Cystic Fibrosis

Microbiology and Host Response

Edith T. Zemanick, MD, MSCS[a], Lucas R. Hoffman, MD, PhD[b,*]

KEYWORDS

• Cystic fibrosis • Inflammation • Infection • Microbiology • Neutrophil • Biomarker

KEY POINTS

- Cystic fibrosis (CF) lung disease involves a cycle of mucus obstruction, inflammation, and infection in the airways, and each of these elements affects the others as disease progresses.
- Observations from the earliest studies of CF disease in the 1930s and 1940s showed these elements, but the understanding and treatment of each has evolved over time.
- CF respiratory microbiology has also evolved as new treatments have been introduced, as people have lived longer with this disease, and as detection methods have become more sophisticated.
- The CF airway also shows altered host-defense, and imbalances in the airway environment are important for pathophysiology and may indicate both new treatment directions and useful disease biomarkers.
- Because most information regarding the relationships between infection, inflammation, and disease severity come from observational studies, their causal relationships are not always clear.

INTRODUCTION

The earliest published descriptions of cystic fibrosis (CF) lung disease described the following triad of pathophysiologic elements that still form the basis of most current models:

- Airway obstruction
- Infection
- Inflammation

In her landmark 1938 publication describing the pathologic and clinical features of children who died of this disorder, Dorothy Andersen[1] identified the common features

Disclosure: The authors have nothing to disclose.
[a] Children's Hospital Colorado, University of Colorado School of Medicine, 13123 East 16th Avenue, B-395, Aurora, CO 80045, USA; [b] Departments of Pediatrics and Microbiology, Seattle Children's Hospital and University of Washington, 4800 Sand Point Way Northeast, MS OC.7.720, Seattle, WA 98105, USA
* Corresponding author.
E-mail address: lhoffm@uw.edu

Pediatr Clin N Am 63 (2016) 617–636
http://dx.doi.org/10.1016/j.pcl.2016.04.003 **pediatric.theclinics.com**
0031-3955/16/$ – see front matter

of "bronchitis, bronchiectasis, pulmonary abscesses arising in the bronchi," which were plugged with "tenacious, greenish gray mucopurulent material," and that "*Staphylococcus aureus* was the usual bacteriologic agent."[1,2] From these findings, she and others began treating children with CF with antibiotics targeting *S aureus*, specifically sulfonamides and penicillin.[2] This approach was followed by several important developments. First, the children generally improved clinically. Second, cultures showed that they were increasingly infected with penicillin-resistant *S aureus*, as well as pathogens not seen before antibiotics, including *Pseudomonas aeruginosa*.[3]

These early observations are instructive on many levels. The primary defect that causes CF, mutational dysfunction of the CF transmembrane conductance regulator (CFTR), leads to a cycle in the airways of defective mucus clearance, obstruction, infection, and inflammation. Improvements in nutrition, mucus clearance, and treatment of inflammation and infection have led to dramatic improvements in CF respiratory morbidity and mortality[4]; however, current treatments have not been able to halt disease progression. As patients live increasingly longer, their respiratory microbiology evolves,[4] perhaps driven by elements of care intended to mitigate their lung disease (such as antibiotics and attending clinics at CF care centers). Put differently, the treatments that have so greatly helped people with CF are often followed by microbiological changes, which in turn may alter their clinical course. The causal relationships between specific pathogens, clinical changes, and constantly evolving therapies are difficult to sort out.

Andersen and di Sant'Agnese[2] made special mention of the apparent link between infection and inflammation. Although these are omnipresent features of CF lung disease, the causal relationships between them are controversial. Observations from a variety of studies of patients[5] and, most recently, animals engineered with CFTR mutations[6] have led some investigators to postulate that infection is required for CF airway inflammation, whereas others have suggested that inflammation can precede infection.[7] Although these disputes continue, great progress has been made in defining the mediators and mechanisms driving the intense inflammation within CF airways, identifying not only new candidate therapeutic targets but also promising biomarkers of early disease.

This article reviews the current understanding of the roles of infection and inflammation in CF lung disease pathogenesis. Although these two features of the CF airway are mechanistically linked by data from observational studies and, as a result, in current pathophysiologic models, for simplicity this article considers them separately. Although this article touches on therapeutic approaches to both infection and inflammation, clinicians are currently experiencing a period of particularly rapid evolution in CF treatment strategies and protocols. Therefore, where appropriate, this article refers readers to recent, in-depth reviews of CF therapeutic strategies[8,9] for more information. Similarly, there have been several excellent reviews of CF respiratory microbiology and inflammation in general that readers may find useful.[10–16]

CYSTIC FIBROSIS MICROBIOLOGY

The Evolving Role of Methodology

Dorothy Andersen and her contemporaries identified several important characteristics of CF lung disease. For example, she and others who later built on her work[17–20] noted that the microbes infecting CF lungs were nearly always confined to airway luminal mucus, rather than invading tissue. The role of *S aureus* was highlighted; however, other bacteria were quickly recognized as important CF pathogens. Blending