Cystic Fibrosis

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Guideline originally developed by Gulnar Com, MD May 31, 2011.

Key Points

- Cystic fibrosis (CF) is an inherited disease of the secretory glands that affects the respiratory, gastrointestinal, glandular, and reproductive systems.
- CF is inherited in an autosomal recessive fashion.
- Pulmonary disease remains the leading cause of morbidity and mortality in patients with CF.
- Multidisciplinary standardized treatment at CF Foundation-accredited care centers account for significant improvement in patient survival.

Epidemiology

- In the United States, CF occurs in approximately 1: 3,000 Caucasians and far less commonly in other races.
- Median survival for CF patients in the United States is 39.3 years.

Pathophysiology

Overview

- CF is caused by reduction or dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride and bicarbonate regulator located in the airways, sweat glands, hepatobiliary system, and reproductive tracts.
- In CF the combination of reduction in chloride transport and unregulated excessive sodium transport leads to the classic ion and water hydration defects that occur in the

- Pancreas and vas deferens in utero
- Airways, biliary tract, intestines, reproductive tracts, and sweat glands after birth

Organ System Involvement/Clinical Features

Lower Respiratory Tract Involvement

- Lung disease continues to be the major cause of morbidity and mortality.
- Clinical symptoms vary widely. Typical respiratory manifestations of CF include
  - Persistent, productive cough
  - Hyperinflation of lung fields and peribronchial thickening on chest radiograph
  - Pulmonary function tests consistent with obstructive airway disease
- As the disease progresses, chronic bronchitis and, in most cases, progressive bronchiectasis develop and are accompanied by acute exacerbations.
- Exacerbations are characterized by increased cough, tachypnea, dyspnea, increased sputum production, malaise, anorexia, and weight loss.
- Digital clubbing often is seen in patients with moderate to advanced disease.
- The airways become a reservoir for chronically infected mucopurulent secretions, first colonized by *Hemophilus influenzae* and *Staphylococcus aureus* and later by *Pseudomonas aeruginosa*. In most cases the initial isolation of *Pseudomonas* is the nonmucoid form that later changes to the mucoid form. Once the mucoid form of *P aeruginosa* colonizes the lungs, it is virtually impossible to eradicate.
- Methicillin-resistant strains of *S aureus* (MRSA) are increasing and a cause for concern. CF patients appear susceptible to colonization and infection of other microbes including *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex, nontuberculous mycobacteria (especially *Mycobacterium avium* complex and *Mycobacterium abscessus*), and the filamentous fungus *Aspergillus fumigatus*.

Upper Respiratory Tract Involvement

- The upper airway is severely affected in CF.
- Chronic pansinusitis is found in more than 99% of CF patients, due in part to mucous gland hyperplasia, abnormal chloride ion transport by the sinus epithelial cells, and colonization with bacteria.
- Chronic sinusitis may contribute to lower respiratory tract infection by acting as a reservoir of infection.
- Sinus involvement is complicated by nasal polyposis in 6% to 40% of patients.
  - Nasal polyps should be suspected if nasal air flow is obstructed, the nasal bridge widens, or there is persistent epistaxis or loss of taste and appetite.
  - Polyps appear in childhood and can recur after initial resection.
  - If the disease is left untreated, serious bony erosions can occur.

Pancreatic Disease

- Dysfunctional CFTR produces a deficiency in exocrine pancreatic secretions because of progressive plugging of the pancreatic ducts by viscous secretions. The loss of pancreatic enzyme activity leads to intestinal malabsorption of fats and proteins and, to a lesser extent, carbohydrates.
- Common symptoms and signs of pancreatic insufficiency include malabsorption with frequent, bulky, foul-smelling stools that may be oily (steatorrhea), poor weight gain or failure to thrive, and deficiencies of fat-soluble vitamins A, D, E, and K. Severe untreated pancreatic insufficiency occasionally presents with a syndrome of edema, hypoproteinemia, electrolyte

loss, and anemia.
- Both children and adults with residual pancreatic function may develop recurrent episodes of pancreatitis.
- CF-related diabetes (CFRD) develops due to dysfunction of the endocrine pancreas.
    - CFRD affects up to 50% of CF patients by 30 years of age.
    - The prognosis for CF patients is worse if they also have CFRD.
    - Current CF guidelines recommend CRFD screening with an oral glucose tolerance test starting at 10 years of age.

Gastrointestinal Disease

- Meconium ileus is characterized by obstruction of the bowel by meconium in a newborn infant and is the presenting problem in 10% to 20% of newborns with CF.
- Small bowel obstruction, known as distal intestinal obstructive syndrome (DIOS), may occur in older children. When identified early, DIOS usually can be controlled medically. Surgery may be needed for severe obstruction.
- Rectal prolapse, which may be related to constipation and/or malnutrition, rarely occurs in children with CF.

Hepatobiliary Disease

- Liver disease can result from biliary tract obstruction and inflammation.
- In CF focal biliary cirrhosis appears in 10% to 20% of infants by 1 year and in up to 80% of adults.
- Bile salts can help reduce biliary sludging.

Infertility

- More than 95% of men with CF are infertile because of defects in sperm transport although spermatogenesis is not affected.
- Females with CF are less fertile than normal healthy women, likely due to malnutrition and tenacious cervical mucus. Because females with CF may become pregnant, they should be counseled about contraception and childbearing.

Musculoskeletal Disorders

- CF patients have reduced bone mineral content and increased rates of fractures and kyphoscoliosis.
- CF arthropathy occurs in 2% to 9% of patients and is characterized by brief episodes of joint pain and swelling. These features are occasionally accompanied by painful nodular skin lesions and purpura.

Sweat Gland Effects

- In CF patients sweat gland function is abnormal. Inadequate reabsorption of salt results in increased salt content of sweat secretions. Many times, a CF patient first presents because parents are concerned that the child tastes salty.
- Heavy exercise can lead to increased salt losses and profound hyponatremic dehydration.

Diagnosis

Diagnostic Criteria in Screened Populations

- Newborn screening may lead to earlier intervention and improved outcomes.
- In Arkansas, serum immunoreactive trypsinogen (IRT) is used as the initial screening test followed by DNA analysis for infants with abnormal screening (see Figure).

Figure. Newborn screening for cystic fibrosis algorithm

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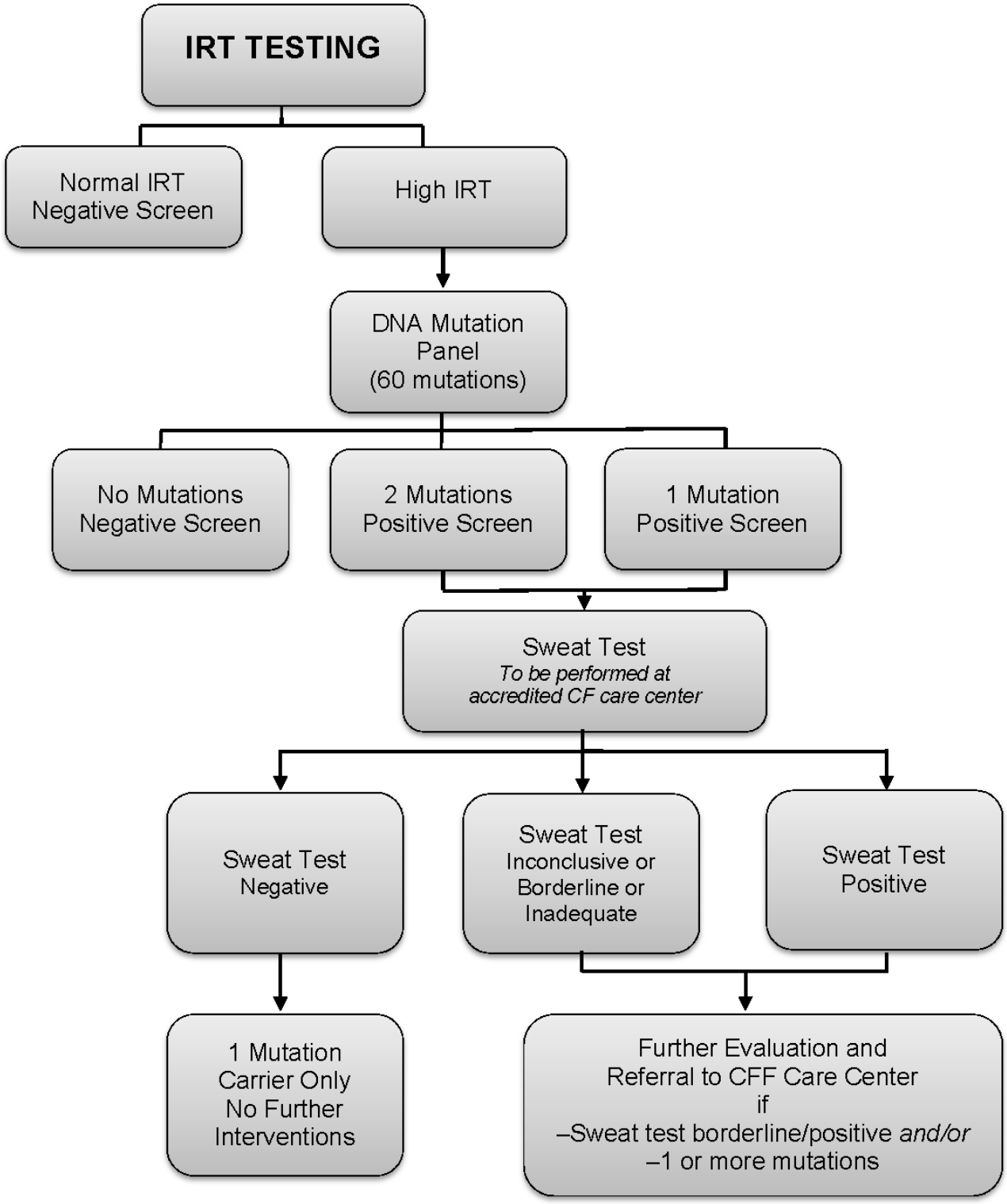
Figure. Newborn screening for cystic fibrosis algorithm



Diagnostic Criteria in Nonscreened Populations

- Two criteria must be met for a diagnosis of CF (Table 1).
- The criteria of clinical symptoms are not required for siblings of CF patients.
- All patients need to have CF DNA analysis performed.

Table 1. Diagnostic Criteria for Cystic Fibrosis

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***Both* of the following criteria must be met for a CF Diagnosis**	
1	Clinical symptoms consistent with CF in at least 1 organ system, AND
2	Evidence of CFTR dysfunction (any of the following): • Elevated sweat chloride >60 mmol/L (on 2 occasions) • Presence of 2 disease-causing mutations in CFTR, 1 from each parental allele • Abnormal NPD

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; NPD, nasal potential difference.
Information from Sosnay PR, White TB, Farrell PM, et al. Diagnosis of Cystic Fibrosis in Nonscreened Populations. *J Pediatr.* 2017;181S:S52-S57 e52.

Laboratory Tests

Sweat Testing

Description

- Sweat chloride testing remains the gold standard for diagnosing CF.
- Sweat tests should be done only by laboratories accredited by the CF Foundation.

Indications

- Positive CF newborn screening results (ie, newborns >36 weeks' gestation and >2 kg body weight with a positive CF newborn screen or positive prenatal genetic test should have sweat chloride testing performed as soon as possible after 10 days of age, ideally by the end of the neonatal period [4 weeks of age])
- Infants with symptoms suggestive of CF (eg, meconium ileus, failure to thrive)
- Older children and adults with symptoms suggestive of CF (eg, chronic respiratory infections, chronic sinusitis, nasal polyposis, digital clubbing, male infertility)
- Siblings of a patient with confirmed CF diagnosis

Interpretation

Results of sweat testing can help determine CF diagnosis (Table 2).

Table 2. Interpretation of Sweat Testing Results

To view a larger image on your device, please click or touch the image.

Value	Interpretation	Diagnosis
<29 mmol/L	Normal	CF very unlikely
30 to 59 mmol/L	Intermediate	Possible CF or CRMS/CFSPID
>60 mmol/L	Abnormal	Diagnosis of CF

Abbreviations: CF, cystic fibrosis; CFSPID, cystic fibrosis screen positive inconclusive diagnosis; CFTR, cystic fibrosis transmembrane conductance regulator; CRMS, CFTR-related metabolic syndrome.

Source: Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: Consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr*. 2017;181S:S4-15.

Mutation Analysis

Description

- Mutation analysis is DNA testing for CF gene mutations. Knowing specific gene mutations aids in selection of appropriate treatment options.
- A free Mutation Analysis Program is offered by the CF foundation for patients with a confirmed diagnosis.
- Preconception and prenatal diagnosis and carrier detection is possible for CF families. The links between genetic and phenotypic information are collected by an international consortium (Clinical and Functional Translation of CFTR), and results are posted on the consortium's website.

Indications

- Mutation analysis is part of the newborn screening process and also should be ordered in any other patient not identified through the screening program.
- For individuals with an intermediate or positive sweat chloride test result but in whom 2 mutations are not detected by the standard genetic screen, more extensive methods with CFTR full gene sequencing and deletion/duplication analysis should be used to detect CFTR mutations.

Nasal Potential Difference Measurements

Description

Nasal potential difference (NPD) testing uses electrodes in the nasal cavity to take voltage measurements of chloride. CF patients demonstrate a more negative potential difference across respiratory epithelium than normal.

Indications

In instances where CF diagnosis remains unclear or evidence is equivocal, further evidence of CFTR dysfunction (eg, nasal potential difference measurement) is sometimes needed.

Other Tests for Assessment of End Organ Involvement

The tests below should be performed for assessment of end organ involvement in CF patients:

- ***Fecal elastase:*** Exocrine pancreatic function is evaluated by measurement of fecal elastase. This test has shown considerable sensitivity and reliability and is not contaminated by exogenous enzyme administration.
- ***Respiratory culture:*** Sputum, oropharyngeal swabs, bronchoalveolar lavage fluid, or sinus aspirates can be cultured for known CF pathogens.
- ***Computed tomography (CT) scanning:*** This can be used to evaluate sinuses and also pulmonary changes not readily visible on plain radiography.
- ***Semen analysis/ ultrasonography of vas deferens:*** Postpubertal males can have semen analysis, or younger males can be assessed with ultrasound for congenital bilateral absence of the vas deferens.

Management

Collaboration between the primary care physician and the patient's CF care center is important because these patients may require frequent clinic visits and hospitalizations. The standard of care includes 4 annual visits to a CF Foundation-accredited care center.

Airway Clearance

- Daily airway clearance is a crucial component of routine CF management.
- Consider the patient's age when determining the best airway clearance technique.
    - For example, manual clapping is an appropriate airway clearance technique for all ages, but it is the most common technique for infants and young children.
    - Older patients use devices based on either vibratory/oscillatory or positive expiratory pressure principles.
- Other considerations for specific technique/device selection include economics; patient's ability, cooperation, personality, and lifestyle; and experience of CF providers with a specific device.
- Exercise should be incorporated into CF management for patients of all ages. Although it does not take the place of airway clearance, exercise has a positive effect on the patient's mental and physical status.

Agents Promoting Airway Secretion Clearance

Inhaled B_2-adrenergic Receptor Agonists

- Short-acting β-adrenergic receptor agonists can help in the following situations:
    - Before chest physiotherapy to clear airway secretions
    - As rescue medication for CF patients with evidence of airway hyperreactivity manifested either by improvement in pulmonary function or by the patient reporting symptomatic improvement with acute use
    - Immediately prior to inhalation of either nebulized hypertonic saline or inhaled antibiotics to limit nonspecific bronchial constriction

Other Agents

- Inhaled DNase I (dornase alfa)—hydrolyzes DNA in sputum/mucus of CF patients and reduces viscosity of airway secretions thus improving airway clearance
- Inhaled hypertonic saline—hydrates and improves airway clearance of inspissated airway secretions in CF patients

Antibiotics

- Antibiotics (inhaled, oral, and intravenous [IV]) are essential tools for the treatment of both chronic infections and acute exacerbations of CF lung disease.
- Chronic treatment with nebulized antibiotics directed against *P aeruginosa* (eg, tobramycin and aztreonam) appears to improve lung function and is recommended for patients who are chronically colonized with the organism.

Antiinflammatory Therapy

Neutrophilic inflammation is present in the airways of patients with CF.

Macrolide Antibiotics

- Macrolides have antiinflammatory properties.
- Azithromycin is used for its immunomodulatory effect in patients who are chronically infected with *P aeruginosa* (Table 3).
- An electrocardiogram should be performed before starting chronic therapy to rule out prolonged QT syndrome.
- A sputum culture for nontuberculous mycobacteria should be ordered in those patients able to produce sputum.

Table 3. Recommended Dosing of Azithromycin in Children >6 Years of Age

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Weight	Dosing
<40 kg	250 mg/day 3 times a week
≥40 kg	500 mg/day 3 times a week

Ibuprofen

- High-dose ibuprofen can slow the progression of lung disease in CF patients.
- CF Guidelines recommend using ibuprofen in patients 6 to 17 years of age.
    - High doses (20 to 30 mg/kg BID) are recommended with close monitoring while maintaining a serum concentration of 50 to 100 mcg/mL.
    - Drug monitoring is required.

Systemic Glucocorticoids

The CF Foundation recommends against routine chronic use of oral corticosteroids in CF patients aged 6 to 18 years in the absence of asthma or allergic bronchopulmonary aspergillosis because of associated adverse effects.

Pancreatic Enzyme Replacement Therapy

- The mainstay of treatment for pancreatic insufficiency in CF is pancreatic enzyme replacement therapy (PERT). Multiple formulations of pancreatic enzymes exist with different combinations of lipase, protease, and amylase.
- PERT clearly improves fecal fat absorption in most patients with pancreatic insufficiency.
- Dosing of pancreatic enzymes is based upon the units of lipase determined as a function of patient weight or dietary fat intake. The dose should not exceed 10,000 units of lipase/kg/day.

Multivitamins

- Pancreatic insufficiency and CF-related liver disease lead to fat malabsorption that predisposes patients to deficiencies of fat-soluble vitamins.
- The CF Foundation recommends supplementation of these vitamins for all children with CF.
    - Doses are considerably higher than those recommended for individuals without CF.
    - Supplements should be started as soon as CF is diagnosed, including in asymptomatic infants and in individuals without pancreatic insufficiency.

Nutrition

The CF Foundation recommends that CF patients 0 to 2 years of age maintain weight/length >50th percentile and those patients >2 years of age maintain a BMI >50th percentile.

Cystic Fibrosis Transmembrane Regulator Modulators

Ivacaftor (KALYDECO)

- Ivacaftor (VX-770), a CFTR potentiator that helps the CFTR protein to function more normally, is the first medication to treat the underlying cause of CF in patients with specific mutations in the CFTR gene.
- KALYDECO (ivacaftor) therapy is used for CF patients with specific mutations (Table 4).
- Coadministration with CYP3A inducers (eg, rifampin, St. John's wort) decreases effectiveness and is not recommended.

Table 4. KALYDECO Therapy

To view a larger image on your device, please click or touch the image.

CF Mutation	CF Patient Age	Oral Dosing
G551D, R117H, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P or G1349D	Adults and children ≥6 years of age	1 tablet (150 mg) every 12 hours*
	2 to <6 years of age and <14 kg	1 packet (50 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid every 12 hours*
	2 to <6 years of age and >14 kg	1 packet (75 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid every 12 hours*

*Give with fat-containing food

Lumacaftor-Ivacaftor (Orkambi)

- The combination agent lumacaftor-ivacaftor is effective in CF patients homozygous for the F508del mutation, the most common mutation in CF patients in the United States.
  - Lumacaftor (VX-809) is a CFTR corrector that partially corrects the CFTR misfolding.
  - Ivacaftor (VX-770) is a CFTR potentiator that improves CFTR-gating abnormality.
- Orkambi (lumacaftor-ivacaftor) therapy is used for CF patients who are homozygous for F508del mutation (Table 5).
- See Table 6 for Orkambi drug-drug interactions.

Table 5. Orkambi Therapy

To view a larger image on your device, please click or touch the image.

CF Mutation	CF Patient Age	Oral Dosing
F508del homozygous	≥12 years	2 tablets every 12 hours (lumacaftor 200 mg, ivacaftor 125 mg)*
	≥6 to 11 years	2 tablets every 12 hours (lumacaftor 100 mg, ivacaftor 125 mg) *

*Give with fat-containing food

Table 6. Orkambi Drug-drug Interactions

To view a larger image on your device, please click or touch the image.

Class/Agent	Effect	Recommendations
Antimicrobials	Rifampin: ↓ ivacaftor Azole antifungals: ↓ antifungal	Do not coadminister rifampin/ivacaftor Use voriconazole and monitor levels Use others and monitor effectiveness Use fluconazole
Antihistamines	↓ or ↑ levels of cetirizine, loratadine, fexofenadine	Monitor symptoms
Corticosteroids	↓ corticosteroids	Monitor; higher doses may be needed
Acid blockers	↓ PPI levels (especially lansoprazole) ↓ or ↑ ranitidine	Monitor effectiveness of PPI Use ranitidine
SSRI antidepressants	↓ SSRI (especially escitalopram) No interaction with paroxetine	Monitor effectiveness of SSRI
Hormonal contraceptives	↓ estrogen and progesterone	Not reliable as birth control Generally continued for other indications
St. John's wort		Coadministration not indicated

Abbreviations: PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitors.

Resources

For Health Care Providers

The following are helpful resources for healthcare providers:

- CF Foundation website
  - For Clinicians
  - CF Clinical Care Guidelines
  - CF Patient Registry
  - Partnerships for Sustaining Daily Care
  - Prior Authorizations
  - Clinical Trials
  - Mutation Analysis Program
- Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report
- Cystic Fibrosis: Clinical Manifestations and Diagnosis (*UpToDate*)

For Patients

Here are resources for parents, caregivers, and patients:

- CF Foundation: For Parents and Guardians
- What is Cystic Fibrosis? (National Institutes of Health)
- Cystic Fibrosis News Today
- CF Foundation Facebook page
- CF Foundation YouTube channel

This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

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