Cystic Fibrosis

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Case Presentation

Dillon T., a 19-year-old young man, presents for his initial visit to establish care with an adult primary care physician. Although he plans to attend a Cystic Fibrosis Foundation-accredited care center, he recognizes that he needs a physician closer to home as he lives 3 h away from the nearest cystic fibrosis (CF) center. Dillon was diagnosed with CF shortly after birth secondary to meconium ileus. His sweat chloride test result was 105 mmol/L, and his genotype is homozygous Phe508del. Up until this visit, Dillon was treated by a pediatric pulmonologist for his healthcare. His parents are divorced, and Dillon is cared for by his mother. He has completed high school and will be starting college in the fall close to home but will be living on campus. He is 1 year delayed in his education secondary to multiple hospitalizations that necessitated his starting kindergarten a year late. At that time, he required a percutaneous endoscopic gastrostomy (PEG) tube for supplemental feeding as he was severely underweight. The PEG tube has since been removed, and his weight is improved on oral pancreatic enzyme supplementation.

His past medical history is also significant for a pneumothorax at age 17 years. This required chest tube placement but resolved without further intervention. When he goes to the beach with family and friends, he is self-conscious about the surgical scars on his chest and abdomen.

Dillon is prescribed daily airway clearance therapy consisting of the following inhaled medications via a nebulizer: a short-acting bronchodilator, hypertonic saline (7 %), dornase alpha, and an antipseudomonal antibiotic. He also has a pneumatic oscillating vest (a.k.a. "The Vest"), which he uses for chest physiotherapy. He has a daily cough, worse in the morning upon awakening, which produces yellow/green sputum. He admits to intermittent noncompliance with doing his airway clearance therapy twice daily as prescribed. He says that he is better on school days. He frequently oversleeps and skips treatments when his routine is unstructured on holidays, during the summer, and on the weekends. He is admitted for intravenous (IV) antibiotics once or twice per year for exacerbations of his CF-related bronchiectasis. Sputum cultures have shown methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa,*

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and screening for non-tuberculous mycobacterial respiratory infections has been negative. He takes azithromycin, 500 mg, 3 times per week year round.

He takes pancreatic enzyme replacement therapy with meals to treat exocrine pancreatic insufficiency. Dillon almost never forgets this medication because without pancreatic enzymes, he suffers severe gastrointestinal discomfort and produces oily foul-smelling stools. He has occasionally required osmotic laxatives for constipation. Dillon was also found to have glucose intolerance on an oral glucose tolerance test (OGTT) performed last year. He does not take insulin. He has congenital bilateral absence of the vas deferens (CBAVD). He has had unprotected sex on multiple occasions because he has been told that male CF patients are infertile. He has tried smoking tobacco on a few occasions with his friends but noticed that he suffered dyspneic episodes afterward. He reports occasional alcohol intake but denies binge drinking.

He emphasizes his hope that he will be able to establish with an adult-oriented practice, as his pediatric provider has told him he now needs to start seeing an adult provider. He admits that he was quite apprehensive in making this appointment and has canceled several prior appointments due to anxiety over this transition, as he has been through so much with his pediatrician.

Case Discussion

Dillon has a classic presentation of cystic fibrosis ("Appendix") [1]. He also has the most common genetic cause of CF, two copies of F508del, a deletion of the amino acid phenylalanine at position 508 of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. More than 2000 variations in the CFTR gene have been discovered. Of those, 23 were previously identified by the American College of Medical Genetics as clearly CF-causing (if an individual has one of these mutations on each chromosome inherited from his or her parents, he or she will have CF disease and symptoms).

The remaining 1700 plus mutations vary across a spectrum of CF presentations and symptom manifestations. They may cause CF with a full spectrum of symptoms, CF with variable symptoms, milder forms of CF, or have no effect or association with CF [2]. The clinical spectrum for symptom manifestation in CF ranges from asymptomatic individuals to chronic rhinosinusitis to male infertility to the symptoms classically associated with CF.

The diagnosis of CF is often made soon after birth when there is no meconium passed. As Dillon's case illustrates, abdominal distention, feeding intolerance, and vomiting appear, suggesting a meconium ileus. This is a common initial presentation for patients with CF and occurs in approximately 20 % of newborns that are eventually diagnosed with CF by the sweat chloride test, which is considered the gold standard for diagnosis [3].

Pancreatic dysfunction causes both endocrine and exocrine symptom manifestations in CF patients. Dillon has been diagnosed with CF-related diabetes (CFRD). It is important for primary care physicians to recognize CFRD as the most common comorbidity in people with CF, occurring in $\sim$20 % of adolescents and 40–50 % of adults. Appropriate screening and workup for symptoms related to diabetes presentation should be considered in CF patients [4].

While CFRD shares features of type 1 and type 2 diabetes mellitus, CFRD is a distinct clinical entity. It is primarily caused by insulin insufficiency, although fluctuating levels of insulin resistance related to acute and chronic illness also play a role. Interestingly, there are no documented cases of death from atherosclerotic vascular disease in patients with CFRD, despite the fact that some patients with CFRD now live into their sixth and seventh decades [5].

The diagnosis of CFRD is made by performing an oral glucose tolerance test (OGTT): measurement of fasting glucose followed by a 75 g glucose challenge and a 2-h post-challenge plasma glucose measurement. A plasma glucose $\geq$200 mg/dL is diagnostic of CF-related diabetes. Dillon's glucose tolerance test result was a

glucose level of 285 mg/dL. The hemoglobin A1c (HgA1c) test is not sufficiently sensitive for diagnosis of CFRD and thus should not be used as a screening test. A HgA1C level <6.5 % does not rule out CFRD because this value is often spuriously low in CF patients. However, an HgA1C $\geq$ 6.5 % does confirm the diagnosis of CFRD. Furthermore, a fasting plasma glucose $\geq$ 126 mg/dL will also confirm the diagnosis [5].

Dillon's history is also notable for the presence of a pneumothorax. This complication, along with hemoptysis, is more common among individuals with CF as compared to the general population, and specific guidelines exist for management. It is critical to note that pleurodesis, a therapy used to treat recurrent pneumothorax, may be deferred after a single pneumothorax in CF. Pleurodesis may have a negative effect on future candidacy for lung transplantation, which may be critical for extending Dillon's life expectancy [6].

Dillon is infertile, as are the majority of men with CF. Naturally, men with CF are subject to the same sexually transmitted infections as men without CF and safe sex practices are to be encouraged. If parenthood is desired, genetic counseling is advised and spermatozoa can be surgically harvested by a urologist. Many men with CF elect to have sperm donated instead. Finally, it must be remembered that women with CF remain fertile and may become pregnant without fertility treatment.

Definition, Epidemiology, and Natural History of Cystic Fibrosis

The association between abnormal sweat chloride, salt loss, and illness in children was made in the nineteenth century as shown by the adage, "Woe to the child who tastes salty from a kiss on the brow, for he is cursed and soon must die." In 1938, Dorothy Anderson made the first association between pancreatic disease, lung disease, and intestinal disease. Dr. Anderson called the disease, "cystic fibrosis of the pancreas." She was the first to utilize pancreatic enzyme replacement therapy (PERT) to treat affected children [7].

In 1952, Paul di Sant'Agnese discovered abnormalities in sweat electrolytes that are associated with CF. A sweat test was subsequently developed and improved over the next decade. This test remains in widespread use for establishing the diagnosis of cystic fibrosis. In 1989, Francis Collins, Lap-Chee Tsui, and John R. Riordan discovered the first gene mutation for CF, F508del (see case discussion). The nomenclature for this mutation has evolved from "delta F508" to "F508del" to "Phe508del" with the latter being the most current and accurate terminology.

For a child to be born with CF, one gene with CFTR abnormalities must be inherited from each parent (CF gene homozygous). People carrying one gene for CF are clinically unaffected but carry the risk of passing on this gene to subsequent offspring (CF gene heterozygous). One out of 25 persons of European descent is a carrier for a CF-causing gene mutation. However, abnormalities in the CFTR gene can be found in all races. CF is the most common lethal genetic mutation in persons of European descent [8].

The cystic fibrosis transmembrane conductance regulator (CFTR) is in an epithelial cell surface chloride channel. Changes in CFTR function have the greatest deleterious effects on the respiratory tract and the pancreas in most patients. Cystic fibrosis causes bronchiectasis and CF has become a paradigm for this condition. Bronchiectasis causes airflow obstruction and a chronic productive cough. Most patients who die from complications of CF do so because of respiratory failure.

The life expectancy for patients living with CF has increased dramatically secondary to therapeutic advances in nutrition, pancreatic enzyme replacement therapy, inhaled airway clearance therapy (mucolytics), anti-inflammatory medications, and aggressive use of antibiotic therapy. In 1970, the median predicted survival was 16 years. Today, the median predicted survival is close to 40 years of age. An increase in survival has led to many patients needing to transition their care from pediatric providers to adult physicians including primary care and specialists [9].

Currently, there are approximately 30,000 patients within the United States and 70,000 worldwide living with CF. Most of the patients in the US participate in the CF Foundation's Data Registry. Patient information is collected by CF care centers that are accredited by the CF Foundation (CFF). There are more than 120 CF care centers that form a nationwide network. These centers are held accountable for informing best practices and infection-control guidelines [1].

Medical and Mental Health Assessment

Living with CF creates tremendous psychological, financial, and physical burdens for patients and their families. Patients with CF are aware of their limited life expectancy. The treatments are expensive and time-consuming. Patients are afflicted with chronic cough that may be disruptive to close personal contacts and in group settings such as classrooms. Exacerbations of bronchiectasis are unpredictable and may disrupt planned activities and employment. Extended hospital stays and frequent clinic visits can become part of a hopeless cycle for some. Disease progression often leads to decreased exercise tolerance and inability to complete activities of daily living.

Given the tremendous psycho-social burden this creates, patients with CF are prone to anxiety, depression, and other psychological disorders such as sleep disturbance, substance abuse, and suicide. These issues fluctuate as patients transit from childhood into adolescence and adulthood. Dramatic differences exist between pediatric and adult healthcare systems including physical location, structure, patient responsibilities, and caregiver's mindsets. Physicians should be sure to screen for mental health issues in addition to treating the acute and chronic conditions associated with CF [10].

Care of Cystic Fibrosis and Associated Medical Conditions

Overview

The routine care of cystic fibrosis is best provided by one of the nationwide CF Foundation (CFF) Accredited Care Centers. Many of the medications require experience with prescribing, prior authorization from third-party payers, and specialty pharmacy dispensing. The time and costs involved in the provision of these services would be prohibitive to a clinic that sees an occasional CF patient. The current guidelines for CF-specific care include quarterly clinic visits with submission of sputum samples for analysis via specialized CF culture. Pulmonary function testing is recommended twice yearly. All accredited CF care centers have multidisciplinary care teams that include social workers, dietitians, respiratory therapists, and clinical coordinators. Another key service delivered by accredited CF centers includes the collection of data, which is submitted to the CF Foundation Registry. This is a valuable resource for tracking the CF population as a whole, leading to improved clinical care delivery and population health management.

The development of the care center network by the CFF occurred in the early 1960s. These centers were established to ensure the rapid adoption of new CF therapies and developments by providers to maximize care for CF patients. In addition to providing care, these centers serve as a focus for CF clinical trials, where new CF therapeutics are first introduced. It is in the best interest of patients with CF to be seen regularly at CFF-accredited care centers [11].

Primary care physicians (PCPs) play an important role in the lives of patients with CF. Even medium to large CF care centers do not have daily clinics. As mentioned, some patients live far from CF care centers. Since many of the CF care needs are chronic and recurring, a simple

Table 8.1 Fundamentals of chronic cystic fibrosis therapy

Airway clearance	Antimicrobials	Nutrition	CFTR modulation
Physical vibration • Manual percussion • Oscillating vest • Flutter valve • Vigorous exercise	• Nebulized tobramycin (alternate months) • Aztreonam lysine • Colistimethate (less common)	• High-caloric/high-salt diet • Fat-soluble vitamin supplementation (A, D, E, and K)	Genotype-specific oral medications • Ivacaftor • Lumacaftor/ivacaftor
Surface hydration • Inhaled hypertonic saline	• Oral azithromycin (anti-inflammatory)		
Mucolysis • Dornase alfa	• Aggressive antibiotic therapy for exacerbations		

Modified with permission from Boyle [12]
Not all patients will perform all therapies listed. Treatments are individualized

clinic visit may be able to address problems early and prevent hospitalization (Table 8.1) [12]. Some examples would be helping with adherence issues, treating minor gastrointestinal disturbances such as constipation, and initiating oral antibiotics for mild exacerbations.

Respiratory System

In CF, the respiratory tract secretions lining the airways are thicker than normal. Thus, the name "mucoviscidosis" is more descriptive of the underlying pathophysiology of CF. Most current therapies are aimed at mobilizing the thick airway secretions and decreasing the overgrowth of characteristic bacteria. A typical CF airway clearance regimen starts with a bronchodilator. All patients with bronchiectasis have airflow obstruction and the current thinking is that subsequent therapies are most effective if they are preceded by a bronchodilator such as albuterol.

Following administration of a bronchodilator, 4 mL of 7 % hypertonic saline is inhaled by nebulization. This agent is inexpensive and is an effective way of drawing water from the lung interstitium into the surface layer of the airway. This will decrease the viscosity and allow easier expectoration of secretions by the patient. Current guidelines recommend hypertonic saline twice daily. Some patients find this therapy highly effective and utilize it more frequently. Nebulized hypertonic saline twice daily has been shown to decrease the frequency of exacerbations and improve pulmonary function in terms of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) [13]. Unfortunately, a small number of patients do not tolerate 7 % hypertonic saline because of bronchospasm or cough.

Most patients with CF take a mucolytic agent: dornase alfa. This nebulized enzymatic solution cleaves the long nucleic acid chains that accumulate in the mucosal layer from lysed neutrophils found in purulent sputum. It is taken once or twice daily. Combining medications is not advisable because it dilutes the concentration of the solutions and decreases effectiveness. Unlike hypertonic saline, dornase alpha is not associated with bronchospasm.

All patients with CF should participate in some form of vigorous exercise. This not only helps mobilize respiratory secretions, but also helps to strengthen the overall musculature leading to increased efficiency of the cough. Patients with CF experience all of the benefits of

exercise that non-CF patients experience and this should be encouraged at all clinical encounters.

Many patients with CF, however, do not exercise regularly. Alternative airway clearance therapies are frequently used. These include high-frequency pneumatic chest wall oscillation devices (such as "The Vest"); Acapella (flutter) valves, which create a vibrating column of air upon forceful exhalation; and manual chest physical therapy. All of these modalities seek to apply vibrating energy to the airways to help mobilize secretions for expectoration.

Following the aforementioned airway clearance techniques, patients with pseudomonas colonization often take a nebulized antipseudomonal antibiotic. Currently, there are commercially available nebulized forms of tobramycin and aztreonam in widespread use among CF patients. Specialized pharmacies may create nebulized forms of colistin and amikacin, although these are less commonly used. Nebulized antibiotics are taken after hypertonic saline and dornase alfa.

Since bronchiectasis is an obstructive disease, many patients with CF also take asthma medications such as long-acting beta-agonists and inhaled corticosteroids. Making a distinction between the obstruction of asthma and the obstruction of bronchiectasis may be difficult and may only be a matter of semantics, as the treatments for airflow obstruction are the same in both conditions [14]. Patients are encouraged to take their inhaled medications in the following order: bronchodilator, hypertonic saline/dornase alfa, inhaled antibiotics, and long-acting beta-agonists/inhaled corticosteroids (if being prescribed).

Gastrointestinal System

The gastrointestinal system can be severely affected despite the use of pancreatic enzyme replacement therapy. Patients may suffer from mild to severe functional bowel disorders and from mild to severe liver cirrhosis.

Adult patients with CF have frequent episodes of diarrhea alternating with constipation and/or the distal intestinal obstruction syndrome (DIOS). Constipation refers to the inability to evacuate the colon, whereas DIOS refers to the inability to evacuate the distal small intestine. Both constipation and DIOS may require hospitalization for IV fluids, nasogastric suctioning, anti-emetics, pain control, and aggressive use of osmotic cathartic agents such as polyethylene glycol to help relieve bowel obstruction.

When CF patients present with acute abdominal pain, physicians must consider a broad differential diagnosis, which includes complications such as intussusception. As with the general population, gallbladder disease and acute appendicitis are common causes of acute abdominal symptoms that should be considered.

The complications from cirrhosis are similar to the complications from other causes of chronic liver disease and include the complications of portal hypertension: esophageal varices, splenomegaly, thrombocytopenia, and gastrointestinal bleeding.

As patients with cystic fibrosis live into their fourth and fifth decade, there is a significantly increased incidence of gastrointestinal malignancies. Although there are no established guidelines, screening for gastrointestinal cancer starts at an earlier age in patients with CF. Many CF centers are now affiliated with gastroenterologists with specialized training and experience with CF to assist in managing CF-related gastrointestinal symptoms.

Endocrine System

The incidence of CF-related diabetes increases with age, as was previously reviewed in the case discussion. CF-related diabetes occurs when patients can no longer produce enough insulin to meet the metabolic demands of a large meal. CFRD should not be confused with type 1 diabetes mellitus. Unlike type 1 diabetics, most CF patients with diabetes can still produce insulin at a basal rate. Consequently, CF patients rarely experience diabetic ketoacidosis (DKA). If a CF patient presents with DKA, one should suspect coexisting type 1 diabetes mellitus.

CF-related diabetes is also different from type 2 diabetes mellitus. Patients with CF often suffer

with protein–calorie malnutrition, so there is no insulin resistance as is seen in type 2 diabetes mellitus. Therefore, patients with CF-related diabetes should not be restricted calorically as one would in the treatment of type 2 diabetes mellitus. In fact, a cornerstone of CF care is encouraging and promoting a high calorie/high protein diet. Most CF patients benefit from some form of caloric and nutritional medical food supplementation. Additionally, their diets should be supplemented with the fat-soluble vitamins (A, D, E, and K) due to malabsorption of these vitamins secondary to pancreatic insufficiency.

The treatment of CF-related diabetes starts with moderate aerobic exercise. Pharmacologic treatment consists of insulin therapy. Oral hypoglycemic agents should not be used in CF-related diabetes, as they are not as effective as insulin in improving nutritional and metabolic outcomes [15].

Patients with CF are also at increased risk for reduced bone mineral density, with some studies suggesting 50–75 % of adults with CF have low bone density and increased rates of fractures [16]. Several factors likely contribute to this risk including glucocorticoid therapy, malabsorption of vitamin D, physical inactivity, and poor nutritional status [16]. PCPs can play a vital role in disease prevention by assisting patients in the prevention and treatment of these risk factors.

Acute Care

Unfortunately, since CF is a relatively rare disease, CF care centers often have ambulatory sessions only a few days per week and do not always have availability on the days when patients need to seek acute care. Patients with CF are subject to many of the same acute medical issues as people without CF. They need many of the same medical services that do not require specialized CF knowledge or treatment including preventive healthcare. Some examples include routine immunizations, testing for influenza, routine gynecologic care, and symptomatic treatment for acute medical issues. Ideally, a primary care physician would have an open communication access to a CF care center. It is also optimal for patients to be established with providers in the local healthcare system before needing acute interventions, as CF patients often have complicated medical histories and physical exam findings.

Transplant Evaluation

When patients with CF no longer experience clinical improvement with IV antibiotics, become oxygen-dependent, and have FEV_1 measurements less than 30–35 % of predicted, lung transplantation has become an option for those who meet transplant criteria. These criteria include an adequate social support system to ensure follow-up after hospital discharge. Certain infections, notably *Mycobacterium abscessus* and *Burkholderia cenocepacia,* are contraindications to lung transplantation, as patients tend to have much worse outcomes if these infections are present before transplantation. When patients undergo lung transplantation, they typically transfer care from CF specialists at CF centers to specialists at the lung transplant centers. These patients will still benefit from local established primary, preventive, and acute care management, as the distance from their transplant center may be similar to that from the CF center of care.

Primary and Preventive Care

Persons living with CF are subject to the same non-CF issues as the general population. Having a non-CF specialist general physician can be a valuable asset to the patient and a rewarding collaboration for the physician. Patients who are located greater distances from CF centers often have the greatest need to find local primary care providers and non-CF specialists.

Substance Abuse

The psychological burden of the disease is great, and persons with CF are susceptible to forming

destructive dependencies on alcohol, sedatives, and analgesic drugs.[1] The same defense and denial mechanisms may occur as in the non-CF population. Thus, detecting illicit substance abuse and dependency requires a high level of suspicion. Irregular behaviors, difficulty answering and returning phone calls, noncompliance with medication regimens, complaints of sleep disturbances, or missed appointments may provide early clues to substance abuse issues. Avoidance of tobacco use is critical to CF patients given the impact of tobacco smoke on the pulmonary system in these patients.

Medication Management

CF centers are best suited to help patients manage the specialty medications and interventions used for cystic fibrosis. These include dornase alfa, nebulized antibiotics, pneumatic compression devices, and new classes of medication that actually modify and improve the function of CFTR at the cellular level (e.g., ivacaftor and lumacaftor). These new medications may only be prescribed by CF specialists and require prior authorization from third-party payers. However, the regimen does not change frequently and primary physicians are well-suited to reinforce adherence to high calorie/high protein diet exercise, and airway clearance therapy. Primary care providers can play a critical role in reinforcing the need for medication compliance.

Reproductive Health

In general, men with cystic fibrosis are infertile, with rates estimated at 95 % [17]. The abnormal CFTR gene causes absence of the vas deferens during development. Women, on the other hand, remain fertile and must be counseled on appropriate prophylaxis if pregnancy is not desired. Men who desire children may have sperm harvested by a specialty urologist. Many patients seek assisted reproduction and utilize sperm donation. Adolescents and young adults need counseling on safe sex practices even though the chance of pregnancy is low for male CF patients. Female CF patients are considered high-risk pregnancies and often require care by a high-risk obstetrician [18].

Palliative Care

End-of-life care is individualized. Some patients are not eligible or choose not to undergo lung transplant evaluation. This process is best managed by the physician with the best rapport with the patient and family. This may be the CF multidisciplinary team, though the primary care provider may also be suited for engaging in this discussion. When cystic fibrosis progresses to respiratory failure and mechanical ventilation, the prognosis is uniformly poor. Patients with cystic fibrosis rarely recover from respiratory failure requiring mechanical ventilation. Thus, advance planning may prevent days on mechanical ventilation that create anxiety and discomfort for the patient and the family.

Coordinated Care with Cystic Fibrosis Specialists

Although a majority of the routine care can be handled by local physicians, there will be times when clinical conditions arise that necessitate specialty care by physicians trained in CF. Pulmonary complications of CF including bronchiectasis, hemoptysis, and pneumothoraces are life-threatening emergencies that require prompt attention by specialists. Hemoptysis and pneumothorax occur with greater frequency in the patients with CF as compared to the general population.

Bronchiectasis

Patients with CF are prone to frequent exacerbations of bronchiectasis, and these episodes are best treated in care centers with experience

[1]Ross Klingsberg's personal observation.

treating CF. Exacerbations may occur several times per year in the most severely affected patients. Conversely, some patients with CF rarely experience exacerbations. The frequency of exacerbations increases as the disease progresses. Based upon clinical trials and collective experience of experienced CF care physicians, exacerbations are best treated as aggressively as possible as soon as they are recognized. This usually includes either oral antibiotics for mild exacerbations or IV antibiotics for moderate to severe exacerbations. The choice of antibiotic should be based upon the CF respiratory cultures and on the previous antibiotic history of the patient.

When a person with CF presents with acute symptoms of increased productive cough, fatigue, lassitude, and weight loss, physicians not familiar with CF may erroneously attribute symptoms to "bronchitis." Indeed, the chest radiograph may be unchanged, but the loss of lung function that occurs during CF exacerbations may not be recovered unless aggressive treatment regimens are initiated early in the exacerbation.

The determination of when to treat for an exacerbation of cystic fibrosis is a clinical judgment. When symptoms are mild, oral antibiotics may be used at the highest dose tolerable by the patient. A typical regimen for a mild exacerbation in a patient with pseudomonas and MRSA includes ciprofloxacin 750 mg 2 or 3 times daily and trimethoprim/sulfamethoxazole (double strength) 2 or 3 times daily.

Many patients experience exacerbations and more rapid declines in lung function because of lapses in their CF airway clearance regimen. Consequently, reinstitution of airway clearance is a priority during exacerbations, as this is a "teachable moment." Experienced CF providers will observe this phenomenon frequently. Patients drift away from their daily routine of airway clearance and their lung function declines precipitously. Unfortunately, not all decreases in lung function are reversible and so a lifelong program of adherence to airway clearance therapy must be continually, but tactfully, reinforced.

Hemoptysis

For some patients, hemoptysis may occur daily and thus not require acute evaluation. However, when hemoptysis is noted for the first time or increases in severity, it may be associated with an exacerbation of bronchiectasis. Hemoptysis is characterized as either mild/moderate or severe/massive. This distinction is based upon the volume of blood expectorated. As a general rule, any hemoptysis greater than a cup (approximately 8 oz or 240 mL) constitutes "massive" hemoptysis. Massive hemoptysis should be managed in an acute hospital setting with access to interventional radiology.

There are no clear guidelines for the management of hemoptysis. However, expert opinion is that hypertonic saline and dornase alfa should be discontinued in the setting of massive hemoptysis. Bronchoscopy adds little to the acute evaluation and should not be performed routinely. Bronchial arterial imaging in the form of bronchial arterial computed tomography (CT) angiogram is often requested, as it may help the radiologist locate the bleeding vessel. This test requires special coordination with the radiologist, as the timing of contrast administration is different from the timing of contrast administration for a pulmonary artery imaging study.

When hemoptysis continues or escalates despite antibiotic treatment and cessation of hypertonic saline and dornase alfa, bronchial artery embolization should be considered. The most serious complication of this procedure is inadvertent embolization of an anatomical variant spinal-penetrating arterial branch of the bronchial artery. When this variant is present, embolization can lead to irreversible lower extremity paralysis. The bronchial arterial imaging study can aid in identifying this variant.

Pneumothorax

Pneumothorax is encountered less frequently than hemoptysis. Small pneumothoraces in

clinically stable patients may be observed for resolution but large pneumothoraces require tube thoracostomy for evacuation. Positive pressure ventilation should be avoided during episodes of pneumothorax. Recurrent pneumothoraces are sometimes referred for pleurodesis. However, in patients with advanced lung disease (FEV1 <40 % of predicted) and large pneumothorax, pleurodesis should be deferred until an evaluation for lung transplantation has been performed. Pleurodesis can make removal of the diseased lung prohibitive during the lung transplant procedure.

Transition Care Management of Cystic Fibrosis Patients

The transition from pediatric to adult medicine can be a stressful time for people with CF and their families. Adult healthcare systems have significant differences in patient care delivery compared with pediatric systems of care, with one of the most significant differences being in care management responsibility. Pediatric systems of care often focus on the parents as the primary focus for healthcare education and care management. Adult healthcare system providers often assume, sometimes incorrectly, that the adult patient is capable of managing their own healthcare independently. The transition process will vary from person to person. Some patients are ready to assume personal responsibility for their care and well-being when they reach age 18 or 19 years, while others are not. Caregivers should keep in mind that maintaining and refilling a long list of medications, keeping follow-up appointments every 3 months, and addressing payment are extremely time-consuming tasks for parents and patients. Some individuals rise to the challenge of independence earlier while others need more help. Many adolescents and young adults have adapted to the "sick role," as their care may have led to extended hospital stays where extra attention and special gifts/care are bestowed upon them. It can be extremely challenging at times for adolescents to transit from this system where they may be coddled, to their own detriment, to a system that they may perceive as uncaring and indifferent.

Pediatricians often arbitrarily develop their own criteria for transitioning their patients to adult care. Some use a specific age cutoff, some wait for the first year of college to conclude, some wait for an acute illness and transition when the patient presents to an emergency room, and some transition after the patient becomes sexually active. Once a pediatrician transitions a patient, they often will never see them again. The transition can be emotionally traumatic for some patients as they may have come to trust and rely on a specific physician for nearly 20 years and often through very serious illnesses. This transition can also be difficult for pediatric care providers as they may have developed special bonds with patients and their families over many years. They may have seen these patients through life-challenging events and share concerns that adult healthcare providers may not exhibit the same depth of understanding regarding their patient's issues as they do. Optimal transitions should be planned and occur during times of well-being in the chronic disease process if at all possible and should be viewed as a well-coordinated process rather than as an event. The stress of transition during a sudden acute medical issue can lead to unnecessary stress for the patient and their family [19].

A particular time of concern is the first year of college for those patients who attend. During the first year of immersion in campus life, CF patients often decrease their adherence to therapy. A therapeutic alliance with providers and patience on the part of providers and caregivers are critical in helping the young adult navigate this difficult life change. Treatment adherence usually improves after the first year of college, once daily routines are established.

To better plan for transition, the pediatric team and parents may begin teaching the responsibility for obtaining medications, adherence, and follow-up to the patient as the patient approaches their teenage years. As a patient approaches the transition to adult medicine, the adult and pediatric teams should meet and discuss the particular needs of each patient. There should be a clear plan prior

to the last pediatric visit that delineates the adult physician who will assume care for the person with CF. When the transition occurs smoothly, some of the lapses in treatment can be averted.

Many physicians involved in the care of patients diagnosed with a chronic disease of childhood advocate that transition should begin at diagnosis. Understandably, physical transition will be deferred until the clinically appropriate time. However, early discussions about the process of transitioning to an adult healthcare system help to assure successful experiences and outcomes. In some centers, adult health care providers will meet with parents and pediatric patients during their initial pediatric visits to initiate the concept that a transition plan will need to be enacted at the appropriate time. Care of adolescents and adult CF patients requires a CF-trained specialist. However, the best patient-centered outcomes include the care and input from a multidisciplinary team that will include non-CF-trained physicians in addition to CF care centers.

Conclusion

The progress made to prolong and improve the lives of patients with CF is one of the great success stories of modern medicine. However, with a current life expectancy of around 40 years and with time-consuming and costly therapies that fall far short of a cure, there is much work to be done for this vulnerable and dependent population. Thus, there is an important role for primary care physicians who are part of a care team and can recognize acute situations that require more urgent specialist involvement. What is more, PCPs play vital roles in the lives of people with CF and support both patient and family while increasing patient independence both medically and socially. Caring for patients with CF can be among the most rewarding of doctor–patient relationships.

Appendix

Cystic fibrosis (CF) fact sheet	
Definition and symptoms	**Cystic fibrosis (CF) is an inherited lifelong condition characterized by** • Inherited abnormalities in the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial cell membrane protein and chloride channel • Abnormal CFTR protein disrupts chloride transport and water movement across secretory epithelial membranes • Thick (viscous) mucus buildup in the lungs, pancreas, and other organs • Bronchiectasis (persistent lung infections and progressive obstructive airway disease) • Persistent coughing, at times with phlegm • Hemoptysis and pneumothorax • Exocrine pancreatic enzyme insufficiency with poor growth or weight gain in spite of good appetite • Frequent greasy, bulky stools or difficulty with bowel movements • Male (not female) infertility • Very salty-tasting skin
Prevalence	In the United States • About 30,000 people are living with cystic fibrosis (70,000 worldwide) • Approximately 1000 new cases of CF are diagnosed each year • More than 75 % of people with CF are diagnosed by age 2 years • Nearly half of the CF population is age 18 or older • Predicted median survival: 39.3 years
Genetics and epidemiology	Epidemiology • CF is the most common disorder of autosomal recessive inheritance in Caucasians

(continued)

	• In general, it occurs in 1/3000 Caucasian, 1/6000 Hispanic, 1/10,000 African-American, and 1/90,000 Asian-American births Genetics: • More than 2000 mutations in the CFTR gene have been identified • The most common CF-causing mutation is Phe508del • The most common CF-causing genes are screened for at birth • People with only one copy of the defective CF gene are called carriers, but they do not have the disease. Each time two CF carriers have a child, the chances are – 25 % (1 in 4) the offspring will have CF – 50 % (1 in 2) the offspring will be a carrier but will not have CF – 25 % (1 in 4) the offspring will not be a carrier and will not have CF
Characteristics of adults with CF 18 years and older	• 7 % Masters/Doctoral Level Degree • 28.8 % College Graduate • 33 % Some College • 24.2 % High School Diploma • 41.2 % Married/Co-habitating • 35.3 % Full-time employment • 99.2 % have Medical Insurance • Phe508del homozygotes—46.4 % of CF population • Phe508del heterozygotes—40.1 % of CF population
Associated conditions	Individuals with cystic fibrosis have high rates of comorbid physical and mental health conditions, including • Bronchiectasis • Airway colonization and chronic infections with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Burkholderia* spp. • Allergic bronchopulmonary aspergillosis • Non-tuberculous mycobacterial infection • Exocrine pancreatic insufficiency • CF-related diabetes • Fat-soluble vitamin (A, D, E, and K) deficiency • Osteopenia/Osteoporosis • Male infertility • Hepatobiliary disease (cirrhosis, gallstones, biliary disease) • Pancreatitis • Intestinal obstruction, intussusception • Chronic pain • Depression, anxiety, substance abuse, and suicide
Challenges in transition	• Learning to manage time, finances, housing, employment, education, medication, and frequent physician visits • Challenges impacting the transition to adulthood include – Parental educational and financial status – Proximity to specialized CF care centers – Financial burden of medications and inability to work due to illness – Unpredictable nature of exacerbations requiring intensification of care and usually IV antibiotics and disruption of usual activities – Reluctance on part of patient and parents/caregivers as well as pediatric providers to initiate transition – Difficulty identifying adult generalist willing to accept patient into practice

Adapted from Cystic Fibrosis Patient Registry Annual Data Report 2014 [1]

References

1. Cystic Fibrosis Foundation. Cystic Fibrosis Patient Registry Annual Data Report 2014. https://www.cff.org/2014_CFF_Annual_Data_Report_to_the_Center_Directors.pdf.
2. United States Cystic Fibrosis Foundation, Johns Hopkins University, The Hospital for Sick Children. Clinical and functional translation of CFTR. 2011. www.cftr2.org.
3. Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: cystic fibrosis foundation consensus report. J Pediatr. 2008;153(2):S4–14.
4. Moran A, Dunitz J, Nathan B, Saeed A, Lolme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. 2009;32(9):1626–31.
5. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes. Diabetes Care. 2010;33(12):2697–708.
6. Flume PA, Mogayzel PJ, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC. Cystic fibrosis pulmonary guidelines. Pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care Med. 2010;182(3):298–306.
7. Anderson DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. Am J Dis Child. 1938;56(2):344–99.
8. Tobias E, Connor M, Ferguson-Smith M. Ch 15. Strong family history—typical Mendelian disease. In: Tobias ES, editor. Essential medical genetics, 6E. New Jersey. USA: Wiley; 2011. p. 312.
9. MacKenzie T, Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, Marshall BC. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the cystic fibrosis foundation patient registry. Ann Intern Med. 2014;161(4):233–41.
10. Quittner AL, Abbott J, Georgiopoulos AM, Goldbeck l, Smith B, Hempstead SE, et al. International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. Thorax. 2016;71(1):26–34.
11. Beall RJ. The cystic fibrosis foundation. In: Yankaskas JR, Knowles MR, editors. Cystic fibrosis in adults. Riverwoods. IL. USA: Walters Kluwer Publishers; 1999. p. 477–84.
12. Boyle MP. Adult cystic fibrosis. JAMA. 2007;298(15):1787–93.
13. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med. 2006;354(3):241–50.
14. Flume PA, Robinson KA, O'Sullivan BP, Finder JD, Vender RL, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care. 2009;54(4):522–37.
15. Moran A, Dunitz J, Nathan B, Saeed A, Lolme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. 2009;32(9):1626–31.
16. Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, et al. Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab. 2005;90(3):1888–96.
17. Popli K, Stewart J. Infertility and its management in men with cystic fibrosis: review of literature and clinical practices in the UK. Hum Fertil (Camb). 2007;10(4):217–21.
18. Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care. Chest. 2004;125(1 Suppl):1S–39S.
19. Okumur MJ, Kleinhenz ME. Cystic fibrosis transitions of care: lessons learned and future directions for cystic fibrosis. Clin Chest Med. 2016;37(1):119–26.