharmacies from 25% to 2% ($p=0.003$). Both models improved medication access for patients with CF and increased the efficiency of CF care teams.

7.0 WOMEN'S HEALTH

With PwCF living healthier lives into adulthood, the topic of reproduction and preimplantation genetic diagnosis becomes more relevant. Based on the large variability in mutations for CF, many couples can still be left with an increased risk for CF transmission with current preimplantation genetic screening.

For women with CF who proceeded with pregnancy, the effect on pulmonary status was evaluated by Reynaud et al.[50] using the French CF Registry between 2000-2012 in 36 women with FEV1[?]50% and 113 women with FEV1$>$ 50%. The women were followed over four years, one year prior to pregnancy and two years after pregnancy. Not unexpectedly, the women with lower FEV1 had lower BMI and more IV antibiotics at baseline. Rates of medically assisted conception were similar in both groups. Women with lower lung function more commonly had cesarean sections (43.7% versus 21.2%, $p=0.01$). There was no difference in the frequency of prematurity, however, those with lower lung function were more likely to have infants with lower birth weights (median 2705 grams [range 650-3700 grams] versus 3044 grams [range 1590-3860 grams], $p=0.003$). Maternal mean FEV1 change per year over the time studied was -0.9% (95% CI -2.5 to 0.8) in

the low lung function women while the women with higher lung function decreased by -2.3% (95% CI -3.3 to 0.6). No significant changes in BMI occurred. The authors concluded that pre-pregnancy lung function did not influence pulmonary or nutritional status of the mothers in the 2 years after delivery.

8.0 EAR, NOSE, THROAT (ENT)

Ototoxicity is a concern for individuals who require repeated doses of aminoglycosides for pulmonary infections. Vijayasingam et al.[51] compared the standard of sound booth audiometry to a web-based hearing test, a tablet-based audiometry, and various validated questionnaires (Hearing Handicap Inventory for Adults, Vertigo Handicap Questionnaire, and Tinnitus Handicap Questionnaire). All interventions were completed by each participant, in a multi-center, cross sectional evaluation of 126 adult patients with CF. Similar to other studies, increased age and more days of IV antibiotics increased risk of abnormal audiometry. Specifically, for each year of age older, a patient would have a 12.8% increased risk of abnormal sound booth audiometry (OR 1.127, 95% CI 1.074 to 1.182, $p<0.0001$). After adjustment for age, there was a 6.7% (OR 1.067, 95% CI 1.028 to 1.966) increase in the probability of abnormal sound booth audiometry for each 14-day course of IV antibiotics. Vestibular toxicity (9.5%) and tinnitus (7.1%) were also seen in this cohort. Tablet based screening had high sensitivity, specificity, and negative predictive value, thus the authors concluded that screening with tablet and questionnaires can be easily done in clinic and if any abnormalities, refer for formal audio booth screening.

Conclusion:

Despite the challenges that the COVID global pandemic presented to the CF community in 2020, in terms of delivery of care and research, clinical researchers and basic scientists presented valuable investigations, all of which are vital to advancing CF care. With all the different specialty areas of medicine and mental represented here, the complexity of CF disease and care is easily appreciated. We hope we have been able to give you a glimpse into some of the important work in these areas of non-pulmonary CF clinical care and research that was published in this most memorable year.

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