Update in Cystic Fibrosis 2018

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In this review, we have selected several outstanding studies from the *American Journal of Respiratory and Critical Care Medicine* (*AJRCCM*), the *American Journal of Respiratory Cell and Molecular Biology* (*AJRCMB*), and the *Annals of the American Thoracic Society* (*AnnalsATS*) in 2018 to provide readers with an overview of the important contributions to the rapidly evolving literature in the field of cystic fibrosis (CF) published in these three journals. The featured studies focus on advances in five major themes central to the understanding of the pathogenesis and treatment of CF: *1*) therapies directed at the underlying defect, *2*) early intervention strategies to delay disease progression, *3*) respiratory tract infections, *4*) inflammation, and *5*) epidemiology and outcome measures. Because of word limitations, we regret that not every original contribution could be included.

Advances in Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapies

Over the past decade, management of CF has been transformed with the approval of several small molecules, termed CFTR (cystic fibrosis transmembrane conductance regulator) modulators, used alone or in combination. These modulators consist of two classes of drugs: potentiators that augment opening of the CFTR channel function at the apical membrane of epithelial cells and correctors that assist in transport of nascent protein to the cell surface. These oral therapies have been able to restore CFTR function across a range of *CFTR* mutations. Ivacaftor (potentiator), used in treating patients with at least one copy of *G551D* and other ivacaftor-responsive mutations, was approved by the Food and Drug Administration in January 2012 with extended approval to children aged 12 months and older in 2018. Lumacaftor (corrector)/ivacaftor combination for treatment of patients homozygous for the *F580del* mutation received Food and Drug Administration approval in July 2015 and since August 2018 is approved for use in patients aged 2 years and older. Tezacaftor (corrector)/ivacaftor combination was approved in February 2018 for the homozygous F508del populations aged 12 years and older, as well as for some *F580del* heterozygotes with a residual function mutation on the other allele. Together, these three drug combinations provide therapies for approximately 50% of individuals with CF. All these therapies were approved on the basis of phase 2 and 3 trial efficacy data demonstrating significant improvement in multiple clinical outcomes: percent predicted FEV_1 ($ppFEV_1$), improved body mass index (BMI), and prolonged time to pulmonary exacerbations (PEs) requiring antibiotics. The clinical changes noted for ivacaftor in the G551D population (1) were more robust than seen in the trials of lumacaftor/ivacaftor (2) and tezacaftor/ivacaftor (3, 4). Furthermore, lumacaftor/ivacaftor and tezacaftor/ivacaftor did not demonstrate clinical efficacy in individuals with one *F580del* allele and a second allele with minimal CFTR function. For this reason, a second generation of correctors was added to the tezacaftor/ivacaftor combination to create a triple combination. Two triple-combination therapies (tezacaftor/ivacaftor/445 and tezacaftor/ivacaftor/659) have completed phase 2 trials with good safety profiles and more robust clinical efficacy, both demonstrating at least a 10% increase in $ppFEV_1$ in both the homozygous F508del population and

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patients with one copy of *F580del* and a second minimal function mutation (5, 6). These two triple combinations are currently in phase 3 trials. If approved, therapies may soon become available to over 90% of the CF population.

The recent availability of these approved modulators for a large portion of individuals with CF has led to clinical questions regarding the optimal patients for initiation of therapy. For this reason, the first clinical practice guideline for the use of CFTR modulators was published in *AnnalsATS* in 2018 (7). These guidelines, endorsed by the American Thoracic Society in November 2017, were based on a systematic review of relevant publications and evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. They are not intended to be a standard of care but provide genotype-specific recommendations based on published evidence. For example, the guidelines strongly recommend treatment with ivacaftor/lumacaftor for individuals with two copies of *F580del* older than 12 years of age and an FEV_1 less than 90% predicted. With the addition of new CF therapies, the guidelines will continue to evolve.

These new therapies also provide an unprecedented opportunity to study the changes in pathophysiology and natural history of CF. These drugs are invaluable tools for developing and optimizing biomarkers and clinical outcomes for future therapeutic development. Several studies published in *AJRCCM* in 2018 have furthered understanding of the short-term and long-term consequences of CFTR modulation. A key multicenter observational study of the impact of ivacaftor in individuals responsive to the therapy (GOAL [G551D Observational] study; NCT01521338) was initially published in *AJRCCM* in 2014 (8). The investigators in that study reported clinically significant changes in a range of outcomes, including $ppFEV_1$, mucociliary clearance, and intestinal pH, after initiation of ivacaftor. The GOAL study linked to Cystic Fibrosis Foundation Patient Registry (CFFPR) data also demonstrated that in the year after initiation of ivacaftor, the odds of *Pseudomonas aeruginosa* (*Pa*) positivity were reduced by 35% compared with the year before drug initiation (odds ratio, 0.65; $P < 0.001$) (9). In 2018, this group (10) used data from the GOAL-linked CFFPR to evaluate longer-term changes in $ppFEV_1$, BMI, and rate of PEs requiring hospitalization by comparing patient data ($n = 144$) for the 2 years before ivacaftor initiation with the 2 years after initiation. The key findings were that treated patients demonstrated a 2-year benefit with a reduced decline in FEV_1 and PE rate; an additional encouraging finding was that the 25% of patients who did not demonstrate a short-term improvement in FEV_1 at 1 month had long-term improvements in these parameters. These data are supported by another small study nested within GOAL in which researchers noted improvement in lung clearance index (LCI) with treatment of ivacaftor in children 3–5 years of age (11).

A second study reported the impact of ivacaftor on a key nonpulmonary manifestation: cystic fibrosis–related diabetes (CFRD) and abnormal insulin secretion (12). This is the largest clinical study published on this topic. In it, researchers hypothesized that ivacaftor would improve glucose metabolism as well as insulin secretion. Patients initiating ivacaftor therapy ($n = 12$; 11 children) underwent oral glucose tolerance tests, mixed meal tolerance tests, and arginine-potentiated glucose tests at pretherapy baseline and at 16 weeks after therapy. Seven of the patients had normal and five had abnormal oral glucose tolerance test results at baseline; none had CFRD. The key finding was that multiple measures of insulin secretion improved after therapy, including first-phase responsiveness, even in these young patients with mild glucose abnormalities. This finding provides hope that restoration of CFTR function may impact glucose metabolism and eventually CFRD (13).

To measure the change in CFTR function *in vivo*, Graeber and colleagues (14) evaluated the impact of lumacaftor/ivacaftor on several biomarkers in patients homozygous for F508del mutation aged 12 years and older. Fifty-three patients were evaluated before and after 8–16 weeks of therapy. Clinical outcomes of FEV_1 and BMI were compared with biomarkers, sweat chloride, nasal potential difference, and intestinal current measurement. Lumacaftor/ivacaftor resulted in partial rescue of CFTR function of about 10.2% (interquartile range [IQR], 0.0% to 26.1%) in nasal potential difference and 17.7% (IQR, 10.8% to 29.0%) in intestinal current measurement and a 17.8 mmol/L (IQR, −25.9 to −6.1 mmol/L) reduction in sweat chloride. There was no correlation, however, between the changes in these biomarkers and clinical outcomes. In fact, all patients had some response in these biomarkers, even if no change in FEV_1 was detected. Further studies are needed to validate the role of these biomarkers in development of future modulators (15).

A final study addressed the importance of secondary factors that may impact CFTR expression in the airway and efficacy of CFTR modulators. The authors described the role of the TGF-β (transforming growth factor-β) and microRNA (miR, miRNA)-145 regulatory pathway in reducing CFTR expression in the airways (16). Both TGF-β and miRs are elevated in CF airway secretions, potentially reducing CFTR expression. The authors demonstrated in primary airway epithelial cells that TGF-β, through miRNA-145, inhibits the corrective benefit of lumacaftor. It is possible that the TGF-β and miR pathway contributes to a variable clinical response *in vivo*. More important, antagonism of miRNA-145 reverses this TGF-β inhibition of CFTR function and may be a useful adjunct therapy to enhance CFTR modulation and other therapeutic approaches to restore CFTR function (17).

Clinical Trials Evaluating Early Interventions to Delay Progression of Lung Disease

Over the past two decades, as more therapeutic approaches directed at improving airway clearance and treating airway infection and inflammation have become available, there has been increased interest in starting these therapies as early as possible to prevent the progression of lung disease (18). Three randomized controlled trials in the past year expanded knowledge regarding approved therapies in young patients with CF.

The first study, with a novel antiinflammatory approach in which the investigators used a multivitamin with additional antioxidants, hypothesized that increased systemic antioxidant concentrations would result in an antiinflammatory effect (NCT01859390). Although elevated antioxidant concentrations were achieved, only modest reductions in systemic inflammation after 4 weeks were observed (circulating calprotectin mean difference, −0.13 $\log_{10}$[μg/ml]; $P = 0.03$) (19). Because

current CFTR modulators such as ivacaftor may not have a robust effect on sputum markers of inflammation, including neutrophil elastase activity (mean change [SD], −0.1 [0.37] $\log_{10}$[μg/ml]) (8), additional antiinflammatory approaches may be needed.

A second study assessed the impact on LCI of preventive hypertonic saline in infants with CF who were less than 4 months of age (NCT01619657) (20). The authors found that early introduction of 6% hypertonic saline significantly improved LCI and weight. This study was small ($N = 42$), and additional endpoints, such as chest magnetic resonance imaging scores and exacerbation rates, did not change. However, the study demonstrated that LCI might be a key indicator of efficacy in infants with CF. As we think of advancing novel therapies to the youngest children with CF, we must have robust endpoints such as LCI in this vulnerable population.

The third randomized controlled study (21) is a multicenter, double-blind, randomized, placebo-controlled, 18-month trial (OPTIMIZE [Optimizing Treatment for Early Pseudomonas Aeruginosa Infection in Cystic Fibrosis]; NCT02054156) testing the hypothesis that the addition of thrice-weekly azithromycin (AZ) to tobramycin inhalation solution in children (aged 6 mo to 18 yr) with CF and early *Pa* infection decreases the risk of PEs and prolongs the time to *Pa* recurrence. The study was stopped early by the data safety monitoring board because the prespecified interim boundary for efficacy was reached ($N = 221$; 110 AZ and 111 placebo). The risk for PE requiring antibiotics was reduced by 44% in the AZ group compared with placebo (hazard ratio, 0.56; 95% confidence interval, 0.37–0.83; $P = 0.004$), and there was significant weight gain (1.27 kg) in the AZ group. However, this reduction in PE risk did not track with an effect on *Pa* recurrence or other microbiological endpoints. All three studies demonstrated the importance and challenges of studying the youngest populations and mildest disease states.

Advances in Understanding and Treatment of CF Airway Infections

Chronic infections of airways and sinuses in individuals with CF remain the major cause of morbidity and mortality in CF (22). Although there is increased interest in the contributions and interactions of the respiratory microbiome early in disease (23), with progression, specific bacterial pathogens predominate, including *Pa*, *Staphylococcus aureus* (*Sa*), and nontuberculous mycobacteria (NTM). In the past year, several articles illuminated the epidemiology of both *Pa* and NTM. In addition, several studies provided new insights into the risk and benefit of three established antimicrobial approaches—antistaphylococcal prophylaxis, chronic AZ administration, and the use of facial masks—for inpatient infection control.

Pa remains the most common bacterial pathogen infecting the CF airway after the first decade (24). Variability in clinical course with chronic *Pa* colonization has been attributed to both the host response and adaptations of the pathogen within the CF airway environment. A key contributor to the pathogenesis of chronic *Pa* pulmonary infections is the pathogen's ability to form structured communities that coat mucosal surfaces (i.e., biofilms), enhancing persistence. An *AJRCCM* review of biofilms (25) provided insights into the clinical impact of and potential therapeutic approaches for *Pa* lung infections. Two articles focused on how genetic evolution of *Pa* isolates may be associated with changes in clinical outcomes. A longitudinal whole-genome deep-sequencing study (26) genotyped *Pa* isolated from 32 patients from first isolate until either death of the patient or eradication of the pathogen. The molecular evolutionary trajectory of *Pa* isolates from patients with mild disease, defined as stable health after 25–35 years, versus severe disease, defined as death in less than 15 years, differed. A higher incidence of loss-of-function mutations and mutations associated with antibiotic resistance was noted in the patients with a severe clinical course compared with those with the milder phenotype, reflecting the dynamic interrelationship of host and pathogen. As noted in the accompanying editorial (27), it is not known whether the *Pa* evolutionary trajectories are a cause or an effect of illness severity. A second study (28) used multilocus sequence typing to define clones of over 1,500 *Pa* isolates from 402 individuals at six large Canadian centers. Clones were defined as six of seven shared alleles, and these clones were then correlated with FEV_1, BMI, PE, mortality, or transplant. There was a high degree of genetic diversity with very limited sharing of dominant clones, even within centers, and no significant difference in clinical outcomes across the clones. However, within patients, it was found that changes in sequence typing over time were associated with a significant decline in both FEV_1 and BMI. Although both studies suggest that genetic evolution of *Pa* may impact clinical course, it is not known whether these divergent paths are a cause or an effect of illness severity.

A study based on U.S. patients in the CFFPR from 2010 to 2014 (29) reported that sputum positivity for NTM is becoming increasingly prevalent. Of the 16,153 patients in the CFFPR, 3,211 (20%) had at least one positive sputum culture in the 5-year period studied; approximately one-third were infected with *Mycobacterium abscessus* and two-thirds with *Mycobacterium avium* complex. It is noteworthy that during these five years, the annual period prevalence increased from 11% in 2010 to 13.4% in 2014. In addition, a unique subpopulation of patients with CF was identified: Patients over 60 years old diagnosed with CF later in life had a 33% prevalence of *Mycobacterium avium* complex, suggesting that the prevalence may continue to increase as the CF population ages. This report emphasizes the importance of routine screening for these pathogens, including speciation and ongoing research to develop new therapeutic approaches.

The role of antistaphylococcal prophylaxis has been controversial for decades and was the topic of a Cochrane review published in 2017 (30). In the United Kingdom, flucloxacillin is widely used to prevent *Sa* colonization, whereas *Sa* prophylaxis is not recommended in the U.S. Cystic Fibrosis Foundation care guidelines (31) because of possible emergence of *Pa*. Investigators from both the United Kingdom and the United States (32) undertook a longitudinal observational study of children aged 0–4 years using both the UK CF Registry (1,074 children) and the CFFPR in the United States (3,677 children) from 2000 to 2009, testing the hypothesis that *Sa* prophylaxis is associated with decreased *Sa* but no increased risk of *Pa* acquisition. The risk of *Sa* first detection (hazard ratio, 5.79; 95% confidence interval, 4.85–6.90) and *Pa* first detection (hazard

ratio, 1.92; 95% confidence interval, 1.65, 2.24; $P < 0.001$) is greater in the United States than in the United Kingdom. It is unknown whether these differences can be attributed to *Sa* prophylaxis or to environmental differences in the two countries. A second analysis in the same study (32) evaluated U.K. children who were receiving flucloxacillin ($n = 278$) and not prophylaxis ($n = 306$). In this population, prophylaxis did not reduce the detection of *Sa*, but it increased detection of *Pa*. Although the findings are interesting, attributing causality will require a randomized clinical trial, which is currently being conducted in the United Kingdom.

One study examined the risk/benefit of chronic AZ therapy in children with CF. A retrospective cohort study used the CFFPR (33) to ascertain whether long-term AZ administration is associated with an increased risk of emergence of other multidrug-resistant pathogens. Thrice-weekly AZ users were propensity score matched with nonusers to reduce indication and selection bias. Using Kaplan-Meier curves and Cox proportional hazards regression analyses to compare the incidence of new pathogens in users and nonusers, the incidence of methicillin-resistant *Sa*, NTM, and *Burkholderia cepacia* complex was significantly lower in the AZ users. Importantly, there was no increased incidence of other pathogens among AZ users. It is reassuring that in this predominantly pediatric population (mean age, 12 yr), there does not appear to be increased risk of treatment-emergent respiratory pathogens, including NTM infection, contrasting with earlier reports that AZ could potentially increase NTM acquisition (34).

Reducing patient-to-patient spread of CF pathogens is a high priority for clinical management (35), and infection control guidelines strongly recommend wearing face masks in healthcare settings. An Australian study (36) reported the actual efficacy of surgical masks in reducing spread of *Pa* aerosol droplets in 25 adult colonized patients at a distance of 2 m. Although normal talking is rarely associated with viable *Pa* droplets, an uncovered cough has a 75% incidence of *Pa* aerosolization. Covering the mouth with a hand will reduce the incidence to 50%, whereas a mask significantly reduces aerosolization to 8%, demonstrating the potential value of this simple and inexpensive method to interrupt aerosol spread between patients.

Inflammation and Airway Clearance in CF

Dysfunction of CFTR, a cAMP-regulated anion (Cl^- and HCO_3^-) channel, results in abnormalities in the airway pH, mucus viscoelastic properties, airway surface liquid (ASL) volume, and mucociliary clearance. This abnormal channel predisposes patients to chronic respiratory infections with neutrophil-predominant inflammation involving the lower respiratory tract. A recent study demonstrated that in response to mucopurulent materials, bronchial epithelial cells from patients with CF have normal upregulation of mucin secretion but an absent fluid-secretory response, resulting in more dehydrated mucus and thus further exacerbating mucus adhesion in the airway (37).

There is evidence of dysregulation of both innate and adaptive immunity in the CF lung (38), and pulmonary inflammation is observed very early in life, even in the absence of detectable infection, indicative of dysregulation of the inflammatory response (39). A study published in *AJRCCM* reported that bacterial infection was not necessary for development of inflammatory lung disease in a preclinical model with mucus stasis likely leading to hypersecretion of mucus and bronchiectasis in ferrets genetically deficient in *CFTR*. These ferrets had been treated with lifelong broad-spectrum antibiotics (40), further underscoring the dysregulation of the inflammatory response in the milieu of the CF lung.

Paradoxically, despite the presence of increased numbers of neutrophils in the CF lung, bacteria survive and often thrive in this milieu, supporting a defect in antimicrobial functions of phagocytes in the CF airway (41–43). There are likely multiple factors that contribute to the phagocyte dysfunction in CF, including intrinsic abnormalities in the microbicidal functions of the neutrophils (44–46) and defective epithelial function related to *CFTR* mutations leading to dehydration and increased viscosity of the airway mucus (47). As noted in a study published in *AJRCCM* (46), increased concentrations of proteinases, such as elastase in the ASL, lead to cleavage and inactivation of membrane receptors on the phagocytes and degradation of antimicrobial factors in the ASL (48–50). Thus, although infection may initiate the inflammatory response, a dysregulated host response is responsible for much of the destruction of lung tissue.

Patients with CF also exhibit an exaggerated inflammatory response driven in part by cytokines such as IL-8 produced by bronchial epithelial cells and amplified by exposure to bacterial pathogens such as *Pa*. Several recent studies have provided important insights into molecular mechanisms responsible for this exaggerated inflammatory response. RGS2 (regulator of G-protein signaling 2), a GTPase-activating protein expressed in airway epithelial cells, is a negative regulator of G-protein signaling (51) and represses IL-8 expression in airway epithelial cells (52). RGS2 is known to enhance responsiveness and promote increased secretion of mucins from human airway epithelial cells (53) and may be directly relevant to the pathogenesis of CF lung disease. Expression of RGS2 is regulated by epigenetic factors, including DNA methylation (54). A recent study by Bouvet and colleagues published in *AJRCMB* (55) provided important insights into abnormalities in the control of RGS2 expression in CF airway epithelial cells. Using methylated DNA immunoprecipitation arrays and methylation-specific PCR, they observed that *RGS2* mRNA and protein expression is downregulated in CF airway epithelial cells by a mechanism involving hypermethylation of cytosine residues in the promoters of 13 genes. Importantly, downregulation of *RGS2* resulted in enhanced expression of A100A12, a proinflammatory protein known to drive the inflammatory response in the CF lung. Thus, therapeutic approaches to increase *RGS2* expression might attenuate proinflammatory responses of CF airway epithelial cells.

Another pathway that regulates the exaggerated inflammatory response in CF lungs involves *PLCB3* (phospholipase C-β3). Specific genetic variants in *PLCB3* are associated with slow progression of CF pulmonary disease, and silencing of *PLCB3* in cultured human bronchial epithelial cells results in enhanced inflammatory responses triggered by TLRs (Toll-like receptors) (56). A recent study by Rimessi and colleagues (57) built on this knowledge base and identified a genetic variant, *PLCB3*-S3845L,

as a loss-of-function genetic variant. Human bronchial epithelial cells expressing this variant exhibited attenuated inflammatory responses when exposed to *Pa* or respiratory secretions from the airways of patients with CF. This study underscores the importance of *PLCB3* in control of the inflammatory response in epithelial cells and identifies this pathway as a potential therapeutic target to downregulate the injurious inflammatory response in the CF lung. In an accompanying editorial, McElvaney and McElvaney (58) summarized a feedforward system in the CF lung, where neutrophil proteinases such as elastase enhance IL-8 production by bronchial epithelial cells and leukotriene B_4 production by macrophages, thus recruiting more neutrophils. This system is further amplified by bacterial products. The *PLCB3-S3845L* variant described by Rimessi and colleagues (57) functions to disrupt this feedforward loop and thus attenuates the injurious inflammatory response in the CF lung while leaving antibacterial defenses intact.

A study by Jones-Nelson and colleagues described a novel mechanism whereby activation of TLR5 by *Pa* flagellin results in enhanced neutrophil recruitment into the lung and release of neutrophil elastase leading to epithelial barrier dysfunction and lung injury and increased pathogenicity of *Klebsiella pneumoniae* during coinfection (59). This response could be attenuated by sivelestat, a neutrophil elastase inhibitor, or by antibodies to TLR5. The accompanying editorial by Bratcher and Malcolm (60) discussed the mechanisms underlying polymicrobial infection, focusing on both bacteria-derived toxins such as flagellin and host-derived factors such as proteinases (elastase and other matrix metalloproteinases) in microbial pathogenicity, and suggested therapeutic approaches such as promoting neutrophil phagocytosis to mitigate lung injury.

Advances in CF Epidemiology and Clinical Outcomes

During 2018, significant advances occurred in understanding of both clinical epidemiology and clinical outcome assessment in CF. The advances fall into two general areas: *1*) clinical features associated with survival and decline in lung function and *2*) gaining a better understanding of disparities of care in CF.

Several studies in 2018 brought new insights into the use of biomarkers and clinical outcomes. One of the most essential outcomes in a life-shortening disease such as CF is survival. In an interesting study published in *AnnalsATS*, Saavedra and colleagues (61) used clustering techniques with genomic data from whole blood to identify four different clusters of genes that were associated with very different clinical outcomes. At 5 years, all subjects in the very low–risk cluster were alive and well, whereas 90% of subjects in the high-risk cluster had experienced a major event, defined as mechanical ventilation or ICU admission, referral for lung transplant, undergoing lung transplant, or death ($P = 0.0001$). Another international collaboration evaluated the role of cardiopulmonary exercise testing (CPET) in predicting survival. Ten CF centers in Australia, Europe, and North America provided data to support the use of CPET in a retrospective cohort of 433 patients with CF, the largest study of its kind (62). Using both multivariate Cox proportional hazards modeling and cluster analysis, they identified novel predictors of clinical outcomes based on key CPET endpoints (i.e., $\dot{V}O_2$ peak in percent predicted, peak work rate, and ventilatory equivalent for oxygen and carbon dioxide). Given the challenges that survival prediction has encountered in CF (63), adding more specificity to clinical prediction with a functional test such as CPET will likely improve risk stratification (64). Besides improving understanding of the overall CF population, additional work from the Canadian CF Registry has assessed the survival of persons diagnosed with CF as adults (65). Median 10-year transplant-free survival of this patient population (median age of diagnosis, 34.3 yr) was 87.7%.

Although assessing survival is important, one of the key intermediate endpoints remains lung function. In fact, a recent study published in *AnnalsATS* successfully correlated improved lung function with improved survival (66). Predictors of lung function recovery and, importantly, lung function decline can provide insights into both pathophysiology of disease and clinical care. Recent analyses of data from the NHLBI's "Grand Opportunity" Exome Sequencing Project (LungGO) have revealed that specific single-nucleotide variants in genes involving cilia were found to be associated with both lung disease progression and lung function preservation, adding to the ever-expanding understanding of modifiers of CF lung disease (67). Although genetic factors impact lung function, day-to-day care substantially impacts lung function. One can see the impact of care practices by comparing countries with disparate healthcare systems, such as the United States and Canada. In a longitudinal analysis of lung function and BMI in both the United States and Canada, nutritional status and lung function improved in both Canada and the United States from 1990 to 2013, with the improvements most prominent in the BMI trajectories in the United States, especially in patients born after 1990 (68). This suggests that national efforts to improve nutritional status and lung function in the early 1990s are likely now being seen. Assessments within U.S. healthcare systems can also yield important associations that can inform clinical decision making. An observational study of treatment of exacerbation in the United States suggested that the proportion of the treatment occurring on an inpatient basis was more important than duration of treatment in achieving successful recovery (69).

Other important predictors of patient survival and well-being are disparities based on race, ethnicity, and socioeconomic status (70, 71). A study published in *AJRCCM* reported an analysis of CFFPR data revealing that Hispanic patients with CF have a markedly increased risk of death compared with non-Hispanic patients with CF (hazard ratio, 1.27; 95% confidence interval, 1.05–1.53), even after adjusting for key confounders (69). In two additional studies, one of the key features associated with gaps of care when transferring from pediatric to adult centers was lack of health insurance (72, 73). Gaps in care were much more likely in those U.S. patients with CF who were younger at transfer, lacked health insurance, and had relocated around the time of transition (72). It is key that future studies delve further into how such disparities in outcome can be reduced, be they based on sex, race, ethnicity, or socioeconomic status.

Conclusions

The studies summarized in this review have provided new insights into the molecular pathophysiology of CF and helped improve

understanding of the impact of novel therapies on patients with this genetic disorder. In the next decade, as highly effective CFTR modulators become more widely available to individuals with CF, the community must continue to closely observe and record the physiological and clinical changes that evolve. There will be many important questions to answer about onset and progression of respiratory infection and inflammation and progression of functional and structural lung disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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