Diagnosis of Adult Patients with Cystic Fibrosis

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KEYWORDS

• Cystic fibrosis • Diagnosis • Adult • Bronchiectasis • Genotype

KEY POINTS

- Cystic fibrosis (CF) diagnosed in adulthood typically occurs because of the presence of a residual function (milder) mutation combined with a more severe mutation.
- The phenotype associated with an adult diagnosis is usually milder and limited to fewer organs at the time of presentation.
- The diagnosis is based on identification of CF transmembrane receptor (the gene responsible for CF) dysfunction in the presence of characteristic clinical features of the disease.
- Often the diagnosis is inconclusive at the time of initial evaluation, and may depend on clinical judgment supported by ancillary testing.
- With age, adult diagnosed patients can develop severe bronchiectasis and all features of the classic disease.

NATURE OF THE PROBLEM

Cystic fibrosis (CF) is a disease that is nearly always diagnosed in early childhood.[1] As newborn screening (NBS) has gradually been adopted by all 50 states, the 2013 Cystic Fibrosis Foundation (CFF) Patient Registry reports that 62% of patients are now diagnosed at birth, and 72.4% within the first year of life.[1] However, since the discovery of the genetic basis for CF in 1989, major advances have been made in understanding the potential for variability in the clinical phenotype and onset of symptoms. Thus, although diagnosis by NBS is becoming more common, the diagnosis of CF in adults has also increased.[2] Adults constituted 7.7% of new diagnoses between 1995 and 2000, and 9.0% between 2001 and 2005.[2] As a result, the subpopulation of patients enrolled in the CFF registry diagnosed after the age of 18 years has increased from only 2.8% in 1982 to 4.1% in 2002, and to 7% in 2013.[1,3] This value almost certainly underestimates the number of adult-diagnosed patients with CF in the United States, because less than half attend CF care centers.[4] This increase in incidence is likely caused by a combination of factors, including greater awareness by physicians and the public, widespread availability of CF transmembrane receptor (*CFTR*) mutation testing, and more straightforward diagnostic criteria.[5] Although previously the adult diagnosis was often viewed as a medical curiosity or a missed diagnosis of a childhood disease, it is now understood that it often results from *CFTR* mutations with residual function, resulting in both delayed onset and lesser disease severity.

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Although both scenarios can be challenging, the diagnosis of CF in adults differs fundamentally from the diagnosis prompted by NBS. Most newborns are asymptomatic,[1] and physicians must reconcile the abnormal test result with the apparent lack of a clinical phenotype. In contrast, adult patients present with a clinical phenotype, and the role of the physician is to guide diagnostic testing to prove or disprove the presence of CF. Nearly always the newborn diagnosis is extremely distressing to the family. In contrast, the adult diagnosis is often sought by the patient and is met with a sense of relief, because it may come following years of medical consultations for a variety of symptoms, and allows access to a unified and evidence-based approach to care. However, knowledge of the pathophysiology of CF is incomplete and frequently the adult CF diagnosis remains challenging and inconclusive. This article reviews the criteria used to establish the diagnosis of CF in adults and highlights unique aspects of the genotype and phenotype, with special emphasis on clinical features that lead to diagnosis in these patients.

DIAGNOSTIC CRITERIA

Current diagnostic criteria for CF in the United States follows consensus guidelines developed by the CFF in 2008 (**Box 1**).[5] When applied to adults, all patients must have 1 or more symptoms of CF (**Box 2**) combined with evidence of CFTR dysfunction, through sweat testing and/or genotype analysis. Despite its apparent simplicity, application of the criteria is sometimes difficult in the clinical care setting. Available tests for CFTR dysfunction are imperfect, and the list of phenotypic features consistent with the disease is broad and nonspecific (discussed later).

Sweat Chloride Testing

Evidence of CFTR dysfunction is derived primarily through sweat chloride testing. Acceptable methods and techniques for this test have been reviewed elsewhere,[6] and it is recommended that it is performed by laboratories associated with CF care centers. Sweat chloride analysis was developed primarily for infants, and is less sensitive and specific in adults.[5] It is now well recognized that patients with sweat chloride levels less than the diagnostic threshold of 60 mmol/L can develop CF,[5,7–9] and this is most commonly seen when the age of diagnosis is less than 18 years.[2] In our experience, a diagnosis of CF is unlikely with a chloride level less than 30 mmol/L, which is the lower limit of the established indeterminate range. When collecting sweat for testing from older individuals, clinicians should be careful to determine whether an adequate volume of sweat was collected to help ensure the reliability of the chloride level.

Cystic Fibrosis Transmembrane Receptor Genotype Analysis

CFTR is the gene responsible for CF. As with sweat chloride testing, analysis of the *CFTR* genotype can be inconclusive for a variety of reasons. In the CFF registry, 86.4% of the population has at least 1 copy of F508del and 46.5% are F508del homozygotes.[1] However, a vast array of molecular abnormalities have been detected within *CFTR*, and often the less common mutations are those that afford residual CFTR function, which are linked to the less severe phenotype typical of the adult diagnosis.[10] Although F508del is the most common allele in adult-diagnosed cohorts,[2,11–13] these patients often have a genotype that includes 1 or more class IV to VI mutations or an unidentified genetic abnormality.[2,12–18] In rare cases, a severe genotype, including homozygote F508del, is identified in a patient diagnosed as an adult,[10,12,13,19] which likely reflects the contribution of a growing list of genetic modifiers of CF.[20–24] Other genetic abnormalities of *CFTR* may contribute to the presentation of the milder

Box 1
Diagnostic criteria for CF in adulthood

*Presence of symptoms of CF (see **Box 2**) or a family history*

And 1 of the following:

- Sweat chloride value greater than or equal to 60 mmol/L
- Two identified CF-causing mutations
- Sweat chloride value 40 to 59 mmol/L with no or 1 CF-causing mutation, but with family history and/or ancillary testing and clinical presentation strongly suggestive of CF.

Adapted from Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr 2008;153:S10.

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Box 2
Phenotypic features consistent with a diagnosis of CF

Chronic sinopulmonary disease, manifested by:

Persistent colonization/infection with typical CF pathogens[a]

Chronic cough and sputum production

Persistent chest radiograph abnormalities[b]

Airway obstruction by examination or spirometry testing

Sinus disease[c]

Digital clubbing

Gastrointestinal and nutritional abnormalities, including:

Intestinal:

- Meconium ileus
- Distal intestinal obstruction syndrome
- Rectal prolapse

Pancreatic:

- Pancreatic insufficiency
- Recurrent acute or chronic pancreatitis
- Pancreatic abnormalities on imaging

Hepatic:

- Prolonged neonatal jaundice
- Chronic hepatic disease[d]

Nutritional:

- Failure to thrive (protein-calorie malnutrition)
- Hypoproteinemia and edema
- Clinical or laboratory evidence of fat-soluble vitamin deficiencies

Salt loss syndromes

Acute salt depletion

Chronic metabolic alkalosis

Genital abnormalities in male patients

Obstructive azoospermia

[a] *Staphylococcus aureus*, nontypable *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*.
[b] May include bronchiectasis, atelectasis, infiltrates, and hyperinflation.
[c] Radiographic or computed tomography (CT) abnormalities of the paranasal sinuses, presence of nasal polyps.
[d] Clinical or histologic evidence of focal biliary cirrhosis or multilobular cirrhosis.
Adapted from Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr 2008;153:S4–14; with permission.

phenotype, include the noncoding 5T allele of the polythymidine tract in intron 8 (IVS8),[10,25] as well as large sequence deletions, duplications, and in-cis distribution of benign polymorphisms.[26–28] Even with extensive sequencing of all exons and intron/exon junctions, only a single mutation is identified in more than a quarter of individuals with the diagnosis of mild or atypical CF.[28] Even if 2 *CFTR* abnormalities have been identified, only a small percentage of the more than 1800 identified genetic changes have been rigorously confirmed as CF-causing mutations.[29] In many cases, available reports linking phenotypic characteristics to a rare mutation are very limited and may describe a patient of a much younger age. Some CFTR mutations that are thought not to

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cause disease based on studies in young patients or in vitro models have later been reported in adult-diagnosed patients with CF with disease phenotype, further complicating the interpretation of genetic testing in the adult population.

Other Considerations

If sweat chloride testing and genotype analysis are not conclusive in adults with features consistent with CF, clinical judgment plays a role in making the diagnosis, and ancillary testing can often prove invaluable in this regard (discussed later).[5] Comprehensive investigation for other potential causes of disease, and close follow-up to determine the individual response to CF-directed therapies, are additional and important considerations to help inform clinical judgment. Difficulties in reconciling laboratory testing and clinical manifestations in newborns and infants have led to several new terms and proposed classifications, including CFTR-related metabolic syndrome, CFTR-related disease, CF screen positive, inconclusive diagnosis, and delayed CF.[30] However, there is little consensus surrounding these classifications, and they are rarely applied to adults. A new consensus conference will be convened in October 2015 under the sponsorship of the CFF to review this rapidly evolving field.[30]

CLINICAL MANIFESTATIONS

Adults diagnosed with CF can eventually develop all of the clinical features associated with the classic childhood disease, although usually at the time of diagnosis clinically relevant involvement is more limited (see **Box 2**). The most important features are discussed here.

Pulmonary Manifestations

Respiratory symptoms are the most common feature leading to the adult CF diagnosis.[2,11,13,31–33] Bronchiectasis is usually present and is easily detected by high-resolution computed tomography (CT) scanning. When young, these patients are often given the diagnosis of either asthma or chronic obstructive pulmonary disease based on obstructive physiology, bronchodilator response, and chronic sputum production. Cohorts of adult-diagnosed patients with CF show less severe lung disease compared with childhood-diagnosed cohorts, despite being significantly older.[4,11,32,34] However, for patients who survive past 40 years, 85% of patients with the adult diagnosis died of respiratory-related complications or transplant-related complications, which was similar to the 87% of childhood-diagnosed patients surviving past 40 years.[4]

Airway Infections

Recurrent or chronic airway infection is often the finding that leads to the consideration of CF in adults. Although patients with CF diagnosed as adults have a lower frequency of *Pseudomonas aeruginosa* infection (both mucoid and nonmucoid) than childhood-diagnosed patients,[11,12,31,32] it is still the most common airway infection in most reports.[2,11,12,31,34] Some investigators have reported a greater prevalence of *Staphylococcus aureus*, which is another common respiratory pathogen in CF.[33] Other typical CF pathogens, such as *Burkholderia cepacia*, can also be recovered, as well as pathogens not usually seen in the general CF population. Detection of nontuberculous mycobacteria (NTM) in the sputum correlates strongly with increasing age in patients with CF,[35–39] and is especially common in adult-diagnosed patients with CF.[2] We detected NTM 3 times more often in the adult diagnosis group ($P<006$), with *Mycobacterium avium* complex representing the most commonly detected species.[12] In a national epidemiologic study of NTM in CF, the age of mycobacteria-positive individuals was greater (26 vs 22 years), and subjects tended to have milder abnormalities in lung function (forced expiratory volume in 1 second [FEV_1], percentage predicted, 60% vs 54%).[35] Although age of diagnosis was not analyzed in that study, those data support the observation made by many investigators that older patients with milder disease are predisposed to infection with NTM, which may be the presenting feature at the time of diagnosis.[35,37,39,40]

Chronic Sinusitis

Chronic or recurrent sinusitis and nasal polyps are also common in patients with CF diagnosed as adults.[31,33] In a cohort of patients with CF with residual function mutations, mild lung disease, and an average age of diagnosis of 42.6 $\pm$ 17.2 years, we found that sinus CT findings were markedly worse than in a control group of patients without CF with chronic rhinosinusitis.[41]

Gastrointestinal Manifestations

The absence of pancreatic insufficiency (PI) is a major distinction between adult-diagnosed patients and those with the classic disease,[2,4,11,12,31–34] and is likely the primary reason for the diagnosis of CF not being made earlier in these patients. Accordingly, these patients have less CF-related diabetes,[4,12,32,34] and better

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overall nutrition.[11,12,32] Some adults present with PI at time of diagnosis and have adopted an extremely low-fat diet in order to reduce the symptoms of bloating and steatorrhea. However, patients with unrecognized, severe PI are usually markedly malnourished and deficient in fat-soluble vitamins. More commonly, adult patients report nonspecific symptoms of intermittent constipations and diarrhea, and often ascribe a beneficial response to low-dose pancreatic enzyme replacement even in the absence of overt PI. Many adults do not initially recognize the connection between these symptoms and their respiratory complaints, and are frequently assigned the diagnosis of irritable bowel syndrome. Over time, progression toward worsening PI can occur, even in the absence of clinically evident pancreatitis.[42–44] Our experience is consistent with that of multiple other groups reporting pancreatic enzyme supplementation in approximately half of patients diagnosed at the age of 18 years or greater.[2,12,32,45]

Pancreatitis

Idiopathic and recurrent pancreatitis is well recognized as a presenting manifestation of CF in adults,[34,46] frequently in the absence of apparent respiratory disease. These episodes can occur episodically over a series of years, with significant associated morbidity. In the original reports, many individuals were identified as having only a single *CFTR* mutation, based on limited genetic screening.[46,47] However, sequencing analysis of *CFTR* confirms that increased risk of pancreatitis requires 2 *CFTR* mutations (or a 5T allele) when other hereditary forms of pancreatitis are excluded.[48] Adults diagnosed with CF based on the clinical presentation of pancreatitis with the confirmed presence of 2 *CFTR* mutations are often considered to represent a single-organ manifestation of CF. However, with more extensive testing, many of these individuals have additional findings consistent with CF, including abnormal sweat testing, congenital bilateral absence of the vas deferens (CBAVD), sinusitis, and chronic bronchial infection with CF-typical pathogens.[48]

Congenital Bilateral Absence of the Vas Deferens

Absence of the vas deferens is nearly universal in male patients with CF, and is one of the most sensitive predictors for the presence of 2 clinically significant *CFTR* mutations in male patients.[49] Detection of CBAVD or other forms of obstructive azoospermia usually occurs in young men undergoing infertility evaluation, in the absence of clinically relevant respiratory complaints.[34] However, these men often have some degree of pulmonary or sinus disease,[50–52] and bronchoalveolar lavage studies of the airways of men with CBAVD and 1 or 2 identified *CFTR* mutations showed bacterial infection and inflammation in the absence of respiratory symptoms.[34] These results support the conclusion that young men presenting with CBAVD as a single-organ manifestation of CF are at risk to develop CF lung disease over time. Very rarely, normal reproductive function is present in men with mild mutations associated with the diagnosis of CF in adults.[49]

Female Gender

The diagnosis of CF in adulthood is made most frequently in women. In a cohort of 109 adult-diagnosed patients more than age 40 years at our center, 72.5% were women ($P = .0038$), and in a comparable cohort from the CFF registry 54.1% were women ($P<.0001$).[4] This finding has been reported by other centers worldwide.[11–13,33] Several factors could contribute to an increased frequency of adult diagnosis in women, including greater persistence in seeking the diagnosis and overall greater use of the health care system. In addition, a bias may exist against referral of men presenting with CBAVD to CF centers, resulting in an underrepresentation of men in databases of patients with adult-diagnosed CF. However, it is also possible that female predominance is based on molecular mechanisms and differences in phenotype.[53–55] Before widespread use of NBS, the CF diagnosis in female infants occurred later than in male infants.[56–58] This delay in diagnosis is also seen in adult-diagnosed patients in the CFF registry, in which the median age of diagnosis for men was 35.7 years compared with 39.2 for women ($P = .0014$).[4]

CLINICAL FINDINGS

Physical Examination

Findings on examination are usually nonspecific. Unlike patients diagnosed in childhood with the classic disease phenotype, adult-diagnosed patients may not be thin or have short stature. because respiratory symptoms are the most common presentation, patients often have a respiratory examination consistent with obstructive lung disease, with a prolonged expiratory phase or wheezing with forced expiration, and occasionally with scattered rhonchi. Nasal mucosa may be inflamed and polyps may be visible. Recurrent middle ear infections and subsequent deafness are not typical features of CF, and if present are

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more consistent with primary ciliary dyskinesia.[59] The abdominal examination is typically benign. Digital clubbing sometimes occurs.

Ancillary Testing

A variety of tests beyond sweat chloride analysis and *CFTR* genotyping may be helpful in establishing the CF diagnosis (**Table 1**). The nasal potential difference (NPD) test can be useful in assessment of patients with inconclusive sweat chloride values. However, access to NPD testing is not widely available beyond large research centers. The test requires a high level of operator training and expertise, and the usefulness of results are limited by a shortage of reference values and validation studies. Current guidelines state that the test should be used only to provide contributory evidence in a diagnostic evaluation.[5]

In adult patients, a high-resolution CT scan can detect even mild bronchiectasis and other early features of the disease.[60] Also valuable is an assessment of pancreatic exocrine function, which, if present, strongly argues in favor of CF, and helps guide treatment as well. A wide range of tests for assessing pancreatic function are available. The fecal elastase assay is usually preferred, but, depending on the setting of care and available resources, other testing could include a 72-hour stool collection, assays of fecal trypsin and chymotrypsin, and serum trypsinogen. Measurement of the fat-soluble vitamins A, D, and E, as well as indirect assessment of vitamin K through measurement of the prothrombin time and International Normalized Ratio (INR), can provide evidence of malabsorption, supporting the presence of PI. As discussed earlier, assessment of pancreatic function may need to be repeated over time, because PI develops gradually in some patients

Table 1
Ancillary testing for the assessment of the CF diagnosis in adults

Tests	Indications and Comments
Respiratory tract cultures	CF-associated pathogens, especially *P aeruginosa* but also *S aureus*, nontypable *Haemophilus influenzae*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and NTM
Exocrine pancreatic function tests	Presence of PI strongly supports CF diagnosis. Available tests include fecal elastase assay, 72-h stool collection, fecal trypsin or chymotrypsin, and serum trypsinogen
Fat-soluble vitamins	Deficiency in vitamins A, D, or E, as well as a prolonged INR (vitamin K), support the presence of fat malabsorption, a symptom of untreated PI
Genital evaluation in men	Genital examination, rectal ultrasonography for detection of vas deferens, semen analysis. Presence of sperm makes the CF diagnosis unlikely
Pancreatic imaging	CT and/or ultrasonography findings of pancreatic atrophy, fatty replacement, or lipomatous pseudohypertrophy are supportive of the CF diagnosis[64]
High-resolution chest CT	Capable of detecting very early radiographic features of CF, and in some cases can suggest alternative causes of bronchiectasis[60]
Bronchoalveolar lavage	Including microbiology assessment
Pulmonary function testing	Spirometry may be normal even with clinically and radiographically significant disease. With more advanced disease, an obstructive pattern of airflow limitation is expected
NPD testing	Useful in the setting of inconclusive sweat chloride values, but not universally available and limited by a lack of reference values and validation studies
Exclusionary testing for ciliary dyskinesia	Measurement of nasal nitric oxide, analysis of ciliary beat or ciliary composition, genetic testing[59]
Exclusionary testing for immunodeficiencies	Immunoglobulin levels, complement levels, leukocyte functional assays
Exclusionary testing for acute recurrent pancreatitis	Evaluation for gallstone disease, sphincter of Oddi dysfunction, anatomic variant of pancreatic ductal anatomy, genotype for *PRSS1* and *SPINK1* mutations[65]

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Box 3
Disease associated with the development of diffuse bronchiectasis

- Infection (primary)
  - Bacteria: *Klebsiella pneumoniae*, *S aureus*, *H influenzae*, *Bordetella pertussis*
  - Mycobacteria: *Mycobacterium tuberculosis*, NTM
  - Mycoplasma
  - Viruses: influenza, adenoviruses, measles, human immunodeficiency virus
  - Fungus
- Allergic bronchopulmonary aspergillosis
- Mucoid impaction
- Bronchocentric granulomatosis
- Primary ciliary dyskinesia
  - Kartagener syndrome
- Young syndrome
- Immunodeficiency states
  - Immunoglobulin (Ig) G deficiency
  - IgG subclass deficiency
  - IgA deficiency
  - Leukocyte dysfunction
  - Lymphocyte dysfunction
  - Complement deficiencies
- Alpha1-antitrypsin deficiency
- Autoimmune or hyperimmune disorders
  - Rheumatoid arthritis
  - Ulcerative colitis
  - Cutaneous vasculitis
  - Hashimoto thyroiditis
  - Pernicious anemia
  - Primary biliary cirrhosis
  - Relapsing polychondritis
  - Celiac disease
- Yellow nail syndrome
- Diseases of tracheal or bronchial cartilage
  - Williams-Campbell syndrome
  - Tracheobronchomegaly (Mounier-Kuhn)
- Inhalation of noxious fumes and dust
  - Anhydrous ammonia, silica, sulfur dioxide, talc, cork, Bakelite, cooking fumes
- Heroin
- Chronic fibrosing diseases
- Chronic gastric aspiration
- Marfan syndrome
- Heart-lung transplant
- Idiopathic (without known cause)

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with CF of all ages who were initially determined to be pancreatic sufficient.[42–44]

Also of high value are respiratory tract cultures, which may include induced sputum and bronchoalveolar lavage. In our experience, patients presenting for evaluation of CF as adults may not have had frequent respiratory cultures during the course of their care, despite a high prevalence of productive cough. The presence of typical CF pathogens, in particular mucoid *P aeruginosa*, is supportive of the CF diagnosis.

Ancillary testing is also valuable for the purpose of eliminating other diagnostic considerations, as discussed later; in particular, the common causes of diffuse bronchiectasis, such as primary ciliary dyskinesia, and immunoglobulin deficiencies. When sweat chloride testing and CFTR genotype analysis remain inconclusive, the elimination of many other plausible causes of bronchiectasis can be an important consideration in deciding to assign the CF diagnosis to an adult.

DIAGNOSTIC DILEMMAS

The CF phenotype includes several signs and symptoms that overlap with a wide variety of obstructive lung diseases, various immunodeficiencies, and a broad range of gastrointestinal disorders. Because the most common presentation is with respiratory complaints, the most frequent consideration is other causes of diffuse bronchiectasis. The differential diagnosis of bronchiectasis is complicated and challenging, and often remains labeled as idiopathic despite exhaustive evaluation. The most relevant causes are listed in **Box 3**. The involvement of an organ outside the respiratory tract is the most important clinical feature in many cases. The same processes that result in bronchiectasis often also involve the sinuses to varying degrees; however, clinically significant involvement of the pancreas, bowel, or vas deferens is not expected in most of the disease processes that result in the common causes of bronchiectasis.

OUTCOMES FOR PATIENTS WITH CYSTIC FIBROSIS DIAGNOSED AS ADULTS

There is a paucity of data concerning response to treatment and outcomes in patients with CF diagnosed in adulthood. We have found that newly diagnosed adult patients with CF receiving multidisciplinary, guideline-based care at a CF center achieve a significant and sustained improvement in FEV_1 from baseline (time of diagnosis) over a period of 4 years.[4] This finding is particularly notable because there is no evidence-based treatment approach specific to adult-diagnosed patients, and available therapies were generally developed for children and adolescents with the classic phenotype, who typically have different *CFTR* mutations, different absorption of nutrition and medications, and different patterns of airway infection. Unexpectedly, we found that, following diagnosis, less than half of adult-diagnosed patients received their care at a CF center.[4] A general lack of familiarity with the adult diagnosis, even within the CF care community, may contribute to a reluctance of these patients to continue long-term follow-up at CF care centers. However, the significant and sustained benefit to lung function observed after initiating typical CF therapy within our center argues in support of both incorporating and aggressively treating patients diagnosed with CF later in life. As expected, adult-diagnosed patients have substantially better survival than the CF population as a whole, with a median survival of 76.9 years for adult-diagnosed patients in our Colorado database, and 68.2 years for patients followed in the CFF Patient Registry.[4] Note that women who were diagnosed as adults enjoyed a distinct survival advantage of 13.5 years in the Colorado database and 9.2 years in the CFF registry database compared with their male counterparts.[4] To our knowledge, this reverse gender gap is the first example of a clinical advantage of women with CF compared with men. However, despite a much longer lifespan, most adult-diagnosed patients followed in the CFF Patient Registry died of respiratory failure (76%) or transplant-related complications (9%), with an almost identical frequency to long-term survivors of the childhood diagnosis.[4]

SUMMARY

Clinical manifestations of adult-diagnosed CF include an extremely diverse spectrum of disease, ranging from mild single-organ involvement to the classic phenotype. As a result of greater CFTR activity associated with residual function mutations, these patients generally have less severe lung and gastrointestinal involvement despite achieving a greater age than patients diagnosed in childhood. Adult-diagnosed patients can be expected to have a lower prevalence of PI and *P aeruginosa* infections, but over time have a higher frequency of pancreatitis, are at greater risk for NTM infection, and historically have primarily died of respiratory complications.

We believe that CF remains undiagnosed in a significant number of adults, and, when diagnosed, most individuals do not receive care at CF centers. Thus, these patients are under-represented in the

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CF patient registries. Physicians encountering patients with bronchiectasis of unknown cause, especially when associated with chronic infection with *P aeruginosa*, *S aureus*, or NTM, should consider CF regardless of the age and associated symptoms. Clearly, CF must be included in the differential diagnosis of recurrent idiopathic pancreatitis or CBAVD, but other symptoms that may be diagnosed as irritable bowel syndrome should also be considered as possible manifestations of CF. When CF is suspected, the work-up typically requires both a sweat chloride test and *CFTR* genotyping, associated with ancillary testing as clinically indicated. Physicians need to be mindful that their understanding of the genetic basis of CF continues to evolve, and the clinical phenotype within an individual may not be fully evident until late adulthood. Thus, follow-up is often warranted in cases in which a conclusive diagnosis is not possible at the time of presentation. If CF is diagnosed, referral to a CF care center for aggressive disease management should be encouraged.

Going forward, patients with the adult diagnosis may be well positioned to benefit from recent advances in CF care. In particular, the CFTR potentiator ivacaftor has now been approved for use in patients with the *Arg117His-CFTR* mutation,[61] which is frequently associated with the adult diagnosis.[4] This result was predicted by in vitro studies in which ivacaftor induced significant improvements in chloride transport in cell lines expressing *Arg117His* and a range of other residual function mutations that are commonly associated with the adult diagnosis.[62] Case reports have documented a favorable response to CFTR modulation treatment in individual patients with these mutations,[63] and an n-of-1 trial was recently completed to examine this effect in predominantly adult-diagnosed patients (NCT01685801), with a trial of ivacaftor in combination with VX-661 for patients with residual function mutations underway (NCT02392234). Regardless of the results of these trials, the adult diagnosis of CF should be pursued aggressively when clinical suspicion exists, because patients have been shown to respond to conventional CF therapy.[4] The adult CF diagnosis allows a unified approach to multisystem complaints, allows the patient to alert family members who are potential carriers, and often provides a sense of relief for patients who have struggled to conceptualize progressively worsening symptoms in the absence of a diagnosis or rational treatment plan.

REFERENCES

1. 2013 annual data report; Cystic Fibrosis Foundation patient registry. 2014.
2. Keating CL, Liu X, Dimango EA. Classic respiratory disease but atypical diagnostic testing distinguishes adult presentation of cystic fibrosis. Chest 2010;137:1157–63.
3. Nick JA, Rodman DM. Manifestations of cystic fibrosis diagnosed in adulthood. Curr Opin Pulm Med 2005;11:513–8.
4. Nick JA, Chacon CS, Brayshaw SJ, et al. Effects of gender and age at diagnosis on disease progression in long-term survivors of cystic fibrosis. Am J Respir Crit Care Med 2010;182:614–26.
5. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr 2008;153:S4–14.
6. LeGrys VA, Yankaskas JR, Quittell LM, et al, Cystic Fibrosis Foundation. Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. J Pediatr 2007;151:85–9.
7. Groves T, Robinson P, Wiley V, et al. Long-term outcomes of children with intermediate sweat chloride values in infancy. J Pediatr 2015;166:1469–74.e1-e3.
8. Highsmith WE, Burch LH, Zhou Z, et al. A novel mutation in the cystic fibrosis gene in patients with pulmonary disease but normal sweat chloride concentrations. N Engl J Med 1994;331:974–80.
9. Stewart B, Zabner J, Shuber AP, et al. Normal sweat chloride values do not exclude the diagnosis of cystic fibrosis. Am J Respir Crit Care Med 1995;151:899–903.
10. Noone PG, Knowles MR. 'CFTR-opathies': disease phenotypes associated with cystic fibrosis transmembrane regulator gene mutations. Respir Res 2001;2:328–32.
11. Gan KH, Geus WP, Bakker W, et al. Genetic and clinical features of patients with cystic fibrosis diagnosed after the age of 16 years. Thorax 1995;50:1301–4.
12. Rodman DM, Polis JM, Heltshe SL, et al. Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. Am J Respir Crit Care Med 2005;171:621–6.
13. Modolell I, Alvarez A, Guarner L, et al. Gastrointestinal, liver, and pancreatic involvement in adult patients with cystic fibrosis. Pancreas 2001;22:395–9.
14. Choo-Kang LR, Zeitlin PL. Type I, II, III, IV, and V cystic fibrosis transmembrane conductance regulator defects and opportunities for therapy. Curr Opin Pulm Med 2000;6:521–9.
15. Durno C, Corey M, Zielenski J, et al. Genotype and phenotype correlations in patients with CF and pancreatitis. Gastroenterology 2002;123:1857–64.
16. Hubert D, Bienvenu T, Desmazes-Dufeu N, et al. Genotype-phenotype relationships in a cohort of adult cystic fibrosis patients. Eur Respir J 1996;9:2207–14.

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17. McKone EF, Emerson SS, Edwards KL, et al. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. Lancet 2003;361:1671–6.
18. McKone EF, Goss CH, Aitken ML. CFTR genotype as a predictor of prognosis in cystic fibrosis. Chest 2006;130:1441–7.
19. Burke W, Aitken ML, Chen SH, et al. Variable severity of pulmonary disease in adults with identical cystic fibrosis mutations. Chest 1992;102:506–9.
20. Cutting GR. Modifier genes in mendelian disorders: the example of cystic fibrosis. Ann N Y Acad Sci 2010;1214:57–69.
21. Joly P, Restier L, Bouchecareilh M, et al. DEFI-ALPHA cohort and POLYGEN DEFI-ALPHA clinical research hospital programme. A study about clinical, biological and genetics factors associated with the occurrence and the evolution of hepatic complications in children with alpha-1 antitrypsin deficiency. Rev Mal Respir 2015;32(7):759–67 [in French].
22. Coutinho CA, Marson FA, Marcelino AR, et al. TNF-alpha polymorphisms as a potential modifier gene in the cystic fibrosis. Int J Mol Epidemiol Genet 2014;5:87–99.
23. Blackman SM, Commander CW, Watson C, et al. Genetic modifiers of cystic fibrosis-related diabetes. Diabetes 2013;62:3627–35.
24. Bradley GM, Blackman SM, Watson CP, et al. Genetic modifiers of nutritional status in cystic fibrosis. Am J Clin Nutr 2012;96:1299–308.
25. Chillon M, Casals T, Mercier B, et al. Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. N Engl J Med 1995; 332:1475–80.
26. Taulan M, Viart V, Theze C, et al. Identification of a novel duplication CFTRdup2 and functional impact of large rearrangements identified in the CFTR gene. Gene 2012;500:194–8.
27. Ni WH, Jiang L, Fei QJ, et al. The CFTR polymorphisms poly-T, TG-repeats and M470V in Chinese males with congenital bilateral absence of the vas deferens. Asian J Androl 2012;14:687–90.
28. Strom CM, Crossley B, Buller-Buerkle A, et al. Cystic fibrosis testing 8 years on: Lessons learned from carrier screening and sequencing analysis. Genet Med 2011;13:166–72.
29. US CF Foundation JHU, The Hospital for Sick Children. The clinical and functional translation of CFTR (CFTR2). 2011. Available at: http://cftr2.Org. Accessed December 2, 2015.
30. Levy H, Farrell PM. New challenges in the diagnosis and management of cystic fibrosis. J Pediatr 2015; 166:1337–41.
31. Shwachman H, Kowalski M, Khaw KT. Cystic fibrosis: a new outlook. Medicine 1977;56:129–49.
32. McCloskey M, Redmond AO, Hill A, et al. Clinical features associated with a delayed diagnosis of cystic fibrosis. Respiration 2000;67:402–7.
33. Widerman E, Millner L, Sexauer W, et al. Health status and sociodemographic characteristics of adults receiving a CF diagnosis after age 18 years. Chest 2000;118:427–33.
34. Gilljam M, Ellis L, Corey M, et al. Clinical manifestations of cystic fibrosis among patients with diagnosis in adulthood. Chest 2004;126:1215–24.
35. Olivier KN, Weber DJ, Wallace RJ Jr, et al. Nontuberculous mycobacteria. I: Multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med 2003;167:828–34.
36. Esther CR Jr, Esserman DA, Gilligan P, et al. Chronic mycobacterium abscessus infection and lung function decline in cystic fibrosis. J Cyst Fibros 2010;9: 117–23.
37. Aitken ML, Burke W, McDonald G, et al. Nontuberculous mycobacterial disease in adult cystic fibrosis patients. Chest 1993;103:1096–9.
38. Levy I, Grisaru-Soen G, Lerner-Geva L, et al. Multicenter cross-sectional study of nontuberculous mycobacterial infections among cystic fibrosis patients, Israel. Emerg Infect Dis 2008;14:378–84.
39. Fauroux B, Delaisi B, Clement A, et al. Mycobacterial lung disease in cystic fibrosis: a prospective study. Pediatr Infect Dis J 1997;16:354–8.
40. Olivier KN, Weber DJ, Lee JH, et al. Nontuberculous mycobacteria. II: Nested-cohort study of impact on cystic fibrosis lung disease. Am J Respir Crit Care Med 2003;167:835–40.
41. Ferril GR, Nick JA, Getz AE, et al. Comparison of radiographic and clinical characteristics of low-risk and high-risk cystic fibrosis genotypes. Int Forum Allergy Rhinol 2014;4(11):915–20.
42. Couper RT, Corey M, Durie PR, et al. Longitudinal evaluation of serum trypsinogen measurement in pancreatic-insufficient and pancreatic-sufficient patients with cystic fibrosis. J Pediatr 1995;127:408–13.
43. Couper RT, Corey M, Moore DJ, et al. Decline of exocrine pancreatic function in cystic fibrosis patients with pancreatic sufficiency. Pediatr Res 1992;32:179–82.
44. Bronstein MN, Sokol RJ, Abman SH, et al. Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. J Pediatr 1992;120:533–40.
45. Simmonds NJ, Cullinan P, Hodson ME. Growing old with cystic fibrosis - the characteristics of long-term survivors of cystic fibrosis. Respir Med 2009;103: 629–35.
46. Sharer N, Schwarz M, Malone G, et al. Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Engl J Med 1998;339:645–52.
47. Cohn JA, Friedman KJ, Noone PG, et al. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med 1998;339:653–8.
48. Noone PG, Zhou Z, Silverman LM, et al. Cystic fibrosis gene mutations and pancreatitis risk: Relation to

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epithelial ion transport and trypsin inhibitor gene mutations. Gastroenterology 2001;121:1310–9.
49. Groman JD, Karczeski B, Sheridan M, et al. Phenotypic and genetic characterization of patients with features of "nonclassic" forms of cystic fibrosis. J Pediatr 2005;146:675–80.
50. Kerem E, Rave-Harel N, Augarten A, et al. A cystic fibrosis transmembrane conductance regulator splice variant with partial penetrance associated with variable cystic fibrosis presentations. Am J Respir Crit Care Med 1997;155:1914–20.
51. Culard JF, Desgeorges M, Romey MC, et al. A novel splice site mutation in the first exon of the cystic fibrosis transmembrane regulator (CFTR) gene identified in a CBAVD patient. Hum Mol Genet 1994;3:369–70.
52. Claustres M, Guittard C, Bozon D, et al. Spectrum of CFTR mutations in cystic fibrosis and in congenital absence of the vas deferens in France. Hum Mutat 2000;16:143–56.
53. Morea A, Cameran M, Rebuffi AG, et al. Gender-sensitive association of CFTR gene mutations and 5T allele emerging from a large survey on infertility. Mol Hum Reprod 2005;11:607–14.
54. Strom CM, Crossley B, Redman JB, et al. Cystic fibrosis screening: lessons learned from the first 320,000 patients. Genet Med 2004;6:136–40.
55. Sun W, Anderson B, Redman J, et al. CFTR 5T variant has a low penetrance in females that is partially attributable to its haplotype. Genet Med 2006;8:339–45.
56. Farrell P, Joffe S, Foley L, et al. Diagnosis of cystic fibrosis in the Republic of Ireland: epidemiology and costs. Ir Med J 2007;100:557–60.
57. McCormick J, Sims EJ, Mehta A. Delayed diagnosis of females with respiratory presentation of cystic fibrosis did not segregate with poorer clinical outcome. J Clin Epidemiol 2006;59:315–22.
58. Lai HC, Kosorok MR, Laxova A, et al. Delayed diagnosis of US females with cystic fibrosis. Am J Epidemiol 2002;156:165–73.
59. Werner C, Onnebrink JG, Omran H. Diagnosis and management of primary ciliary dyskinesia. Cilia 2015;4:2.
60. Dodd JD, Lavelle LP, Fabre A, et al. Imaging in cystic fibrosis and non-cystic fibrosis bronchiectasis. Semin Respir Crit Care Med 2015;36:194–206.
61. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. Lancet Respir Med 2015;3:524–33.
62. Van Goor F, Yu H, Burton B, et al. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. J Cyst Fibros 2014;13:29–36.
63. Yousef S, Solomon GM, Brody A, et al. Improved clinical and radiographic outcomes after treatment with ivacaftor in a young adult with cystic fibrosis with the P67l CFTR mutation. Chest 2015;147:e79–82.
64. Lavelle LP, McEvoy SH, Ni Mhurchu E, et al. Cystic fibrosis below the diaphragm: abdominal findings in adult patients. Radiographics 2015;35:680–95.
65. Testoni PA. Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment. World J Gastroenterol 2014;20:16891–901.

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