Cystic Fibrosis 2017—The Year in Review

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It is always an exciting challenge to write a Year in Review artcicle identifying the best publications in the preceding year; in this case from October 2016 until the AARC meeting in October 2017. This is particularly true for cystic fibrosis (CF), where there has been an explosion of new data, new medications, and new understanding of the pathophysiology of the disease. PubMed lists more than 2,500 papers published during those 12 months, many of them outstanding. I am indebted to many colleagues and friends who are leaders in the CF community, active readers of the pediatric pulmonary listserv, and scientists and clinicians engaged in the care of CF, for offering their suggestions regarding which articles should be included in this review. I believe that you will enjoy reading this curated selection of manuscripts that I have tried to organize by theme. *Key words: cystic fibrosis; CFTR modulators; adherence to therapy; CF outcomes; CF exacerbations; risk factors.* [Respir Care 2018;63(2):239–242. © 2018 Daedalus Enterprises]

Introduction

Just as beauty is in the eye of the beholder, it is impossible to identify the very best published articles on any topic over a 12-month period. For the topic of cystic fibrosis (CF), PubMed lists > 2,500 articles published between October 2016 and October 2017. To identify those with the greatest potential impact and interest to readers, I read the abstracts of all original research articles on CF published in English—well over 1,500! I selected just over 100 of these and read the full papers to pick those that I believed would be of greatest interest. However, to reduce bias, I invited the readers of the ped-lung list serve, our international community of pediatric pulmonary providers (including respiratory therapists), to send me their choices, and I also personally contacted many friends who are well-known CF clinicians and scientists, asking for their suggestions. Those who contributed are listed in the Acknowledgments. These many suggestions have been curated to produce this review. It is my hope that you will enjoy these beautiful articles.

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What CF Research Is Important for Patients and Clinicians?

The first of the articles that I highlight asks the question, "What are the top research priorities in CF from the view-

Table 1. Research Priorities

1. What are the effective ways for simplifying the treatment burden of people with CF?
2. How can we relieve gastrointestinal symptoms, such as stomach pain, bloating, and nausea, in people with CF?
3. What is the best treatment for non-tuberculous mycobacteria in people with CF (including when to start and what medication)?
4. Which therapies are effective in delaying or preventing progression of lung disease in early life in people with CF?
5. Is there a way of preventing CF-related diabetes in people with CF?
6. What motivation, support, and technologies are effective in helping people with CF improve and maintain adherence to treatment?
7. Can exercise replace chest physiotherapy for people with CF?
8. Which antibiotic combinations and dosing plans should be used for CF exacerbations, and should antibiotic combinations be rotated?
9. Is there a way of reducing the negative effects of antibiotics, such as resistance risk, and adverse symptoms in people with CF?
10. What is the best way of eradicating *Pseudomonas aeruginosa* in people with CF?

From Reference 1.
CF = cystic fibrosis

point of the health care providers who care for these patients and from the persons with CF themselves?"[1] This is quite different from setting research priorities from the perspective of researchers. Table 1 lists these top priorities; as you can see, this is a mix of research to identify the "best treatments" to prevent disease progression and to find therapies that are effective in mitigating CF symptoms and improving quality of life. The treatment burden of CF is high in terms of the cost of therapies and the amount of time consumed by these treatments. This makes adherence challenging. Many of these questions address adherence and decreased treatment burden. It is worth noting that many of these questions can be answered by studies conducted by respiratory therapists; particularly questions 4, 6, and 7.

The Pathophysiology of CF Airway Disease

It is known that CF is caused by abnormalities in the CF transmembrane conductance regulator (CFTR) protein. Although > 2,000 mutations of this protein have been reported in the SickKids database (http://www.genet.sickkids.on.ca/Home.html, *Accessed December 12, 2017*), not all of these are known to cause disease. A key question remains: "How do abnormalities in CFTR lead to chronic airway infection, inflammation, and bronchiectasis?"

The CFTR protein actively transports chloride and bicarbonate toward the airway surface, secondarily bringing water with these ions. CFTR also affects other ion channels, most notably blocking the influx of sodium into the cell through the epithelial sodium channel. The CFTR abnormality has been shown to produce a number of changes in the airway, including acidification and decreased water and ion transit. This has led 2 large and well-respected CF research groups to have different theories as to how CFTR produces airway disease. In the CF community, this controversy has been playfully referred to as the salt wars. The group at the University of North Carolina at Chapel Hill has staked their claim that CF pathogenesis is due to dehydration of the airway surface fluid, with a decreased osmotic drive for water transport into the airway lumen leading to collapse of the periciliary fluid layer in CF and a subsequent decrease in mucociliary transport.[2] This has led to the development of osmotic agents such as hypertonic saline and dry powder mannitol to attempt to restore the periciliary fluid layer. On the other side of this controversy, the CF research group in Iowa points out the importance of airway acidification as noted in 2 landmark articles published in the past year. An article published by this group demonstrates that airway acidification can initiate abnormalities in airway host defense in CF mice, and that host defense can be restored by restoring the pH balance.[3] A second study from this group demonstrates that the acidic pH in the airway of both CF animal models and human airway cells from patients with CF will increase airway surface-liquid viscosity without changing airway mucin composition or volume. Furthermore, by increasing the pH of the airway surface liquid to a more neutral pH, its viscosity will decrease to normal.[4] Studies such as these have led to active investigation into the evaluation of alkaline solutions such as bicarbonate as a potential therapy for CF airway disease. It is likely that there is truth in both of these theories, and that these complex interactions together lead to CF airway disease.

How Can We Change Long-Term CF Outcomes?

A study from Australia evaluated what we have learned from studying early lung disease in infants and preschool children with CF and how can we use this information to decrease long-term morbidity and mortality.[5] These researchers demonstrate that pulmonary function, as percent of predicted FEV_1, has consistently improved over the past 3 decades when examined as age by year of birth cohort. Because early-life studies demonstrate that most children with CF have bronchiectasis by age 5, primary prevention must start early. They conclude by noting that newborn screening programs will enable earlier implementation of new CF treatments to improve longevity and quality of life for the next generation of people with CF.

A group from Canada showed that a 3-step protocol for early eradication of *P. aeruginosa* in young, asymptomatic children had a cumulative success rate of > 88%.[6] This was an aggressive protocol that began with 28 days of inhaled tobramycin for new-onset *Pseudomonas*, followed

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by a second course for subjects with persistent positive respiratory culture after step 1, and ending with 14 days of intravenous antibiotics followed by 28 days of inhaled tobramycin for subjects who had a subsequent positive culture after step 2. They evaluated all pediatric subjects who underwent this protocol from January 2010 to December 2015 (128 subjects with a total of 213 new-onset *Pseudomonas* infections) and showed that step 1 alone was able to clear 77% of the newly acquired infections.[6]

A provocative study compared survival of subjects with CF in Canada and the United States.[7] From 2009 through 2013, there was a divergence in survival between patients in these 2 countries, with a dramatically increased (> 10 y) survival advantage for CF patients in Canada. This was true regardless of patient sex, age at diagnosis, genotype, or the presence of pancreatic sufficiency. It is possible that better access to lung transplantation in Canada, better post-transplant survival, and differences in the health care systems in these 2 countries may, in part, explain the Canadian survival advantage. Of note, when United States patients insured by Medicaid or Medicare or without health insurance were excluded from the analysis, the survival differences between the 2 countries disappeared.[7]

CFTR Modulators

CFTR abnormalities are organized into 6 classes depending on how the CFTR protein is produced, processed, and how it transports at the airway surface. In Class III and Class IV mutations, the abnormal CFTR protein makes its way to the airway surface but functions inefficiently in transporting chloride and water. Potentiator medications such as ivacaftor increase the open probability of the CFTR channel, which in turn improves and may even normalize ion transport. It is now known that ivacaftor therapy decreases sputum *Pseudomonas* density and airway inflammation, and it produces modest improvement in radiographic lung disease in patients who have the gly.551.asp (old nomenclature: G551D) mutation. However, *Pseudomonas* airway infection persists, suggesting that a combination of controlling infection and improving CFTR function may be necessary in targeting CF treatments.[8]

The Class II mutations include the most common CFTR mutation, phe508del (old nomenclature: F508del). This mutation produces a misfolded CFTR protein that is degraded in the endoplasmic reticulum before it can be chaperoned to the airway surface. However, even this abnormal protein partially functions as a chloride channel once it reaches the luminal surface of the airway. Therefore, medications like lumacaftor, referred to as correctors, prevent degradation of the protein in the endoplasmic reticulum, allowing it to be transported from the Golgi to the airway surface where a potentiator like ivacaftor can increase the probability that this remains open to transport ions and water. The combination of lumacaftor and ivacaftor, marketed as Orkambi (Vertex Pharmaceuticals, Boston, Massachusetts), has been approved as therapy for patients who have at least 1 phe508del CFTR mutation. An extension study of 2 of the initial treatment studies of Orkambi therapy in subjects homozygous for phe508del reported that pulmonary function improvement, improvements in nutritional status, and decreased exacerbation rates continued to be observed even after > 2 y of therapy. Furthermore, comparing the rate of lung function decline of these subjects to matched United States CF Foundation patient-registry control subjects showed that treatment with Orkambi was associated with a 42% slower rate of FEV_1 decline.[9]

There is active development of new CFTR modulators, as well as a search for therapy to treat the profoundly increased neutrophilic inflammation that characterizes CF airway infection leading to bronchiectasis. Thymosin alpha 1 is a human polypeptide that has been used for many years to treat hepatitis and some forms of cancer. Thymosin alpha 1 has been shown to decrease airway inflammation in CFTR mice, to increase CFTR maturation and translocation from the endoplasmic reticulum to the plasma membrane (as a corrector), and to increase the cell membrane ion channel activity (as a potentiator) in human CF airway cells. These effects were at least as great as that seen with Orkambi. Thymosin alpha 1 has been used for many years and has an excellent safety profile. It is possible that this drug could be an effective single molecule-based therapy for treating CF.[10]

Exacerbations and Risk Factors

A pulmonary exacerbation of CF is usually identified by an increase in cough and sputum and a decrease in pulmonary function. This is treated with oral intravenous antibiotic therapy, either at home or in hospital. A systematic review compared in-patient intravenous antibiotics for a CF pulmonary exacerbation with out-patient intravenous therapy. Even using home intravenous therapy, hospital-based therapy was more effective at restoring lung function.[11] A similar review looked at the relationship of antibiotic treatment to recovery after an acute decline in pulmonary function, demonstrating that a "wait and see attitude" can lead to irreversible decline in pulmonary function, suggesting that all exacerbations with a decrease in FEV_1 should be treated early and aggressively.[12] This was particularly true in subjects who had the best baseline lung function, and therefore the most to lose. In CF subjects with normal lung function at baseline, there was dramatically better improvement with early institution of therapy. The odds ratio of recovery of FEV_1 to baseline with hospital therapy compared with no intervention was 2.79; overall, in-patient treatment had a greater likelihood than

out-patient therapy to lead to full recovery (odds ratio 1.94).

Adherence to Therapy

A novel recorder was used to objectively measure CF subject adherence to airway clearance therapy by high-frequency chest wall compression. It was shown that greater adherence was associated with better baseline pulmonary function and fewer exacerbations during the pre-study and baseline periods. Furthermore, and as no surprise, children who had caregivers who assisted with therapy had the highest adherence, while independent adults had the lowest. Neither the electronic monitoring nor monthly technician visits affected adherence, and when comparing self-reported adherence by diary to that with the recorder, self-report was shown to be an inaccurate measure of adherence.[13]

Miscellaneous

Wrinkling of the palm skin when immersed in water is called aquagenic wrinkling. This is far more common both in people with CF, including those who have non-classic disease, and in CF carriers. Up to 84% of CF patients develop this wrinkling within 3 min of immersing their hands in water, and 25% of CF exhibit this in 5–7 min. It has been suggested that CFTR modulator therapies may ameliorate this wrinkling condition.[14]

Summary

This selection of recent articles gives a flavor of the important topics in the field of CF today, with an emphasis on those of interest to the respiratory therapist. There has been tremendous progress in our understanding of CF pathogenesis and in identifying new therapies and interventions. As many before me have said, we all look forward to the day when CF stands for "cure found."

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