

# Contents

## **Preface: Cystic Fibrosis in the Era of Highly Effective CFTR Modulators** xiii

Clemente J. Britto and Jennifer L. Taylor-Cousar

## **Toward a Broader Understanding of Cystic Fibrosis Epidemiology and Its Impact on Clinical Manifestations** 579

Kimberly A. McBennett and Pamela B. Davis

The incidence of cystic fibrosis remains constant in North America and Western Europe is 1 in 3500 live births, but survival and quality of life have improved. The cystic fibrosis population has shifted toward the adult age range with a concomitant shift in the spectrum of complications. Survival increased because of aggressive symptomatic therapy, earlier diagnosis by newborn screening, and the introduction of modulators of the cystic fibrosis transmembrane conductance regulator, so that predicted median survival age is now about 50 years. In the United States, members of low socioeconomic status populations or members of racial or ethnic minorities have benefitted less from these advances.

## **Genetics of Cystic Fibrosis: Clinical Implications** 591

Anya T. Joynt, Garry R. Cutting, and Neeraj Sharma

Cystic fibrosis (CF) is a multiorgan disease caused by a wide variety of mutations in the cystic fibrosis transmembrane conductance regulator gene. As treatment has progressed from symptom mitigation to targeting of specific molecular defects, genetics has played an important role in identifying the proper precision therapies for each individual. Novel therapeutic approaches are focused on expanding treatment to a greater number of individuals as well as working toward a cure. This review discusses the role of genetics in our understanding of CF with a particular emphasis on how genetics informs the exciting landscape of current and novel CF therapies.

## **Update on Innate and Adaptive Immunity in Cystic Fibrosis** 603

Emanuela M. Bruscia and Tracey L. Bonfield

Cystic fibrosis (CF) pathophysiology is hallmarked by excessive inflammation and the inability to resolve lung infections, contributing to morbidity and eventually mortality. Paradoxically, despite a robust inflammatory response, CF lungs fail to clear bacteria and are susceptible to chronic infections. Impaired mucociliary transport plays a critical role in chronic infection but the immune mechanisms contributing to the adaptation of bacteria to the lung microenvironment is not clear. CFTR modulator therapy has advanced CF life expectancy opening up the need to understand changes in immunity as CF patients age. Here, we have summarized the current understanding of immune dysregulation in CF.

## **Novel Applications of Biomarkers and Personalized Medicine in Cystic Fibrosis** 617

Jennifer S. Guimbellot, David P. Nichols, and John J. Brewington

As routine care in cystic fibrosis (CF) becomes increasingly personalized, new opportunities to further focus care on the individual have emerged. These opportunities are increasingly filled through research in tools aiding drug selection, drug monitoring and titration, disease-relevant biomarkers, and evaluation of therapeutic benefits. Herein, we will discuss such research tools presently being translated into the clinic to improve the personalization of care in CF.

**Emerging Approaches to Monitor and Modify Care in the Era of Cystic Fibrosis Transmembrane Conductance Regulators**

631

Clemente J. Britto, Felix Ratjen, and John P. Clancy

As we characterize the clinical benefits of highly effective modulator therapy (HEMT) in the cystic fibrosis (CF) population, our paradigm for treating and monitoring disease continues to evolve. More sensitive approaches are necessary to detect early disease and clinical progression. This article reviews evolving strategies to assess disease control and progression in the HEMT era. This article also explores developments in pulmonary function monitoring, advanced respiratory imaging, tools for the collection of patient-reported outcomes, and their application to profile individual responses, guide therapeutic decisions, and improve the quality of life of people with CF.

**The Impact of Highly Effective Modulator Therapy on Cystic Fibrosis Microbiology and Inflammation**

647

Lindsay J. Caverly, Sebastián A. Riquelme, and Katherine B. Hisert

Highly effective cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator therapy (HEMT) corrects the underlying molecular defect causing CF disease. HEMT decreases symptom burden and improves clinical metrics and quality of life for most people with CF (PwCF) and eligible *cftr* mutations. Improvements in measures of pulmonary health suggest that restoration of function of defective CFTR anion channels by HEMT not only enhances airway mucociliary clearance, but also reduces chronic pulmonary infection and inflammation. This article reviews the evidence for how HEMT influences the dynamic and interdependent processes of infection and inflammation in the CF airway, and what questions remain unanswered.

**Novel Approaches to Multidrug-Resistant Infections in Cystic Fibrosis**

667

Thomas S. Murray, Gail Stanley, and Jonathan L. Koff

Patients with cystic fibrosis (CF) often develop respiratory tract infections with pathogenic multidrug-resistant organisms (MDROs) such as methicillin-resistant *Staphylococcus aureus*, and a variety of gram-negative organisms that include *Pseudomonas aeruginosa*, *Burkholderia* sp., *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and nontuberculous mycobacteria (NTM). Despite the introduction of new therapies to address underlying cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, MDRO infections remain a problem and novel antimicrobial interventions are still needed. Therapeutic approaches include improving the efficacy of existing drugs by adjusting the dose based on differences in CF patient pharmacokinetics/pharmacodynamics, the development of inhaled formulations to reduce systemic adverse events, and the use of newer beta-lactam/beta-lactamase combinations. Alternative innovative therapeutic approaches include the use of gallium and bacteriophages to treat MDRO pulmonary infections including those with extreme antibiotic resistance. However, additional clinical trials are required to determine the optimal dosing and efficacy of these different strategies and to identify patients with CF most likely to benefit from these new treatment options.

**Update on Clinical Outcomes of Highly Effective Modulator Therapy**

677

Alex H. Gifford, Jennifer L. Taylor-Cousar, Jane C. Davies, and Paul McNally

Based on the cystic fibrosis transmembrane conductance regulator (CFTR) genotype, approximately 90% of people with cystic fibrosis (CF) are candidates for highly effective modulator therapy (HEMT). Clinical trials conducted over the last 11 years have shown that these oral therapies substantially restore CFTR function, leading to improvements in lung function, nutritional status, and health-related quality of life.

Here, we review safety and efficacy data from phase 3 clinical trials and observational studies which support the use of HEMT in most adults and children with CF. We also discuss opportunities for additional investigation in groups underrepresented or excluded from phase 3 clinical trials, and challenges in the evaluation of the safety and efficacy of HEMT at increasingly earlier stages of CFTR-mediated pathophysiology.

## **Nontuberculous Mycobacterial Infections in Cystic Fibrosis**

697

Stacey L. Martiniano, Jerry A. Nick, and Charles L. Daley

Nontuberculous mycobacteria (NTM) are important pathogens, with a longitudinal prevalence of up to 20% within the cystic fibrosis (CF) population. Diagnosis of NTM pulmonary disease in people with CF (pwCF) is challenging, as a majority have NTM infection that is transient or indolent, without evidence of clinical consequence. In addition, the radiographic and clinical manifestations of chronic coinfections with typical CF pathogens can overlap those of NTM, making diagnosis difficult. Comprehensive care of pwCF must be optimized to assess the true clinical impact of NTM and to improve response to treatment. Treatment requires prolonged, multidrug therapy that varies depending on NTM species, resistance pattern, and extent of disease. With a widespread use of highly effective modulator therapy (HEMT), clinical signs and symptoms of NTM disease may be less apparent, and sensitivity of sputum cultures further reduced. The development of a disease-specific approach to the diagnosis and treatment of NTM infection in pwCF is a research priority, as a lifelong strategy is needed for this high-risk population.

## **Non-Modulator Therapies: Developing a Therapy for Every Cystic Fibrosis Patient**

717

Marie E. Egan

Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy brings hope to most patients with cystic fibrosis (CF), but not all. For approximately 12% of CF patients with premature termination codon mutations, large deletions, insertions, and frameshifts, the CFTR modulator therapy is not effective. Many believe that genetic-based therapies such as RNA therapies, DNA therapies, and gene editing technologies will be needed to treat mutations that are not responsive to modulator therapy. Delivery of these therapeutic agents to affected cells is the major challenge that will need to be overcome if we are to harness the power of these emerging therapies for the treatment of CF.

## **Updates in Nutrition Management of Cystic Fibrosis in the Highly Effective Modulator Era**

727

Alexandra Wilson, Kimberly Altman, Terri Schindler, and Sarah Jane Schwarzenberg

Attainment and maintenance of good nutrition has been an important aspect of management in cystic fibrosis (CF) for decades. In the era of highly effective modulator therapy for CF, the quality of the nutrients we recommend is increasingly important. Our therapy must support our patients' health for many years beyond what we previously thought. Preventing cardiovascular disease, reducing hyperlipidemia, and optimizing lean body mass for active, longer lives now join the long-standing goal of promoting lung function through nutrition. This chapter summarizes recent developments in nutrition in people with CF, with an eye to the evolution of our practice.

## **Update in Advancing the Gastrointestinal Frontier in Cystic Fibrosis**

743

Christopher Vélez, Steven D. Freedman, and David N. Assis

Clinical complications of cystic fibrosis (CF) include a variety of gastrointestinal (GI) and hepatobiliary manifestations. Recent years have witnessed several advances in the understanding and management of these complications, in addition to

opportunities for therapeutic innovations. Herein we review the current understanding of these disorders and also discuss the management of the GI and hepatobiliary complications experienced by persons with CF.

### **Transitions of Care in Cystic Fibrosis**

**757**

Eunice M.M. DeFilippo, Jaideep S. Talwalkar, Zachary M. Harris, Jennifer Butcher, and Samya Z. Nasr

The development of formal transition models emerged to reduce variability in care, including cystic fibrosis (CF) responsibility, independence, self-care, and education (RISE), which provides a standardized transition program, including knowledge assessments, self-management checklists, and milestones for people with CF. Despite these interventions, the current landscape of health care transition (HCT) remains sub-optimal, and additional focused attention on HCT is necessary. Standardization of assessment tools to gauge the efficacy of transfer from pediatric to adult care is a high priority. Such tools should incorporate both clinical and patient-centered outcomes to provide a comprehensive picture of progress and deficiencies of the HCT process.

### **Endocrine Complications of Cystic Fibrosis**

**773**

Andrea Kelly, Brynn E. Marks, and Michael S. Stalvey

Endocrine comorbidities have become increasingly important medical considerations as improving cystic fibrosis (CF) care increases life expectancy. Although the underlying pathophysiology of CF-related diabetes remains elusive, the use of novel technologies and therapeutics seeks to improve both CF-related outcomes and quality of life. Improvements in the overall health of those with CF have tempered concerns about pubertal delay and short stature; however, other comorbidities such as hypogonadism and bone disease are increasingly recognized. Following the introduction of highly effective modulator therapies there are many lessons to be learned about their long-term impact on endocrine comorbidities.

### **Management of Mental Health in Cystic Fibrosis**

**791**

Christina Jayne Bathgate, Michelle Hjelm, Stephanie S. Filigno, Beth A. Smith, and Anna M. Georgiopoulos

This article is intended for use among all cystic fibrosis care team members. It covers common mental health concerns and their unique presentations in persons with cystic fibrosis (pwCF) in areas such as depression, anxiety, trauma, behavioral disorders emerging in childhood, sleep, problematic eating patterns, and the impact of substance use. Furthermore, the authors address ways to manage these mental health symptoms through risk assessment, psychological interventions, and/or psychotropic medications. Quick reference tables are provided for evidence-based psychological interventions and medications often used for mental health conditions in pwCF.

### **Family Planning and Reproductive Health in Cystic Fibrosis**

**811**

Lauren N. Meiss, Raksha Jain, and Traci M. Kazmerski

Family planning in cystic fibrosis (CF) is an increasingly important aspect of care, as improvements in care and outcomes lead to a rise in the number of pregnancies and parenthood in people with CF. This article highlights: (1) Health considerations for people with CF related to pregnancy, contraception, and parenthood. (2) Facets of reproductive planning, fertility, and preconception counseling. (3) Relationship-centered reproductive health discussions.

**Update on Lung Transplantation for Cystic Fibrosis****821**

Joseph M. Pilewski

Lung transplantation provides a treatment option for many individuals with advanced lung disease due to cystic fibrosis (CF). Since the first transplants for CF in the 1980s, survival has improved and the opportunity for transplant has expanded to include individuals who previously were not considered candidates for transplant. Criteria to be a transplant candidate vary significantly among transplant programs, highlighting that the engagement in more than one transplant program may be necessary. Individuals with highly resistant CF pathogens, malnutrition, osteoporosis, CF liver disease, and other comorbidities may be suitable candidates for lung transplant, or if needed, multi-organ transplant. The transplant process involves several phases, from discussion of prognosis and referral to a transplant center, to transplant evaluation, to listing, transplant surgery, and care after transplant. While the availability of highly effective CF transmembrane conductance regulator (CFTR) modulators for many individuals with CF has improved lung function and slowed progression to respiratory failure, early discussion regarding transplant as a treatment option and referral to a transplant program are critical to maximizing opportunity and optimizing patient and family experience. The decision to be evaluated for transplant and to list for transplant are distinct, and early referral may provide a treatment option that can be urgently executed if needed. Survival after transplant for CF is improving, to a median survival of approximately 10 years, and most transplant survivors enjoy significant improvement in quality of life.