Cystic Fibrosis: A Successful Model of Transition of Care and Lessons Learned

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15.1 Introduction

Cystic fibrosis (CF) is a life-limiting disease caused by a defect in the functioning of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Dysfunction in this protein leads to a multisystemic disease, leading to lung remodeling, recurrent infection, respiratory failure, pancreatic insufficiency, diabetes, hepatobiliary dysfunction, gastrointestinal obstruction, and reduced fertility. When first described in 1938 by Dr. Dorothy Hansine Andersen, children diagnosed with cystic fibrosis rarely survived beyond early childhood [1]. Today, advances in antimicrobial medicine, protein modulation, and supportive measures allow individuals diagnosed with cystic fibrosis to lead full lives.

15.2 Epidemiology

Cystic fibrosis is the most common autosomal recessive life-limiting disease among individuals of northern European descent. Approximately 1 in 30 Caucasian persons are carriers of dysfunctional CFTR gene, leading to approximately 1 incidence of CF in every 3000 live births [2]. According to the CF Foundation 2018 Annual Data Report, 93% of individuals with CF were White, 5% were African American, 9% were Hispanic, and 4% were other races (answers were not mutually exclusive) (Table 15.1).

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Table 15.1 The Cystic Fibrosis Foundation (CFF) is a large nonprofit organization, which currently supports a network of over 130 accredited CF care centers throughout the United States [3]. As part of this membership, CF care centers contribute information on the health status of their patients to the Cystic Fibrosis Foundation Patient Registry (CFFPR), which is then used to further research, care guidelines, and quality improvement throughout the cystic fibrosis community [3]

CF by the numbers			
	2008	2013	2018
People with CF	25,286	28,030	30,775
Newly diagnosed individuals	1140	1048	852
Detected by newborn screening (%)	43%	60%	62%
Individuals with first CF event at less than 60 days after birth (%)	56%	70%	71%
Mean age at diagnosis for all people with CF	3.6	3.8	4.2
Median age at diagnosis for all people with CF	5	4	3
Mean age (years)	18.9	20.2	22.2
Median age (years)	16.9	17.9	19.8
Adults 18+ years (%)	46%	50%	55%

Data taken from [4]

15.3 Genetics

First identified in 1985, the cystic fibrosis transmembrane conductance regulator protein gene codes for a cAMP-activated ion channel protein mainly expressed in the airway, gastrointestinal tract, sweat glands, and genitourinary system. The CFTR protein serves two main functions through the transport of chloride and bicarb. First, CFTR chloride secretion plays an important role in maintaining hydration along the internal surfaces of tracts within the GI, sinopulmonary, and genitourinary systems. Second, CFTR bicarbonate secretion maintains pH in airway epithelium, which serves an important role in innate immunity [5]. The consequence of a dysfunctional CFTR protein therefore leads to dehydrated, viscous mucus as well as impairments in mucociliary clearance and microbial defense [6].

Although over 2000 mutations to the CFTR protein have been identified, each dysfunction has been grouped into six classes, which roughly correlate to the severity of the phenotypic presentation and are not mutually exclusive [4, 7]. Mutation classes I–III result in an absent or completely dysfunctional CFTR protein, leading to more severe symptomatic presentations of the disease. In contrast, CFTR mutation classes VI–VI result in a partially functional but inefficient protein. F508del is the single most common mutation, with at least one mutation present in 85% of CFFPR participants and a homozygous F508del noted in 44% [4].

15.4 Pathophysiology

Pulmonary System

Lung disease is the main source of morbidity and mortality among individuals with cystic fibrosis [2]. Within the Lung, CFTR dysfunction leads to pH

imbalance, the accumulation of thickened mucus, and an inability to conduct mucociliary clearance [6]. This creates an environment ideal for bacterial growth and propagation while hampering the individual's ability to clear pathogens from the respiratory tree. The immune response to bacterial overgrowth attracts both inflammatory cell products and proteases, which leads to airway wall inflammation. Over time, recurrent cycles of infection and inflammation cause the progressive development of an irreversible bronchiectasis, which further inhibits the body's ability to mitigate new and recurrent lung infections. Ultimately, approximately 90% of patients with cystic fibrosis will die from respiratory failure, unless they receive a lung transplant [7].

Bacterial colonization and infection drives the progression of lung disease in cystic fibrosis. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, MRSA, *Haemophilus influenzae*, *Achromobacter*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia* are the most common bacteria grown for cystic fibrosis airway. *S. aureus* is the most prevalent bacteria in younger individuals; however, *P. aeruginosa* becomes increasingly common as individuals age with worsening bronchiectasis [4] (Fig. 15.1). The mucoid morphotype of *P. aeruginosa*, a pathogenic strain that has uniquely adapted to living in CF airways, is particularly important in chronic CF bronchiectasis. Although relatively avirulent, the chronic inflammatory response caused by mucoid *P. aeruginosa* is disproportionately responsible for lung remodeling with earlier infection correlating with the severity of future lung disease [8, 9]. The presence of nontuberculous mycobacterium (NTM) such as *M. avium complex* and *M. abscessus* has also been associated with a more severe lung disease [10]. Although relatively uncommon a decade ago, the prevalence of reported NTM has dramatically increased in the past decade to approximately 14% among patients with cystic fibrosis [4] (Fig. 15.2).

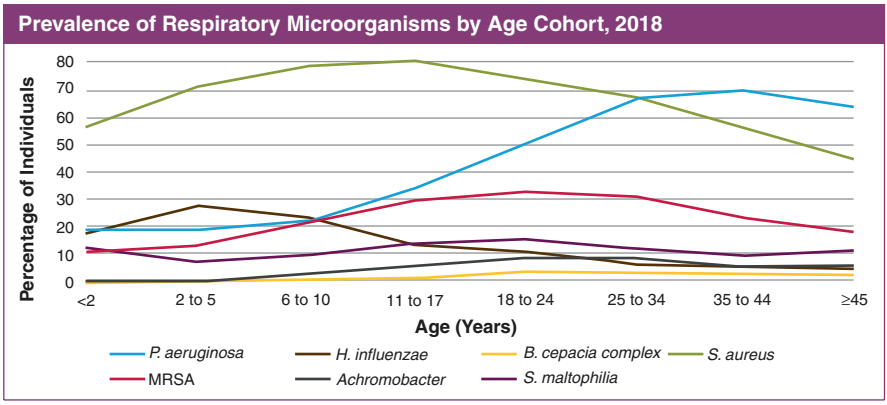

Fig. 15.1 Graph demonstrating the prevalence of specific microorganisms in relation to age cohort in 2018. (Reproduced from reference [4])

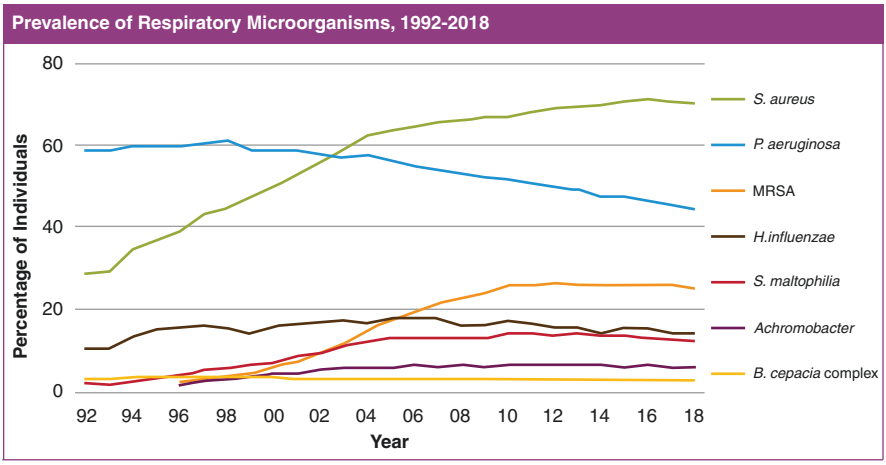

Fig. 15.2 Graph demonstrating the changes in the microbiome in cystic fibrosis patients over the previous 25 years. (Reproduced from reference [4])

Gastrointestinal System

Pancreas

When cystic fibrosis was first described in 1938, severe malnutrition due to pancreatic insufficiency was the main unifying feature of the disease [1]. Dysfunction of the CFTR protein leads to dysfunction in the hydration of secretions within pancreatic ductal lumens. This causes thickened secretions, which cause ductal obstruction, leading to the pooling of exocrine pro-enzymes within the pancreatic ductal network. Over time, local irritation from pro-enzyme accumulation leads to progressive scarring and fibrosis, hampering both the exocrine and endocrine functions of the pancreas [11].

Disruption of the exocrine function of the pancreas leads to malnutrition due to an inability to appropriately digest complex proteins, carbohydrates, and lipids. Although almost all individuals with cystic fibrosis experience some degree of pancreatic dysfunction, overt pancreatic insufficiency is seen in approximately 85% of cases and is associated with the more severe class I–III CFTR genotypes [12].

Endocrine function of the pancreas is primarily manifested as CF-related diabetes (CFRD).

Although CFRD is typically uncommon in children, abnormal glucose tolerance is seen in 40% of patients by 10 years of age [13]. CFRD prevalence rises throughout adolescents with approximately 50% of patients meeting diagnostic criteria as adults [14]. Although adults do not generally die from DKA or macrovascular consequences related to CFRD, the associated hyperglycemia and increased catabolic state caused by diabetes lead to a pathogen-promoting environment that significantly contributes to pulmonary complications of CF [14].

Hepatobiliary

CFTR dysfunction within the bile ducts of the liver leads to scattered areas of decreased bile flow, ductal obstruction, and chemokine upregulation throughout the hepatobiliary tree. These areas of multifocal inflammation can eventually lead to a peribiliary fibrosis described as CF liver disease (CFLD). The continuum of liver disease associated with CFLD includes a progression of focal biliary cirrhosis to multilobular biliary cirrhosis and eventually pulmonary hypertension [11].

Due to the variable dispersion of fibrosis throughout the liver, the diagnosis of CFLD is difficult to make. The most widely accepted definition requires a 12-month period including two or more of the following features: hepatomegaly, abnormal liver function tests, ultrasonic evidence of liver dysfunction, or portal hypertension [15, 16]. Although as many as 40% of individuals with CF demonstrate abnormalities in liver function testing, only 5–10% of patients develop CFLD [12].

Bowel

Within the bowel, chloride and bicarbonate are essential for the formation of the loose, well-hydrated mucus, which assists with conducting stool throughout the GI tract. As a result, CFTR dysfunction leads to the formation of the dense stool associated with meconium ileus, distal intestinal obstruction syndrome (DIOS), and constipation [17, 18].

Meconium ileus occurs when thick, dense meconium physically obstructs the intestinal tract during the neonatal period. Typically occurring on either side of the ileocecal junction, the obstructing meconium leads to proximal small bowel distention, which is complicated by volvulus, ischemic necrosis, perforation, or peritonitis in approximately 50% of cases [12]. Due to its neonatal presentation, meconium ileus is often the first presenting symptom of CF, occurring in approximately 15% of CF births, with very few cases occurring in babies without cystic fibrosis [19]. Although occurring later in life, DIOS also presents as an acute ileocecal obstruction with a similar mechanism to meconium ileus. The risk of DIOS increases with age, with a lifetime prevalence of approximately 15% in adult patients and a high risk for recurrence at approximately 50% [20].

15.5 Reproductive Health

Cystic fibrosis affects the fertility of both men and women, although by different mechanisms. In men, CFTR dysfunction leads to approximately 98% infertility rate due to obstructive azoospermia from a congenital bilateral absence of the vas deferens (CBAVD). In men with CF who are born with the vas deferens intact, alterations in ejaculate pH create an additional hurdle to conception by altering sperm motility [21].

Although women with CF typically have normal reproductive anatomy, reduced CFTR function causes concentrated, thick cervical mucus, which impedes the traversal of sperm in the reproductive tract [21]. In addition, decreased bicarbonate secretion lowers the pH within the uterine cavity, further hampering sperm motility.

Even so, it is estimated that up to 50% of women with cystic fibrosis can conceive a child by natural means [22]. Once conceived, the majority of pregnancies result in a successful birth with conflicting data suggesting a potential increased risk for low birth rate or prematurity correlating with the severity of the mother's lung disease [23, 24].

15.6 Cystic Fibrosis Transitions of Care

Transition Concepts

Healthcare transition is the process of moving an adolescent's healthcare from a pediatric-oriented care setting to an adult-oriented care setting [25, 26]. This includes supporting each young adult through the process of engaging in their own healthcare through transition preparation, the transfer of care, and integration in an adult-oriented healthcare system. During these stages, the young adult gains increasing responsibility for self-care through treatment adherence, communicating with the healthcare team, and maintaining appointments [27]. This educational period begins prior to adolescents and continues until they are able to assume full responsibility for their own care [28].

In contrast, the transfer of care refers to the actual event or series of events through which adolescents move their care from a pediatric model to an adult model of care. The goal of a transition program is to prepare a young adult for the transfer of care and to support the individual with uninterrupted healthcare that is patient centered, developmentally appropriate, flexible, and comprehensive [28].

Why Is Transition Medicine Important to Cystic Fibrosis?

As recently as the 1980s, the life expectancy for an individual diagnosed with cystic fibrosis rarely extended past early adulthood [29]. In the past 40 years, advancements in pharmacology, surgical interventions, healthcare systems, and psychosocial support have led to a steady increase in both the quality of life and the longevity that a person with cystic fibrosis can hope to enjoy. According to Cystic Fibrosis Foundation Registry data, the population of adults with cystic fibrosis first exceeded the population of children with cystic fibrosis in 2014 [30]. This same data set predicts that babies with cystic fibrosis born between 2014 and 2018 will have an average life expectancy of 44 years [31]. As a result, most individuals with cystic fibrosis will require healthcare within an adult-oriented healthcare system at some point in their life.

For many chronic diseases, the beneficial outcomes associated with transition are well known. Although there is limited data on the medical benefits associated with CF transitions, patients within an established CF transition program showed no decline in function during the transfer from pediatric to adult care [32]. Patients and families also consistently report improved healthcare experience when transitioned

appropriately and effectively [33]. In recognition of the importance of facilitating appropriate transitions, the CF Foundation requires an established transition process between pediatric and adult providers in order to obtain accreditation as a cystic fibrosis center [34].

Models of Transition

In 2011, three major primary care organizations (AAP, AAFP, and ACP) produced a joint clinical report updating prior guidelines pertaining to transitions of care for patients with chronic medical conditions. They identified six core elements to a successful transition and suggested a timeline for initiating each step, intended to provide practitioners with a flexible framework for approaching transitions of care in a variety of care settings [35] (Fig. 15.3).

In addition, the Cystic Fibrosis Foundation has mandated that all CFF-accredited cystic fibrosis centers follow one of four models for transition to adult-oriented care (table below) with the expectation that >90% of patients past their 21st birthday will be transferred to an adult program [29] (Table 15.2).

Challenges During Transition

Healthcare transitions are inherently complicated, occurring within the context of other important adolescent milestones including the progression toward independence in social, educational, and financial aspects of life. In addition to these challenges, the several other key complicating barriers commonly experienced by individuals with CF are discussed below.

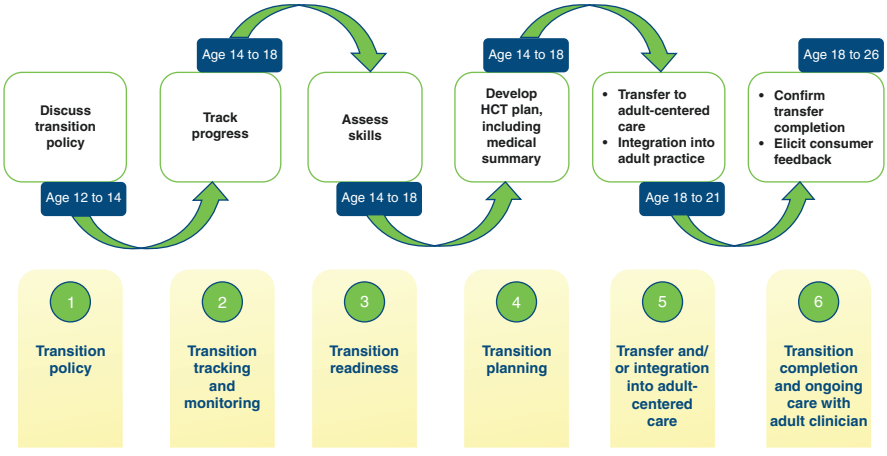

Fig. 15.3 Six core elements to a successful transition in the context of a suggested timeline. (Data taken from reference [35])

Table 15.2 Proposed models of adult CF care by the CF Foundation. (Modified from reference [36])

Models for Adult CF Programs	Primary care provider	CF-specific care provider	Location of outpatient clinic	Role of program director	Inpatient location
1	All adult patients have an adult care PCP	CF care is provided by local CF center team	Adult patients are cohorted to adult specific clinics	Programs with >20 adult patients should identify an adult care provider to attend clinic	Age-appropriate setting is encouraged
2	Adult program physicians provide inpatient and outpatient care to all patients in the adult program	CF-center team has adult experience and routinely interacts with adult program physicians	Outpatient care is provided in adult or pediatric clinics, but adult patients are cohorted	Adult program director should see patients for sick visits and receive telephone calls	Adult hospital or adult inpatient unit
3	Same as for model 2 except there is a separate coordinator for the adult program				
4	Same as for model 2 except there is (1) separate adult team and coordinator and (2) outpatient care is provided in the adult outpatient department				

Complexity of Health History

Remembering and understanding lifelong medical histories with multiorgan complications and the involvement of multiple subspecialty providers is a challenging task for anyone and often leads to significant reliance on parental assistance and a potential for parental dependence. It can especially be difficult for parents to "let go" and allow their children to find their own routines for care [37].

Unclear Responsibilities of Co-managing Providers

The majority of individuals with cystic fibrosis identify their pulmonologist as their "main doctor," even though they have established a primary care provider. However, less than 40% of these individuals reported counseling on sexual health, mental health, tobacco use, alcohol use, or safety from either provider within the past year [38].

Time and Financial Burden of Treatment Regimens

In one survey, individuals with CF reported spending an average of 108 min on treatment activities each day [39].

Financial Stressors

A majority of adolescents with chronic diseases report gaps in their insurance coverage or extended periods without insurance [40]. Medication price has specifically

been noted by adolescents with CF as a significant barrier to adherence to treatment regimens [41].

Social Impact of Illness

Conflicts or perceived threats to relationships with parents, other family members, or friends have been cited as significantly detrimental for medical adherence [37].

Sexual Health Disparity

Adolescent women with CF report a lack of routine counseling regarding sexual and reproductive health [42]. These individuals are also less likely to have ever used contraception or have been tested for STDs when compared to the general population, suggesting potential gaps in sexual healthcare [43]. In addition, many CF providers note significant discomfort or a lack of training in addressing sexual health [44].

Peer Group Limitations

Peer support is noted to be particularly important to adolescents with chronic illness during the process of establishing independence in their healthcare routines [37]. However, opportunities for face-to-face peer interactions are limited in cystic fibrosis due to the risk of transferring resistant organisms among patients. However, many online communities have formed to provide virtual peer-to-peer support.

Additional Resources

Cystic Fibrosis Foundation

A large, well-funded, non-profit organization that supports the cystic fibrosis community while funding research and advancing healthcare related to CF (https://www.cff.org/).

Got Transition/Center for Health Care Transition Improvement

A cooperative agreement between the Maternal and Child Health Bureau and The National Alliance to Advance Adolescent Health focused on improving the transition from pediatric to adult healthcare (https://www.gottransition.org/).

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