

Cystic Fibrosis

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Educational Objectives:

1. Review initial presentation and workup for cystic fibrosis.
2. Review potential complications and management of cystic fibrosis.
3. Discuss mechanisms and indications for CFTR modulators.

Scenario 1: Mr. D is a 32-year-old man who presents to your clinic with a new diagnosis of possible cystic fibrosis (CF). He first developed respiratory symptoms at age 12, with frequent cough (small amount of sputum production), intermittent dyspnea, wheezing, and nasal congestion with frequent sinus pressure, which was labeled asthma and allergic rhinitis for years. He also has acute respiratory infections 1-3 times per year and was often given oral antibiotics for "bronchitis." He has never had steatorrhea or difficulty maintaining weight, although he did have pancreatitis in college once, which was attributed to alcohol, although he says he has never been a heavy alcohol user. He and his wife have been unsuccessfully trying to have children.

Question 1: What testing would you recommend to determine whether or not Mr. D has CF?

Guidelines (<https://www.sciencedirect.com/science/article/pii/S0022347616310484>) for CF diagnosis recommend starting with sweat chloride testing, followed by CFTR genetic testing if sweat chloride is in the indeterminate range (30-59). See the flow chart on the next page for more specific steps in the diagnostic algorithm.

An appropriate clinical picture combined with a sweat chloride ≥ 60 mmol/L and/or two CF-causing mutations is considered diagnostic of cystic fibrosis. An appropriate clinical picture includes disease affecting 2 or more systems:

Pulmonary: bronchiectasis and/or chronic sinusitis

GI: pancreatitis and/or pancreatic insufficiency

GU: Congenital bilateral absence of vas deferens (CBAVD)

If sweat chloride testing is positive (≥ 60 mmol/L), confirming the diagnosis of CF, it is still helpful and recommended that CFTR genetics should be tested, as new therapies for CF are mutation-specific. Therefore, knowing the exact CFTR mutations can impact treatment decisions. Also, there are some mutations (e.g., a splicing mutation called 3849+10kbC->T) that are known to lead to false-negative sweat chloride (≤ 30 mmol/L). These mutations tend to lead to a milder clinical phenotype that is less likely to be diagnosed in childhood. Therefore, in cases where clinical suspicion for CF is high despite a negative sweat chloride test, genetic testing should be performed in consult with a dedicated CF center.

When ordering CFTR genetic testing, the ideal scenario is to have full CFTR gene sequencing plus deletion/duplication analysis and intron polyT analysis. There are several private genetic testing companies (ex: Ambry and Invitae) that perform this more detailed testing. Many companies also allow simultaneous genetic testing for primary ciliary dyskinesia if that is also on your differential diagnosis. The reason for more complete genetic testing is that the common CF mutations identified with initial screening tests lead to more severe disease. If someone has made it to adulthood without CF being identified, then they are unlikely to have solely the common mutations.

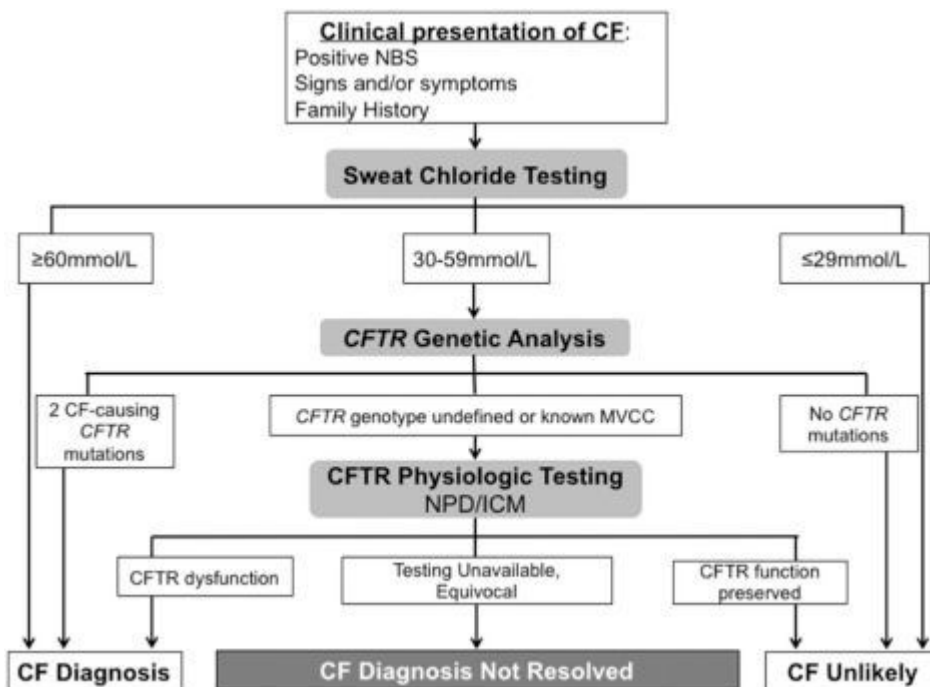


Figure 1. Diagnostic algorithm for CF testing. Adapted from Farrell P, White T. Introduction to Cystic Fibrosis Foundation Consensus Guidelines for Diagnosis of Cystic Fibrosis. J Pediatr. 2017. ¹

To look up a CFTR mutation to know if it is potentially disease-causing, go to <https://cftr2.org/>

Question 2: Our patient is confirmed to have CF based on a positive sweat chloride test and confirmed by genetic testing, what further testing would be appropriate?

Guidelines recommend obtaining sputum cultures in all CF patients. Both bacterial and AFB cultures are indicated to identify potential pathogens of concern. Baseline pulmonary function tests and a chest x-ray are also warranted. Other tests that are recommended as part of annual labs in CF include:

CF related disorder	Guideline-based screening
Liver disease	LFT's and GGT annually
Pancreatic insufficiency/malabsorption	Vitamins A,D, E annually
Diabetes	Oral glucose tolerance test annually and can attain hgbA1c
Cystic fibrosis exacerbations and pulmonary colonization	Sputum culture and AFB. CXR annually
Osteopenia/Osteoporosis	DEXA scan every 5 years
Colorectal Cancer	Colonoscopy every 5 years, starting at age 40

(Adapted from the Clinical Care Checklist for Adult Care in Cystic Fibrosis, Copyright 2019, Cystic Fibrosis Foundation. Available at <https://www.cff.org/Care/Clinical-Care-Guidelines/>)

Question 3:Mr. D's testing returned with no significant abnormalities except for a sputum culture that grew *Pseudomonas Aeruginosa*. What baseline pulmonary therapies should be initiated? What therapies specific to *Pseudomonas* should be initiated?

Pulmonary Hygiene: Numbered in the order to be given per CF foundation

1. Inhaled bronchodilators-SABA, LABA, or LAMA. Exclude ICS
2. Mucous modification
 - a. Inhaled Mannitol- A DPI formulation of Mannitol that has approved approval by FDA in 2020 for hydration and mobilization of respiratory secretions.
 - b. Nebulized hypertonic saline - Hydrates respiratory secretions to help mobilize mucus more effectively; improves lung function and decreases exacerbations
 - c. Nebulized DNase/dornase/Pulmozyme - Breaks down DNA in sputum, which decreases sputum viscosity (since DNA is highly viscous) to help mobilize sputum; improves lung function and decreases exacerbations
3. Perform airway clearance therapies-All patients should perform and include:
 - a. Percussion and postural drainage.
 - b. Positive expiratory pressure devices (PEP)
 - c. Activecycle of breathing technique
 - d. Autogenic drainage (AD)
 - e. Oscillatory PEP devices (OPEP)

- f. High –frequency chest compression (HFCC) devices
 - g. Exercise
- None of these has been proven to be superior to others
4. ICS or ICS LABA combination if patient with asthma or asthma overlap syndrome
 5. Inhaled antibiotics if they apply which include:
 - a. Nebulized and powdered inhaler tobramycin - Approved for CF patients with *Pseudomonas aeruginosa* in their sputum; improves lung function and decreases exacerbations
 - b. Nebulized aztreonam lysine (Cayston) - Approved for CF patients with *Pseudomonas aeruginosa* in their sputum; improves lung function and decreases exacerbations
 - c. Inhaled Colistin-Not FDA approved but used for patients with CF patients with *Pseudomonas aeruginosa* in their sputum; improves lung function and decreases exacerbations
 - d. Inhaled amikacin-Approved for treatment of Mycobacterium Avium Complex

Assuming this is his first infection with *Pseudomonas*, attempts at eradication should be made which would include inhaled tobramycin for 28 days. Oral antibiotics have not been shown to increase the rate of eradication if not having a true exacerbation. If patient were to be deemed colonized (repeat cultures positive despite attempts at eradication and likely a mucoid phenotype) would initiate Tobramycin for 4 weeks every other month and initiate chronic Azithromycin (if the patient has concomitant bronchiectasis.)² Every other month administration of inhaled tobramycin has been shown to decrease rates of resistance vs continuous administration. In Europe inhaled Colistin has been employed continuously and noted no significant increase in resistance. During the month off Tobramycin some providers employ additional inhaled therapies, but no significant benefits have been proven with this strategy.

Question 4: Mr. D asks whether he should call his primary care physician or the pulmonary clinic when he has a respiratory infection. What would you advise that he do?

Whereas the general population tends to do well with watchful waiting in the context of respiratory infections (since most are self-limited viral infections), more aggressive use of antibiotics is warranted in CF. This is because patients are colonized with bacterial pathogens and even viral infections can more easily lead to secondary bacterial infection in CF patients. While antibiotics are not automatically prescribed for every infection, it is preferred to have patients contact their CF program rather than primary care as long-term outcomes are better with a more aggressive approach to antibiotic use.

Question 5: How can we help decide whether he also has asthma or whether his history of unexplained dyspnea and wheezing were all due to undiagnosed CF?

CFTR mutation carriers are at increased risk of asthma compared to non-carriers. Similarly, CF patients have an increased risk of asthma. It can be difficult to differentiate the patients with asthma from those without since asthma symptoms can also manifest in CF patients without asthma. If clear allergic triggers for respiratory symptoms are present, this suggests an asthmatic component to respiratory disease in CF patients. Pre- and post-bronchodilator testing can be helpful as well. In some patients the diagnostics are ambiguous but they may be labeled as having asthma based on clinical response to asthma medications.

Scenario 2: Mr. W is a 19-year-old man with cystic fibrosis (F508del homozygous) diagnosed in infancy. He has been treated at a CF center throughout his life. He has been very active throughout his childhood and felt healthy from a respiratory standpoint most of the time, but he does have exacerbations requiring IV antibiotics 1-2 times per year. He has pancreatic insufficiency and takes pancrelipase, thus is generally able to maintain his weight apart from transient drops associated with exacerbations. He had an adenovirus infection just before turning 18, and his health has been worse since. He doesn't feel quite as sick as when he has an acute exacerbation. His sputum isn't as thick, dark, and copious as when he has a "typical exacerbation," but he does have more sputum production than his prior baseline. His weight is also below his baseline, but not dropping as much as usual for an exacerbation. His baseline FEV1 used to be 75-80% predicted, but lately it has been 55-60%. He has received two courses of IV antibiotics with a slight improvement in symptoms and FEV1 increase to the low 60s, but has not returned to his prior state of health at any point.

Question 6: Assuming he is on all of the usual CF maintenance medications, is this his new baseline health status or can we do anything else for him? What other testing should we consider?

This may be his new baseline, but a decline in lung function not responding to IV antibiotics warrants further assessment to determine if there are any modifiable causes. This can include re-checking sputum bacterial cultures to determine if there is a new pathogen or increased resistance of previously identified pathogens, checking sputum AFB cultures, checking sputum fungal cultures, and checking IgE as an initial assessment for ABPA.

Scenario 3: Ms. H is a 36-year-old woman with cystic fibrosis who presents to clinic with complaints of decreased stool output and cramping abdominal pain (diffuse, but worse on the right side of her abdomen) along with an occasional sense of bloating in her abdomen. She has a decreased appetite and mild nausea without vomiting. No fevers, chills, or night sweats, but she has lost about 5 lbs, which she attributes to decreased appetite. No respiratory symptoms beyond her baseline cough and sputum production.

Question 7: What is most likely cause of Ms. H's symptoms? Would you recommend any other diagnostic testing?

The most likely cause of her symptoms is distal intestinal obstruction syndrome (DIOS), which used to be called meconium ileus equivalent. DIOS is more common in patients with pancreatic insufficiency and is caused by inspissated intestinal contents that completely or partially block the small intestinal lumen, most commonly at the ileocecal junction. Patients typically present with abdominal pain and a palpable "mass" of intestinal contents in the right lower quadrant. An abdominal x-ray may show impacted stool in the distal small intestine and ascending colon, as well as possible small bowel dilation and/or air-fluid levels. In addition to an x-ray, it may be helpful to get a CBC, LFTs, amylase, lipase, and urine studies to assess for other causes of abdominal pain.

Question 8: What treatment approach is most likely to help her?

Patients with DIOS usually respond well to rehydration and treatment with osmotic laxatives and/or enemas. Surgery is a last resort for management of DIOS and is generally reserved for patients with peritoneal signs on exam or evidence of intestinal ischemia. If surgery is necessary, the goal is to remove as little bowel as possible; in some cases, the stool can be manually mobilized through the intestine during a laparotomy to avoid resecting bowel.

Question 9: We try the treatment approach that we discussed in the answer to question 8 and it seems to be having no impact on her symptoms at all. She is continuing to lose weight. What less common complications of CF should we consider next? What testing should we consider?

The differential diagnosis for abdominal pain in CF can include any of the things that can cause abdominal pain in patients without CF, so the differential is quite long. However, here are some things for which CF patients are at increased risk:

- Complications of frequent use of antibiotics, including C. diff colitis or small intestinal bacterial overgrowth.
- Adhesions (if they required prior surgery for meconium ileus or other abdominal pathology)
- There is some evidence that CF patients are at increased risk for GI malignancies, even at relatively young age. Colon cancer screening is recommended starting at age 40 in people with CF.
- Intussusception is possible in adults with CF, typically with inspissated intestinal contents acting as the lead point.
- Fibrosing colonopathy is characterized by severe fibrosis of the intestine and has historically been associated with high doses of pancreatic enzymes. It is much less common since the 1990s, although it is unclear how much of this is due to changes in the dosing of pancreatic enzymes or due to changes in how enzymes are manufactured. It is now considered an extremely rare condition.

If DIOS management is not helping, CT of the abdomen and pelvis is indicated to evaluate for the above possibilities.

Scenario 4: Mr. S is a 48-year-old man with cystic fibrosis (F508del homozygous). He has been surprisingly healthy for someone with his genotype. He has never been consistent about using respiratory therapies and rarely has acute pulmonary exacerbations; he can't remember the last time he needed antibiotics. His lung function has gradually declined over the years, with FEV1 currently 55% predicted, but he isn't bothered much by respiratory symptoms so he hasn't been willing to use nebulizers frequently or do much for airway clearance. He has pancreatic insufficiency and takes pancrelipase. He now returns to clinic for the first time in 18 months, and early in the conversation says he heard there might be some new treatment for CF; he wants to hear more about it.

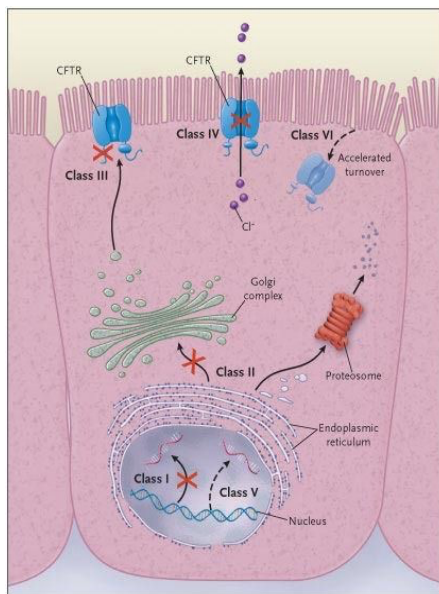
Question 9: What new treatments are available for CF? How do they work? What are the potential side effects and complications? Is it appropriate for him to start one of the new treatments?

There are Four new medications approved in recent years targeting the underlying defect that causes CF:

1. Kalydeco (ivacaftor) - FDA approved in 2012
2. Orkambi (lumacaftor/ivacaftor) - FDA approved in 2015
3. Symdeko (tezacaftor/ivacaftor) - FDA approved in 2018
4. Trikafta (elexacaftor/tezacaftor/ivacaftor) - FDA approved in 2019

To understand the mechanism for these drugs, it helps to outline how CFTR mutations lead to absent or decreased CFTR function.

CFTR is a chloride-ion transport protein in the epithelial lining of cells. Specific CFTR mutations lead to dysfunction at different points in CFTR transcription, translation, cellular processing, and actual function as an ion channel. The diagram below (from NEJM 2005; 352:1992-2001) shows different classes into which CFTR mutations are grouped.



- Class I - primarily stop codon mutations; premature truncation of the protein
- Class II (includes F508del, the most common mutation) - protein misfolding, leads to lysosomal degradation before the protein traffics to the cell membrane
- Class III - gating mutations; the protein reaches the cell surface but the analogy is a gate that won't open
- Class IV - decreased (but not absent) ion channel activity; usually more mild clinical manifestations
- Class V - decreased amount of CFTR produced (usually due to intron splicing mutations); usually more mild clinical manifestations
- Class VI - decreased stability of CFTR at the cell surface leading to accelerated turnover; usually more mild clinical manifestations

The below chart is based on information from 2019 - Patient Registry Annual Data Report³

Drug	FDA approval	Class approved in	Major side effect
Ivacaftor	Ages 6 months if contains 1 of 38 mutations	3,4,5	Cataracts and LFT elevation
Orkambi	Homozygous for F508del Ages 2+	2	Cataracts, LFT elevation, respiratory symptoms
Symdeko	Homozygous for F508 or F508 and one of 26 (26 of the 38 for which ivacaftor is approved) approved mutations Ages 6 +	2,3,5	Cataracts and LFT elevation
Trikafta	Homozygous or heterozygous for F508del Approved for 12+.	2	Cataracts and LFT elevation

Ivacaftor is referred to as a **CFTR potentiator**, producing increased chloride-channel activity when CFTR protein is actually at the cell surface. By itself, it does not help class I or II mutations, but can improve CFTR function in Class III, IV, and V.

Lumacaftor, Elexacaftor, and Tezacaftor are called **CFTR correctors**. They help stabilize CFTR with F508del mutations to interfere with lysosomal degradation so it can reach the cell surface, where Ivacaftor can potentiate its function. Orkambi (lumacaftor/ivacaftor) was approved first, but was difficult for patients to tolerate; many patients had chest tightness, wheezing, and dyspnea on Orkambi. Symdeko (tezacaftor/ivacaftor) has been noted to have no increase in respiratory events which includes chest discomfort, wheezing, and dyspnea. In fact, in a pooled analysis of the existing trials noted respiratory events were 11.3% in patients treated with Symdeko vs 14.7% in placebo. ⁴

Trikafta (elexacaftor/tezacaftor/ivacaftor) was approved by the FDA in October 2019 as the first **triple combination** therapy. It was approved for individuals with cystic fibrosis that are 12 and older who have at least one allele with the F508del mutation. The most notable side effect that requires monitoring and medication adjustment is elevation in LFT's and hepatic impairment.

Note that the approved mutations for Symdeko consist of patients homozygous for F508del and a lot of mutations for which Kalydeco (ivacaftor alone) is approved. Symdeko does not have a statistically significant benefit for patients who have one copy of F508del and one copy of a mutation that does not respond to Ivacaftor. Trikafta has received approval in all patients with at least one copy of F508del, although it received approval based on improvement of FEV1 by 13.3% in patient with F508del and minimal function mutation (Not a mutation in which Ivacaftor or Symdeko have been proven helpful). Trikafta has been shown to increase the FEV1 of homozygous F508del patients by 11% as compared to those already receiving Symdeko.

The addition of Trikafta has expanded the eligibility of patients with CF for modulator therapy to approximately 80.5% of CF patients in the CF registry. Of the remaining 19.5%, 10% are children too young for therapy and the remaining 9.5% have a non-responding, missing, or unknown genotype. Those likely to be non-responders are in classes 1 and 6. Thus non-responder patients (which is estimated to be 7% of the population) are unlikely to receive approval for modulators and will require genetic based therapies (which are on the horizon with technologies such as inhaled lipid mRNA based therapies)

Another advantage of these medications is they can be taken orally, which is far more convenient for CF patients whose other treatments (nebulizers, airway clearance modalities, etc) are time-intensive.

Cost is a major disadvantage to CFTR modulators (all cost approximately \$300,000 per year however they are currently covered by insurance with a qualifying mutation) and the need to monitor LFTs for potential hepatotoxicity.

Scenario 5: A 26-year-old woman with cystic fibrosis and worsening respiratory disease (frequent exacerbations, FEV1 30% predicted) presents to clinic with right-sided chest pain that started yesterday. She had been feeling worse in the preceding few days, with some increased cough and sputum production, but had not felt as bad as she usually does with a CF exacerbation.

Question 10: What are the most likely potential causes of her chest pain? What should we do next?

Spontaneous pneumothorax can develop in cystic fibrosis. Although most respiratory infections associated with CF are airway infections associated with bronchiectasis, pneumonia is also a possibility and can often cause chest pain in CF patients. Starting with a chest x-ray is a reasonable approach in this clinical setting.

Of course, if there are PE risk factors, a CT chest may also be appropriate.

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