Highlights from the 2016 North American Cystic Fibrosis Conference

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Abstract

The 30th annual North American Cystic Fibrosis Conference (NACFC) was held in Orlando, FL, on October 27-29, 2016. Abstracts were published in a supplement to Pediatric Pulmonology. This review summarizes several major topic areas addressed at the conference: the pathophysiology of cystic fibrosis (CF) lung disease, clinical trials, clinical management issues, and quality improvement. We sought to provide an overview of emerging concepts in several areas of CF research and care, rather than a comprehensive review of the conference. Citations from the conference are by first author and abstract number or symposium number, as designated in the supplement.

KEYWORDS

antibiotic therapy, clinical trials, cystic fibrosis (CF)

1 | PATHOPHYSIOLOGY OF CF LUNG DISEASE

A major theme of the 2016 NACFC was developing therapeutic strategies to normalize Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein function in all patients with CF.[1] As noted in the plenary sessions, workshops, and symposia, achieving this goal will require a variety of approaches to address the numerous disease causing CFTR mutations, including development of more potent correctors/potentiators for F508del-CFTR, improved drugs for premature truncation mutations, and gene therapy or stem cell based approaches for those with CFTR mutations not amenable to pharmacological treatment.

Nearly, 90% of CF patients in North America harbor at least one copy of the F508del mutation.[2] Data were presented on two next-generation correctors, VX-152 and VX-440, both of which significantly enhanced processing and trafficking of F508del-CFTR when combined with first generation correctors and potentiators in cell-culture assays (Grootenhuis et al., 188). Similarly, the novel corrector ABBV/GLPG-2222 exhibited increased potency in correcting F508del-CFTR relative to existing CFTR correctors (Singh et al., 192). Novel approaches to improve transport of F508del-CFTR also showed promise, with a high-throughput screening strategy used to identify small molecule inhibitors of the Disabled-2 (Dab2) endocytic adapter that modulate internalization of CFTR (Madden et al., 2). These inhibitors can enhance activity of the F508del mutant in conjunction with correctors and potentiators. While promising, many of these new drugs are just entering human trials, so their ability to provide safe and effective improvement in CFTR activity remains unproven.

While drugs designed to rescue F508del-CFTR will help patients who carry at least one copy of that mutation, they are not likely to benefit those with other mutations. Premature termination codon (PTC) mutations in CFTR can be treated using readthrough agents that bypass the stop codon and permit expression of full length CFTR. While initial clinical studies with readthrough agents based on aminoglycosides were disappointing (possibly due to interactions with inhaled tobramycin[3]), a high-throughput screening strategy recently identified the herbal extract escin as having substantial readthrough activity (Sharma et al., 198).[4] However, previous studies have suggested that escin and other readthrough agents may require combination therapy with CFTR modulators to achieve clinically relevant functionality.[5] Indeed, several investigators demonstrated that combinations of readthrough agents with other CFTR modulators including correctors, potentiators, and nonsense mediated decay inhibitors can improve CFTR activity in PTC mutants (Mutyam et al., 189; Bihler et al., 190).

Although, the strategies outlined above should benefit the majority of CF patients, there remain some whose mutations can

only be addressed via genetic approaches. The most common method for gene therapy has been use of viral vectors, and a study in the CF pig demonstrated the feasibility of using lentivirus or a hybrid piggyback/AAV vector to restore CFTR activity (Vallecillo-Viejo et al., 194). More recently, CRISPR/Cas9 technology has emerged as an exciting new approach toward targeted gene repair, and this methodology was shown to correct a deep intronic splicing mutant in human tracheal epithelial cells (Sanz et al., 195). While promising, this approach will likely need to be paired with stem cell technologies to deliver cells with repaired CFTR to the lung (Ghaedi, S12.4), which remains an emerging technology.[3,6] An alternative approach is to utilize targeted RNA editing to correct mutations after translation, which was shown to restore functional CFTR activity in a PTC mutation (Vallecillo-Viejo et al., 194), though utility is somewhat limited by potential off target effects.

While strategies to improve CFTR function offer the best hope for an eventual cure for CF, even the best drugs to date do not completely eliminate disease. There remains an urgent need for improved therapies to address the airway mucus abnormalities, infection, and inflammation that characterize CF. One promising novel approach lies in use of the sphingosine-1-phosphate lyase inhibitor LX2931, which was shown to reduce airway inflammation in a F508del-CFTR mutant mouse model (Veltman et al., 201). Similarly, hypothiocyanite was shown to inactivate bacterial thioredoxin reductase and enhance bacterial killing (Day et al., 76). Mucus has also been shown to be an important therapeutic target, with many animal models demonstrating the presence of dehydrated mucus with abnormal viscoelastic properties (Rowe and Birket, S01.2), with even very young children with CF having elevated concentrations of rheologically abnormal mucus (Esther et al., 81).

Developing new therapies requires appropriate models and biomarkers to assess therapeutic effects, and several investigators presented recent advances in these tools. One emerging model is the use of specialized culture techniques to grow epithelial cells obtained from patient biopsies into spheroid "organoids" that can swell or shrink in response to CFTR modulators (Berkers et al., S12.3). Assays based on organoids obtained from airway cells were shown to predict responses of rare CFTR mutations to modulators better than total protein or chloride current measures (Cholon et al., 11), and the viscoelastic properties of mucus from these organoids correlates with the efficacy of CFTR modulators (Mellnick et al., 149). In addition, intestinal organoids were shown to be useful in developing patient specific, high-throughput screening platforms for novel therapies (Vonk et al., 200).

Ideally, new therapeutic strategies would be tested in animal models, but generating a cost-effective animal model that faithfully recapitulates human disease remains elusive. One potentially exciting new approach is using CRISPR/Cas9 technology to generate CFTR deficient rabbits, which appear to exhibit many of the airway and liver phenotypes of clinical disease but are less expensive to maintain than the CF pig or other larger animal models (Xu et al., S12.2). CRISPR/Cas9 was also shown to be useful in quickly creating mouse models with specific CFTR mutations (Valerio et al., 150; Hodges et al., S12.1), which may find value in testing efficacy of novel CFTR modulators even though CF mice do not develop significant airways disease. Existing models including CF ferrets and pigs continue to provide important insights, with the CF ferret shown to develop bronchiectasis even in the absence of bacterial infection (Rosen et al., 151) and studies with the CF pig suggesting that airway acidification via ATP12A may be a novel therapeutic target (Shah et al, S13.3).

2 | CLINICAL TRIALS

With the recent successes of CFTR modulators, ivacaftor and lumacaftor/ivacaftor, many of the clinical trials highlighted at the 2016 NACFC focused on treatments aimed at restoring CFTR function. Currently, CFTR modulators are available for approximately 50-55% of people with CF.[7,8] In 2016, lumacaftor/ivacaftor approval by the FDA was expanded to include children with CF ages 6-11 years, homozygous for the F508del-CFTR mutation. Studies are on-going to extend this approval into younger age groups. Speakers at the conference reinforced the continued need for respiratory treatments even as CFTR treatments advance. Clinical trials in anti-infective therapies and airway surface liquid restoration were featured.

2.1 | CFTR modulators

Data from the open label extension study of lumacaftor/ivacaftor along with real-world experiences were presented by several investigators. The PROGRESS study, a long-term, double-blind, parallel group extension study of lumacaftor/ivacaftor that followed the TRAFFIC, and TRANSPORT clinical trials, was presented and subsequently published (Konstan et al., 180).[9] Participants ages 12 years of age and older homozygous for the F508del-CFTR mutation (n = 1030) who completed 24 weeks of treatment in TRAFFIC or TRANSPORT were eligible to enroll in PROGRESS. Participants received lumacaftor/ivacaftor at one of two dosing levels for up to 96 weeks. Efficacy results for participants on FDA approved dosing of lumacaftor/ivacaftor (n = 516) were presented. The study struggled with a high number of withdrawals, particularly following commercial availability, with 82% of participants completing week 72 but only 42% completing week 96. Safety findings were similar to that seen in TRAFFIC and TRANSPORT with respiratory symptoms most common and elevations in liver transaminases >3× upper limit of normal (ULN) in approximately 8% of patients, with no emergence of new adverse events over 96-120 weeks (including the initial study periods) of treatment. Reduction in pulmonary exacerbations (PEx) documented during the initial clinical trials persisted, and improvement from baseline in body mass index (BMI) continued to increase in PROGRESS. Although decline in FEV_1 over time occurred, the annualized rate (−1.33% [CI −1.8 to − 0.85]) was 42% less in the treated group compared to a matched control group from the CF Foundation Patient Registry (CFFPR).

The impact of ivacaftor on clinical outcomes was examined using data for the CFFPR and the UK CF patient registry (Bessonova et al., 497). Data from 2014 were used to compare patients on ivacaftor (n = 1256 US, 411 UK) to matched untreated patients (n = 6800 US,

2069 UK). The relative risk of death, organ transplantation, hospitalization, and PEx were significantly lower in the US population on ivacaftor compared to the untreated group, and similar trends were seen in the UK. The rate of *Pseudomonas aeruginosa* (Pa) infection also trended lower in the ivacaftor group. Separately, UK patient registry data were used to examine clinical outcomes in patients on ivacaftor during the first two years of commercial availability (2013-2014) (Volkova et al., 495). Mean FEV_1 and BMI improved compared to patients not on ivacaftor, while annual risk of PEx, hospitalizations, and prevalence of CF related diabetes (CFRD) and distal intestinal obstruction syndrome (DIOS) were reduced.

In September 2016, the FDA approved lumacaftor/ivacaftor for use in children ages 6-11 years with two copies of the F508del-CFTR mutation; results from the open label, phase 3 trial that supported this approval were presented (Milla et al., 179).[10] Patients (n = 58) received lumacaftor/ivacaftor for 24 weeks. Safety findings were similar to those observed in older patients with respiratory related events most common; 19% of participants experienced elevated liver transaminases >3× ULN. Discontinuation due to adverse event was required in one patient due to elevated liver transaminases and one due to rash; both resolved after discontinuation. Sweat chloride levels decreased (mean −24.8 mmol/L; 95%CI −29.1 to −20.5%, P < 0.0001), BMI increased (mean +0.64; 0.46 to 0.83, P < 0.0001), and CFQ-R quality of life score and lung function index both improved at 24 weeks, whereas there was not a statistically significant change in FEV_1 % predicted (mean +2.5% [CI −0.2 to 5.2], P = 0.07). Lumacaftor/ivacaftor is currently being studied in children ages 2-5 years with two copies of the F508del-CFTR mutation (Clinical Trials NCT02797132).

Ivacaftor for patients with CF who carry the R117H or specific gating mutations is FDA-approved down to age 2 years. Results from KLIMB, an 84-week extension study of the KIWI clinic trial evaluating long term safety and efficacy of ivacaftor for children ages 2-5 years with a CFTR gating mutation, were presented (Rosenfeld et al., 177). Children (n = 33) received weight based dosing of ivacaftor. Safety data and clinical outcomes were similar to the KIWI study.[11] Two patients discontinued treatment due to elevated liver transaminases. Sweat chloride values decreased significantly (mean [SD] −54.7 [26] mmol/L, P < 0.0001). Significant improvements in BMI z-score and pancreatic function measures (fecal elastase and immunoreactive trypsinogen) were similar to that seen in KIWI.

Results of a Phase IIa study of a novel potentiator, GLPG1837, for patients with the S1251N-CFTR gating mutations were presented (De Boeck et al., 253). Patients (n = 7; data provided for 5) were treated for 4 weeks with two dose levels of GLPG1837 administered sequentially for two weeks each. No serious adverse events were reported and a dose-dependent decrease in sweat chloride was seen. A Phase 2a open label study of GLPG1837 in those with the G551D-CFTR mutation (n = 26) also demonstrated significant decreases in sweat chloride; FEV_1 % predicted improved to pre-ivacaftor washout levels. Serious adverse events included non-cardiac CPK increase, DIOS in one patient, and PEx in one patient. GLPG2222, a novel F508del-CFTR corrector, was also evaluated in a phase I sequential dosing study (Van de Steen et al., 252). GLPG2222 appeared to be safe and well tolerated. A phase II study of GLPG2222 is now ongoing (NCT03045523) and a second corrector is entering phase 1 with the goal of a triple combination CFTR modulator (Singh et al., 192).

Additional CFTR modulators are currently in pre-clinical and phase I trials. CTP-656 (deuterated ivacaftor), a CFTR potentiator, was compared to ivacaftor in a single dose, cross-over study, and dose escalation study (Uttamsingh et al., 224). CTP-656 appeared safe and well tolerated and PK data supported once daily dosing. A phase 2 clinical trial for CF patients with gating mutations is underway (NCT02971839). Preliminary phase I results studying PTI-428, a CFTR amplifier (a mutation agnostic therapy that selectively increases the amount of CFTR protein in the cell), were presented and no safety concerns were identified among CF or healthy controls (n = 18), although final study results were not available (Mouded et al., 187). Finally, QR-010, a novel oligonucleotide that repairs CFTR-encoded mRNA theoretically resulting in normal CFTR protein, was studied in a phase I open label study of nasal topical effect on NPD measurements in people with one or two copies of the F508del-CFTR mutation (Henig et al., 764). The proof of concept study demonstrated that QR-010 restored CFTR function with change in chloride response after 4 weeks of treatment; nasal application was safe and well-tolerated. A phase 1b trial with an inhaled formulation of QR-010 is currently recruiting participants (NCT02532764).

2.2 | Antibiotics

Levofloxacin inhalation solution (LIS) is approved for patients with CF with chronic Pa infection by the European Medicines Agency (EMA) and in Canada, but is not yet approved by the FDA for use in the US The EMA approved LIS based on results demonstrating non-inferiority compared to inhaled tobramycin (TIS) over 24 weeks (28 day treatment on/off cycles) in patients with CF ages 12 years and older with chronic Pa infection (MPEX 209 Study).[12] Conversely, a placebo-controlled, double blind, 28-day study of LIS did not meet its primary outcome of time to next PEx, with no significant difference between groups.[13] Results of a subgroup analysis of patients ages 18 and older enrolled in the MPEX-209 study were presented (Fisher et al., 436). Outcome measures were defined as changes in lung function between baseline and the end of each treatment cycle and risk of PEx. Mean FEV_1 change from baseline at the end of treatment was significantly higher for LIS compared to TIS after the second and third treatment cycle. Time to PEx was increased in the LIS group (P = 0.028) compared to TIS. In March 2016 the US FDA granted LIS Qualified Infectious Disease Product (QIDP) designation, and further regulatory discussions are ongoing.

Inhaled dry-powder vancomycin (AeroVanc) is in development for CF patients with persistent Methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Pharmacokinetic (PK) results from a phase II study of AeroVanc were presented (Marich et al., 282). CF patients (P = 87) were enrolled in the randomized double-blind placebo-controlled study, and a subgroup of 13 patients on treatment were evaluated for sputum and blood PK. Sputum concentrations accumulated throughout the month and were maintained above the MIC of 2 mcg/mL at two dosing levels (32 and 64 mg BID) with minimal systemic exposure and no plasma accumulation (Marich C et al., 282). Data were

presented from an ongoing Italian early MRSA eradication trial comparing treatment with trimethoprim/sulfamethoxazole and rifampin versus observation in subjects with new onset MRSA infection. Data on the 61 patients enrolled to date showed a trend toward lower MRSA positive culture rate at 6 months with therapy but did not reach significance (Neri et al., 309).

2.3 | Restoration of the airway surface liquid layer

Inhaled mannitol, approved for adults 18 years and older with CF by the EMA, but not yet approved in the US or Canada, was studied in a phase II, randomized, double-blind, placebo-controlled study in children with CF (De Boeck et al., 215). Children ages 6–17 years ($n = 92$, mean [SD] FEV_1 72% [11.6]) were randomized to receive 8 weeks of inhaled mannitol or placebo. Following 8 weeks of treatment, there was a significant improvement in FEV_1 for those on therapy with a 4.97% relative difference between groups (CI 1.53, 8.42, $P = 0.005$). Pulmonary exacerbations were 30% lower in the inhaled mannitol group, and adverse events were less common compared to those who received placebo.

3 | CLINICAL MANAGEMENT ISSUES

3.1 | Infection

Highlights of microbiology presentations were treatment guidelines and novel antimicrobial approaches. The Toronto CF center presented a 3-step Pa eradication protocol (Blanchard et al., 335). Since, 2009 patients with new onset Pa receive a single course of TIS followed by a repeat cycle in those failing to clear; patients with ongoing Pa positive cultures are treated with 2 weeks of IV therapy. Results from 124 children showed eradication in 81% and 86% after one and two cycles of TIS, respectively. Of those requiring IV therapy 38% cleared. The cumulative success rate was 90%.

Chronic, treatment refractory Pa is often described as biofilm growth mode, although recently this concept has been reexamined (Parsek, S18.1). Features consistent with Pa biofilm growth in CF include the localized, difficult to eradicate infections, and biofilm appearance; conversely, CF derived Pa isolates often have poor biofilm forming capacity and bacteria growing in high densities and in stationary phase show decreased killing by antibiotics. Dr. Parsek also presented the cellular metabolic functions consistent with the biofilm versus no biofilm hypothesis. In either case, novel treatment approaches for stationary and biofilm growth are necessary.

One example of a novel therapy targeting biofilms is inhaled alginate oligosaccharide (OligoG), a guluronate oligomer derived from seaweed alginate thought to disrupt bacterial biofilms and reduce sputum viscosity. A Phase II, double-blind, randomized, placebo-controlled, cross-over study in 65 CF adults evaluated the safety, tolerability, and efficacy of OligoG administered for 28 days in patients with CF and Pa infection; final results are pending (Pressler T et al., 209; NCT01465529). In vitro exposure of mature biofilms to colistin with and without OligoG show enhanced killing for the combination (Pritchard et al., 247). Additionally, OligoG interferes with signaling pathways of Pa (Jack et al., 370) and disrupts Pa biofilms directly (Langlois et al., 110).

A non-antibiotic anti-Pa therapy, CAT-5571, thought to enhance autophagy as a means to enhance host degradation of Pa, showed promising results from in vitro cultures and murine infection models (Bonfield et al, 223). Another novel antimicrobial candidate, Mul-1867, is undergoing pre-clinical testing for nebulization treatment of mixed Pa/*Burkholderia* infections. Mice infected intranasally with both bacteria had decreased mortality if treated with Mul-1867 compared to no treatment, or inhaled tobramycin or inhaled aztreonam (Tetz et al., 310). The CF center in Chicago presented their experience with inhaled meropenem in 22 subjects ages 8-44 years (Brackett et al., 322). The main side effect was cough during inhalation, severe enough to stop therapy in one patient, and an allergic reaction in one patient. The 20 subjects completing the 3 week course showed improvement in FEV_1. Response was better in those infected only with Pa compared to three subjects infected with *B. cepacia*.

Vaccination as a means to prevent infection with Pa or *S. aureus* was presented in a symposium (Goldberg, S18.1). Among the challenges are that bacterial epitopes are often shielded from host immune detection and may change from early to later stage infection, and performing clinical trials in infection naïve patients with appropriate, measurable endpoints. Several Pa vaccine studies were negative or inconclusive including an octavalent flagella directed vaccine, a vaccine directed at OPRF that failed, and a bivalent vaccine that had shown promising results but was not further pursued by the company. *S. aureus* vaccine trials in non-CF ventilator associated pneumonia were being evaluated by two companies as of Oct 2016.

Clinical management of mycobacterial (NTM) infections was addressed relevant to the recently published consensus management guidelines (Haworth, S04.1).[14] The rationale for the unusual dosing intervals recommended for NTM treatment in the guidelines in order to decrease side effects and drug interactions was discussed (Olivier, S04.2). Emphasis was placed on the consensus document as a starting point that can serve as a means for observational multi-site studies rather than a definite treatise. The epidemiology of NTM was highlighted, for example, the lower prevalence of *M. avium* complex in younger patients in Europe compared to the US, and the seemingly lower virulence of those infections in Europe (Nick, S04.3). Identification of subspecies of mycobacteria is relevant for prognosis. For example, *M. abscessus* subspecies *massiliense* contains a partial deletion of the erm41 gene, which reduces the risk of developing macrolide resistance compared to the *M. abscessus* ss. *abscessus* which more often carries the *erm41* gene. On the other hand, *M. massilliense* has been implicated in transmission between CF centers.[15] A Cystic Fibrosis Foundation Therapeutics (CFFT) funded biobank for NTM isolates is ongoing in Denver, Colorado to test for any shared clonal lineages within the US (Hasan et al., 307). Information about transplant in the setting of NTM was presented, specifically the "dearth of evidence" around transplant eligibility of individuals with CF infected with NTM, specifically *M. abscessus* (Noone, S04.4). Post-transplant mortality due to mycobacterial infection varies in different publications; yet, surgical site and skin infections due to *M. abscessus* are

frequent. Current consensus guidelines recommend evaluation and, if indicated, therapy for NTM prior to referral for transplant. Further, the complexity of long-term multidrug therapy in the setting of immunosuppression and the risk of post-operative complications needs to be considered.

Several microbiome studies addressed longitudinal aspects of airway infection (Ahmed et al., 356; Acosta et al., 360), ability of microbes to grow in mucins (Hunter, 405), and the metabolic activity of anaerobic bacteria. Growth of anaerobic communities and Pa were tested using an in vitro growth model that simulates zones within mucus plugs progressing from aerobic to anaerobic conditions (Quinn et al., 297). Mathematical modeling tested the observed dynamics in response to changes in pH, size of the "airway" model, and antibiotic administration. Lower pH and wider radius of the "airway" led to an increase in anaerobes and antibiotics killed anaerobic bacteria allowing Pa to thrive. The researchers suggested that this model "supports the observation that CF PEx are associated with a bloom of fermentative anaerobes at lower mucus pH." Dr. Quinn also presented case vignettes supporting the clinical relevance of this "fermentation hypothesis." Sputum samples from patients failing antibiotic therapy were tested using combined 16S rRNA sequencing, transcriptomics and metabolomics. Integrative bioinformatics assessed how metabolite production matched transcriptome profiling and the microbiome detected and all data were available within 48 h (Quinn et al., 304).

Viral infections contribute to disease onset and progression either directly or through interaction with bacteria as presented in several posters demonstrating mechanisms of Pa infection following viral infection of epithelial cells in vitro (Melvin et al., 325; Hendricks et al., 384). The frequency of viruses was examined prospectively for the first 6 months of life in 69 CF infants using nasopharyngeal swabs and PCR detection (Deschamp et al., 374). Overall detection rate was 33% with Rhino- and Coronavirus being most prevalent. Although the odds ratio for being virus positive were enhanced by number of symptoms recorded, only 27% of infants were symptomatic. There was no association between lung function or lower airway inflammation and being virus positive.

The use of palivizumab in CF infants born from 2008 to 2014 was evaluated using the US CFFPR (Fink et al., 347). Of the 4438 infants, 37% (1652) received prophylaxis with a decreasing trend over time. Children who received prophylaxis had lower weight and more respiratory symptoms at time of starting palivizumab and had a higher hazard-ratio for Pa incidence in their first year of life than those without prophylaxis. Lung function available in 441 children at age 6 years showed no difference in FEV_1 between the two cohorts.

3.2 | Transition to adult care

Efforts to enhance the process of transition from pediatric to adult CF care have received support in recent years from the OneCF Learning and Leadership Collaborative, a partnership between the Dartmouth Institute Microsystem Academy and the CF Foundation (CFF). Several centers reported processes and outcomes of their OneCF LLC projects, including overall program development (Barnico et al., 556), development of handoff tools (Metcalf et al., 536), and post-transfer assessments of satisfaction (Johnson, 550; Middour-Oxleret et al., 745) and success (Crowley et al., 670). Optimal timing of transition was assessed emphasizing that it should be individualized based on preparedness and preference; the most useful experiences for patients prior to transfer were meeting with adult physicians in Pediatrics clinic and having a social worker facilitate the transition (Sadeghi et al., 549; Nasr, 668 and S21.1). Age appeared to be the best predictor of transition readiness despite variability in acquisition of disease self-management skills (Lapp, 744) and specific counseling on transition-related topics helps improve readiness skills (Sawicki et al., 677). The importance of tracking progress toward transition goals and using this to target ongoing education for individual patients was emphasized, and can be facilitated by a transition coordinator (Cooney, 705 and S21.3).

3.3 | Lung transplant

Transition from a CF care team to a lung transplant team may occur for individuals with advanced lung disease, and Tallarico described current practices with the goal of developing a formalized transition program for transplant candidates (Tallarico et al., 742). Specialized care for people with CF undergoing transplant was also highlighted in the context of outcomes, with improved outcomes at centers performing more CF lung transplants; overall transplant volume appears to be less important (Hayes et al., 485). Disease characteristics that may predict outcomes are being investigated by linking transplant registry data with the CFFPR (Dasenbrook et al., 482) and US transplant data with Canadian data (Quon et al., 483). The use of CFQ-R to predict wait list and post-transplant survival was also described (Bernstein et al., 484). While concern exists for outcomes of the highest risk patients,[16,17] one center reported no difference in survival between relatively stable patients and "high risk" patients needing substantial respiratory support and bridging therapies (Gray et al., 486). These studies may help transform our approach to referral, listing, and pre- and post-transplant management.

3.4 | Palliative care

The care of people with advanced CF lung disease requires thoughtful communication about goals, wishes, and choices around lung transplant and end of life care. Primary palliative care, in this case meaning palliative care provided by CF care teams rather than palliative care specialists, is receiving greater attention as the value of palliative care is increasingly recognized. Many patients and caregivers lack familiarity with palliative care (Prieur et al., 740). Unmet needs in such areas as symptom management and communication about prognosis, and opportunities to engage patients in advance care planning (ACP) were identified (Hobler et al., 675). Patients with CF ages 13 and older and their caregivers are receptive to palliative care education; education appears not only to increase knowledge but also to reduce fears and uncertainty related to the topic (Hailey et al., 757). While a study of advance care planning (ACP) among US CF centers actually suggests more attention to this issue in recent years than in the past, we know that practices vary from center to center.[18] Basile

reported low frequency of conversations about intensive care options like intubation, and noted variability in people's desires to hear prognostic estimates (Basile et al., 741). Additionally, patient coping style may affect comfort level in participating in ACP and may help inform the approach to ACP (Graham et al., 739), suggesting that counseling around complex treatment options should be individualized.

Given the high prevalence of distressing symptoms in CF, effective symptom management is another important aspect of care, regardless of disease severity. Pain management with opioids is currently receiving national attention, and the use of opioids in CF is fraught with concerns and controversy due to concerns about abuse, addiction, and side effects. One center reported successful implementation of an inpatient non-surgical pain management algorithm emphasizing a multimodal approach (Lehman et al., 558). In addition to pain, routine screening commonly reveals other physical and psychological distress necessitating intervention by CF care team members (Walker et al., 727). Interactions may occur between physical and emotional symptoms; for example, depression is associated with dyspnea, pain, and anxiety regardless of lung disease severity (Daines et al., 701). These associations should prompt providers to consider the impact of physical and emotional symptoms on each other, as well as on an individual's functional status and engagement in daily care.

3.5 | Mental health

Mental health received a great deal of attention at NACFC 2016, with many interesting abstracts and presentations in follow up to the international guidelines established by the CFF and the European CF Society.[19] In a symposium session, members of the CFF Mental Health Guidelines Advisory Committee presented an overview of tasks for education and training, consultation and guidance, and research work groups that will continue to move this important work forward (Smith, S11.4). The role of the mental health coordinator was reviewed, with attention to how mental health providers with different backgrounds and training could effectively serve in this role (Kooney, S11.1; Sher and Dvorak, S11.2).

Mental health screening has caught the attention of patients and caregivers, particularly at care centers receiving financial support from the CFF for mental health coordinators (Homa et al., 580). Several centers reported their experiences with guidelines implementation, including how screening is received by patients and caregivers (Prieur et al., 688; Beenen et al., 718), practical and ethical issues in caregiver screening (Blair et al., 712; Roach et al., 722; Butcher et al., 730), plans for program assessment and quality improvement (Nicolais et al., 674), barriers to implementation (Prieur et al., 689), creative solutions to lack of mental health resources and geographically diverse populations (Prieur et al., 688; Wolfe et al., 713), and the positive impact of mental health interventions resulting from screening (Akmal et al., 693; Smith et al., 707). Frederick reported adverse health outcomes in patients screening positive for depression, with depressed teens having lower FEV_1 than peers, and a worrisome decline in FEV_1 over a 3 year period for teens and adults with depression, from 73.6% to 64.2% predicted versus 71.4% to 70.2% predicted in those without depression ($P = 0.03$) (Frederick et al., 581). Lower health related quality of life scores were also noted across several CFQ-R domains in those with greater symptoms of depression and anxiety (Saez-Flores et al., 680). These findings highlight the critical importance of addressing mental health concerns as a routine part of CF care.

4 | QUALITY IMPROVEMENT

In 2002, the CFF launched a quality improvement (QI) initiative to accelerate improvements and delivery of CF care. Since then, the majority of CF Centers in the US have participated in a formal program to learn QI techniques and apply them to their centers. Centers worldwide share a vision for exemplary care of CF patients. In this section, we highlight some of the important clinical QI work showcased at the 2016 NACFC. We focus on measures of improvement, the concept of co-production, and determination of real world value in the delivery of high quality care.

The CFFPR remains a powerful tool to assess patient outcomes for QI. Schechter and colleagues reported use of CF registry smart reports to generate individual patient run charts of FEV_1 and nutritional measures of BMI and weight-for-length (Schechter et al., 546 and 547). These reports were used by the clinical team as a tool to assess consistent and early recognition of poor outcomes. The center reported a dramatic response in overall improvement in lung function from 83.7% predicted to 100.3% predicted for 6-18 year-olds.

An emerging source of data for QI is the CF Patient and Family Experience of Care Survey (Homa et al., 573, 574). Nearly 60% (164 of 276) of CF programs are actively involved in the measurement of patient and family feedback to individual CF care centers. The increased dissemination of this survey presents the opportunity for centers to measure patient experience, benchmark among centers through available reporting tools, and identify opportunities to improve processes of care.

Measurements of patient experience may be used as outcome measures for centers improving clinic flow, communication, and access to care. Hoffert et al compared two models of clinic flow: traditional individual provider interviews and team interviews. Adoption of the team interview approach reduced patient wait times and overall clinic length and increased patient and staff satisfaction (Hoffert et al., 734). Redesign of clinic flow through process mapping and Plan-Do-Study-Act (PDSA) cycles reduced lobby and wait times, increased quarterly clinic attendance, and increased access for yearly labs and assessments (Powers et al., 735; Phan et al., 736). Use of telemedicine for clinic visits in Western Australia was received by patients in rural and remote areas with high satisfaction and increased clinic attendance (Wood et al., 532). Annual respiratory therapy assessments through video telemedicine encounters increased patient understanding of airway clearance therapies and satisfaction was similar to in-clinic encounters in the use of telemedicine to review airway clearance therapies (Lester et al., 584). Patient experience is a useful tool to assess the impact of the redesign of clinical systems.

Added insight of parent and patient partners is an integral facet in the development of care delivery systems. Co-production is the

concept of an active collaboration between clinicians and patients to produce services. Parent and family partners and CF family advisory boards are increasingly involved in the development of QI interventions, such as preparation for transition from pediatric to adult care and improvement of hospitalization experiences (Johnson, 550; St. Onge et al., 553). An electronic dashboard of individualized trends of FEV_1 and BMI, patient goals, and treatment effects is being pilot tested across five CF centers (Prickett et al., 522; Savant et al., 534). This novel tool, co-created by patients and providers, has increased patient feelings of empowerment to direct pre-visit planning agendas. Co-production incorporates an upstream identification of patient concerns in the creation of care delivery processes, anticipates positive patient experiences, and increases communication of shared goals.

The commitment of care centers for co-production and the use of data sources such as the CFFPR and the patient family experience survey are among the resources for the CF community to assess the value of care. A symposium, entitled "Delivering High-Quality, High-Value Care in the Evolving Health Care Landscape" explored the role of the CF community in assessing the balance between quality and value of care (Dwight and Simon, S7). A panel of experts representing physicians, the CFF, and private and public payers initiated a rich discussion on the challenges to define value and high quality care. Growing costs of CF care and the priorities of public and private sector payers were among themes discussed. Advocacy of the CFF and the power of data tools such as the CFFPR were highlighted as opportunities for the CF community to use and test systems of care to shape the health care landscape. The CF community is at an advantage to tackle the upcoming challenges of determining value with emerging QI work across centers.

Centers are actively assessing patient level factors that influence daily care in the real world to help determine value. The uptake of lumacaftor/ivacaftor use is variable and slower than ivacaftor (Sawicki et al., 496). Systems of care assessing side effects and patient use may be beneficial to assess long-term value (Anstead et al., 290; Ong et al., 554). An integrated CF-specific pharmacy team improved patient adherence as measured by monthly medication possession ratios at the Intermountain Pediatric CF Center through streamlined counseling and assessment of cost, access, and poly-pharmacy (Schwab et al., 569). Encouragement of self-care is being tested through shared goal setting and skill assessment programs (Pociask et al., 551; Browning et al., 578). Clinic attendance improved with financial incentive to alleviate the cost of gas, increasing quarterly visit attendance from 66.7% in 2014 to 94% in 2015 (DuBose et al., 570). Engaging patients with conversations of how to of sustain daily care with emerging and standard therapies are critical in assessing the balance of value and quality of care (Frederick et al., 737).

The CF community continues to benefit from innovative biomedical research, and patients are the key to these important studies. The benefits of clinical research are augmented by QI work testing interventions to decrease the gap between effective clinical practices and real world use. Clinical teams obtain QI training through the CFF's sponsorship of the Dartmouth Learning and Leadership Collaborative and other improvement training. The inaugural CFF QI Fair just prior to the NACFC was an electric showcase of a multitude of QI interventions throughout the CF community, including the introduction of the CF Pilot Learning Network (PLN). The PLN is a QI network of an initial 14 CF programs with a common aim to improve CF care delivery and outcomes and build an infrastructure for collaborative learning. The QI Fair also featured Virtual Improvement Program Fundamentals (VIP-F). The VIP-F promises to provide a remote way for all centers to participate in QI learning and to stay informed on the best techniques for performing QI in their centers. The CFFPR and other tools provide the means to measure improvement efforts. The rigor of QI in CF is evolving toward implementation science, the study of mechanisms by which evidence-based health care interventions are adopted and disseminated. Through the interface and collaboration of QI and biomedical research, the CF community remains at the forefront of its mission to deliver the best care to people living with CF.

5 | SUMMARY

The 2016 NACFC presented updates on many advances in CF research and care. Progress continues to be made in understanding the basic pathophysiology of CFTR, mucus, and infections in the CF lung, with implications for new treatment strategies. Multiple pharmaceutical treatments aimed at improving CFTR activity are in the clinical trials pipeline. Clinical management of CF is evolving rapidly with new approaches to airway infection, and improved management of adults with CF and those with severe lung disease. QI initiatives are expanding in order to move new therapies more effectively into standard clinical practice, with the goal of every person with CF receiving the most up-to date-treatment options and exemplary care from infancy through adulthood.

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