Clinical Practice Guidelines

Cystic Fibrosis

Program Update: 08/31/2014

Approved by:
Andrew Krueger, MD
Patrick A. Flume, MD
Clement L. Ren, MD

Accordant Clinical Practice Guidelines:
Cystic Fibrosis (CF)

Table of Contents

Accordant Clinical Practice Guidelines:
Cystic Fibrosis (CF)

INTRODUCTION

The AccordantCare™ program works with health plans to assess, monitor, and support those with certain complex, chronic conditions. The focus of the program is to improve health outcomes and prevent or limit disease-related complications. AccordantCare offers unique services at no additional charge to the patient, putting them in a strong position to adhere to their treatment plan.

There are several ways AccordantCare augments physicians' efforts. Through regular telephone contact, AccordantCare nurses:

- Keep patients informed about the disease process
- Coach patients in self-motivation and self-care skills
- Encourage patients to alert their physician when new symptoms arise
- Direct patients to resources that help pay for medication, transportation, home modifications, etc.
- Ensure preventive and screening measures are accomplished
- Provide emotional support to patients and caregivers
- Screen for depression
- Find local support groups

We invite physicians to make use of the services offered by AccordantCare and to suggest ways we can further patients' treatment goals. To offer feedback, get more information, ask questions or voice concerns, call toll-free 1-800-948-2497 to speak with a program representative from 8 a.m. to 9 p.m., Monday through Thursday, and from 8 a.m. to 5 p.m. on Friday, Eastern Time. Messages left after hours will be returned the next business day.

Intent of Guidelines

The purpose of this Clinical Practice Guideline is to describe current patterns of practice consistent with national guidelines and standards of care for diagnosis and management. It is not meant to dictate care of patients. Decisions about care are made by the physician and the patient based on the individual needs of that patient.

A patient's health plan may or may not pay for the all medicines, tests, equipment, or services mentioned in this document. Benefits should be checked with the individual's health plan to assure payment.

DISEASE OVERVIEW

Cystic fibrosis (CF) is a genetic (autosomal recessive) disease affecting sodium and chloride ion (salt) transport in epithelial cells. The disease occurs when a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein causes abnormal salt and water transport, resulting in dehydrated, thick secretions. The name derives from the abnormal appearance of the pancreas,

which develops fibrotic changes due to the blockage of pancreatic ducts caused by thick, tenacious secretions.

Abnormal salt transport also causes abnormal secretions in the respiratory, gastrointestinal, and reproductive systems. The most dangerous consequence of CF is progressive pulmonary disease that occurs as the abnormal secretions in the lungs cause chronic inflammation, infection and obstruction, resulting ultimately in respiratory failure. The abnormality of the pancreas causes a defect in digestive enzyme secretion, which leads to malnutrition without optimal treatment.

Cystic fibrosis was once thought to be strictly a childhood disease, since a baby born with CF in 1955 typically did not survive to attend school. Because of improvements in clinical and nutritional care, however, the median age of survival in the US as of 2010 is 38 years.[1] There are approximately 30,000 people in the US with CF.[2]

DIAGNOSIS OF DISEASE[3]

Prenatal Diagnosis

- Gene mutation testing from chorionic villus sampling or amniocentesis, generally performed in a pregnancy with 2 known carrier parents

Newborn Screening

- Immunoreactive trypsin (measured in blood obtained with a heel stick) with or without testing for common CF gene mutations. Protocols and algorithms vary state by state. All infants with positive newborn screening require a sweat test to see whether they are affected
- Pilocarpine iontophoresis (sweat test)

Later Diagnosis of CF

- Pilocarpine iontophoresis (sweat test)
- Gene mutation testing
- Nasal potential difference testing (limited to difficult-to-diagnose cases and only performed at comprehensive CF research programs)

APPROACH TO MANAGEMENT OF PRIMARY CONDITION

Treatment Goals

According to the Cystic Fibrosis Foundation, the main goals of treatment are to[4]:

- make people with CF and their families full members of the care team
- help people with CF achieve normal growth and nutrition status
- diagnose respiratory infections early and ensure that the right therapies are received
- decrease the spread of germs between people with CF
- prevent complications and/or diagnose and treat them early

- provide care regardless of race, age, education or insurance coverage
- support all transplantation and end-of-life care decisions

Recommended non-drug therapies

Airway Clearance Therapies (ACTs)[5]

- Conventional chest physiotherapy
- Active cycle breathing technique
- Autogenic drainage
- Positive expiratory pressure
- Airway oscillating devices
- High frequency chest compression
- Exercise

Oxygen Therapy[6]
Non-invasive ventilation[7]
Proper nutrition
Exercise[5]

Recommended drug therapies

Antibiotics

Aerosolized antibiotics are generally used for eradication of initial infection and for chronic suppressive therapy. Oral antibiotics treat mild exacerbations, while intravenous antibiotics are generally reserved for more severe exacerbations.[8]

Pseudomonas aeruginosa[9]

- tobramycin
- tobramycin inhalation powder (TOBI® Podhaler™)[10]
- aztreonam[11,12]
- colistin
- gentamicin
- ceftazidime

Burkholderia cepacia[13]

- meropenem
- ceftazidime
- chloramphenicol
- tetracycline
- trimethoprim sulfamethoxazole

Staphylococcus aureus[14]

- dicloxacillin
- cephalexin
- clindamycin
- amoxicillin-clavulanat
- trimethoprim sulfamethoxazole

- linezolid

Bronchodilators[6]
β-adrenergic agonists (e.g., albuterol)
inhaled anticholinergic agents

Mucolytic Agents[9]
Pulmozyme® (dornase alfa)
hypertonic saline

CFTR Modulator[15]
Ivacaftor (Kalydeco®): for those with one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N,* or *S549R*.[16]

Anti-Inflammatory Medicines[9]
NSAIDs (ibuprofen)[12]
Chronic macrolides (azithromycin)[12]
Leukotriene antagonists (e.g., montelukast, zafirlukast, eicosapentaenoic acid)

Lung transplant surgery[17]
Patients most likely to benefit from lung transplant include those with[18]:

- a low 5-year predicted survival rate
- hypercapnic respiratory failure
- pulmonary hypertension
- rapidly worsening lung disease
- FEV_1 <30% predicted
- massive hemoptysis
- increasing malnutrition
- increasing hospitalization frequency

PREVENTION AND MANAGEMENT OF COMPLICATIONS

Accordant helps patients and caregivers prevent and manage complications by teaching early warning signs, encouraging adherence to treatment plans, offering supportive care, and recommending physician contact where needed. The list of goals and cooperative interventions listed below does not represent a comprehensive list of complications but reflects some of the more common clinical situations specific to cystic fibrosis. General health topics (e.g., age-appropriate cancer screening) are beyond the scope of this document.

Goal: Improve self-management skills
Cooperative interventions include teaching parents/patients the importance of:

- personal motivation building;
- prevention-focused, behavioral self-management skills development;

- confidence and communication;
- adhering to treatment plan; and
- knowledge development

Goal: Maintain general health
Cooperative interventions include teaching parents/patients to:

- partake in aerobic exercise as an adjunct to airway clearance;
- drink lots of fluids;
- add plenty of salt to diet, especially during heavy exertion and during hot weather;
- perform airway clearance therapy every day at the frequency prescribed by doctor;
- have annual flu and other appropriate vaccinations; and
- transitioning from a pediatric to adult clinic

Goal: Control allergic bronchopulmonary aspergillosis (ABPA)
Cooperative interventions include teaching parents/patients to:

- know the symptoms of ABPA and report them (and any change in respiratory status) to a doctor or nurse;
- follow all medicine schedules as prescribed; and
- get a blood test for IgE every year

Goal: Control asthma
Cooperative interventions include teaching parents/patients to:

- know the symptoms of asthma and report them to a doctor or nurse;
- use inhalers properly;
- use a peak flow meter to monitor airflow;
- learn what triggers asthma attacks and how to avoid the triggers; and
- recognize the signs of asthma that require emergency treatment (e.g., extreme difficulty breathing, bluish color to the lips and face, rapid pulse, sweating, severe anxiety due to shortness of breath, confusion or severe drowsiness).[19]

Goal: Control Pseudomonas infection
Cooperative interventions include teaching parents/patients to:

- know the signs and symptoms of lung infection and report them to a doctor or nurse;
- know the signs and symptoms of pulmonary exacerbation and report them to a doctor or nurse;
- clean and disinfect respiratory therapy equipment;
- practice good hand washing hygiene;
- understand the importance of taking antibiotics as prescribed and of taking the complete regimen; and
- avoid close contact (<3 feet) with other CF patients and follow health care facility infection control procedures to reduce the risk of exposure

Goal: Control *Burkholderia cepacia* infections
Cooperative interventions include teaching parents/patients to:

- clean and disinfect respiratory therapy equipment;
- practice good hand washing hygiene;
- follow health care facility infection control procedures to reduce the risk of exposure;
- understand the importance of taking antibiotics as prescribed and of taking the complete regimen; and
- seek support for the psychological and social issues of isolation

Goal: Cystic fibrosis-related bone disease
Cooperative interventions include teaching parents/patients to:

- ask MD about BMD testing;
- take all vitamin and mineral supplements as prescribed;
- assure vitamin D levels are checked at least annually;[20]
- take precautions with chest physical therapy to avoid rib fractures[21]; and
- perform weight-bearing exercises in the sunshine whenever possible.[22]

Goal: Control cystic fibrosis-related diabetes (CFRD)
Cooperative interventions include teaching parents/patients to:

- understand that people with CF should begin annual screening for CFRD beginning at age 10 in order to diagnose the disease early in its course[23];
- ask their physician once a year for an oral glucose tolerance test to screen for CFRD[24];
- seek ongoing diabetes self-management education from diabetes education programs that meet national standards[23];
- perform self-monitoring of blood glucose at least three times a day if taking insulin[23,25];
- learn carbohydrate counting and other methods of planning meals in order to control blood sugar levels[26];
- know and practice the correct procedure for storing and handling insulin;
- know and practice the correct procedure for the administration of insulin injections;
- understand insulin requirements and the appropriate coordination of insulin injections and food intake[26];
- practice overall good nutrition and maintain the special high-intake needs for people with CF[23];
- know the importance of moderate aerobic exercise
- recognize the following symptoms of hypoglycemia (blood sugar level of less than 60 mg/dL) and how to treat the condition[26]:
    - sudden hunger
    - upset stomach
    - shakiness and weakness
    - more sweat than normal (cold sweat)

  - pale or red face
  - headache
  - confusion
  - blurred or double vision
  - a change in the way the person acts or feels (e.g., acting drunk, crying, feeling nervous, angry)
  - fast heart beat
  - tingling or numbness in lips and mouth
- use caution when driving, especially those at risk for hypoglycemia (blood sugar level less than 70 mg/dL)[27]

Goal: Control gastrointestinal complications
Cooperative interventions include teaching parents/patients to:

- recognize the signs and symptoms of the gastrointestinal complications of CF and report them to a nurse or doctor;
- avoid postural positions during chest physical therapy that exacerbate GERD; and
- avoid drinking alcohol.[28]

Goal: Control pulmonary complications
Cooperative interventions include teaching parents/patients to:

- know the signs and symptoms of hemoptysis and pneumothorax and report them to a doctor or nurse immediately;
- understand the risk for a reoccurrence; and
- follow all prescribed schedules for medicines and airway clearance therapy (which may be modified in the presence of pulmonary complications)
- talk to their doctor about taking high-dose ibuprofen to control inflammation in the lungs

Goal: Control liver and hepatobiliary disease
Cooperative interventions include teaching parents/patients to:

- understand the additional risks involved with drinking alcohol[6];
- understand the signs and symptoms of liver and biliary disease and report them to a doctor or nurse; and
- assure that liver function is measured at appropriate intervals

Goal: Manage proper nutrition
Cooperative interventions include teaching parents/patients to:

- strive for acceptable growth and development as outlined below:
  - 0 to 23 months: weight-for-length = 50th percentile
  - 2 to 20 yrs: BMI-for-age = 50th percentile
  - >20 yrs: BMI of 22 (women) and 23 (men)
- consume 120% to 150% of the recommended dietary allowance for energy per day

- provide young children with the following[29]:
  - high-calorie foods
  - extra salt
  - lots of fluids
  - whole milk at every meal
  - whole-milk dairy products such as cheese, yogurt, and butter
- consume a diet consisting of 35% to 40% of calories from fat,[30] with no specific restrictions (adults)[6];
- take FDA-approved pancreatic enzymes (Zenpep®, Creon®, Pancreaze®, Ultresa™, Pertzye™, Viokace™);[31-35]
- take supplements of fat-soluble vitamins A, D, E, and K[6];
- discuss annual diabetes screening beginning at age 10 with doctor or child's pediatrician[23]; and
- consume energy-rich foods to improve energy intake.[6]

Goal: Control pancreatic insufficiency
Cooperative interventions include teaching parents/patients to:

- recognize the signs and symptoms of pancreatic insufficiency;
- understand the importance of good nutrition to their long-term survival;
- take all enzyme replacement medicines and supplemental vitamins and minerals as prescribed;
- follow all dietary guidelines as prescribed; and
- understand and calculate their body mass index (BMI) or weight-for-length percentile

Goal: Control pulmonary exacerbations
Cooperative interventions include teaching parents/patients to:

- know the signs and symptoms of a pulmonary exacerbation and report them to a doctor or nurse;
- understand and practice effective airway clearance techniques (ACTs) at the prescribed frequency every day;
- understand the importance of taking antibiotics as prescribed and of taking the complete regimen;
- realize that symptoms may not respond immediately to antibiotic therapy and that in some cases lung function may actually decline before it improves[36];
- practice dietary guidelines as specified for individuals with CF;
- realize the importance of taking nutritional supplements as prescribed;
- understand the importance of nebulizer therapy and how to use and care for the equipment;
- avoid tobacco; and
- recognize the need for exercise and perform exercise routines regularly as set forth by a doctor or physical therapist

Goal: Control *Staphylococcus aureus* infections
Cooperative interventions include teaching parents/patients to:

- clean and disinfect respiratory therapy equipment
- practice good hand washing hygiene; and
- understand the importance of taking antibiotics as prescribed and of taking the complete regimen

PATIENT FOLLOW-UP

- Schedule quarterly, multidisciplinary care visits
- Monitor sputum microbiology
- Monitor for GI manifestations
- Assess adherence of airway clearance and medical therapies
- Monitor for bone health
- Provide psychosocial support

PATIENT EDUCATION

- Cystic Fibrosis Foundation: www.CFF.org
- Kids Health: http://kidshealth.org/

References

1. Cystic Fibrosis Foundation. *US Cystic Fibrosis Foundation Annual Regisrty Report 2010*. Bethesda, MD: Cystic Fibrosis Foundation; 2010.
2. About Cystic Fibrosis. Cystic Fibrosis Foundation. http://www.cff.org/AboutCF/. Accessed May 2, 2012.
3. Farrell PM, Rosenstein BJ, White TB. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153:S4-S14.
4. Quality improvement initiative. Cystic Fibrosis Foundation. http://www.cff.org/LivingWithCF/QualityImprovement/. Accessed May 7, 2012.
5. Flume PA, Robinson KA, O'Sullivan BP, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care*. 2009;54(4):522-537.
6. Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care: consensus conference report. *Chest*. 2004;125(1)(suppl 1):1S-39S.
7. Moran F, Bradley JM, Jones AP, Piper AJ. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst Rev*. 2007;(4):CD002769.
8. Susanna A. McColley, MD. Medical Advisory Board 2011 Clinical Review Process.
9. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176(10):957-969.
10. FDA approves TOBI Podhaler to treat a type of bacterial lung infection in cystic fibrosis patients. FDA Website; March 22, 2013. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345123.htm. Accessed May 8, 2013.
11. Cayston (aztreonam) [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2010.
12. Mogayzel PJ, Jr., Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689.
13. Elborn JS. Practical management of cystic fibrosis. *Chronic Respiratory Disease*. 2006;3(3):161-165.
14. Cystic Fibrosis. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics.* 17th ed. Philadelphia, PN: Saunders; 2004:1437-1450.
15. Kalydeco [package insert]. Cambridge, MA: Vertex Pharmaceuticals Incorporated; January 2012.
16. Kalydeco [package insert]. Cambridge, MA: Vertex Pharmaceuticals Incorporated; February 2014.
17. Orens JBEM, Arcasoy S. International guidelines for the selection of lung transplant candidates:2006 Update. *J Heart Lung Transplant*. 2008;25(7):745-755.

18. Flume PA. Pulmonary complications of cystic fibrosis. *Respir Care*. 2009;54(5):618-627.
19. MedlinePlus [Internet]. Bethesda, MD: National Library of Medicine (US); [Asthma; [2011 May 1; cited 2012 May 7]; [about 4 p.]. Available from: http://www.nlm.nih.gov/medlineplus/ency/article/000141.htm.
20. Susanna A. McColley, MD. Medical Advisory Board 2010 Clinical Review Process.
21. Gumery L, Dodd M, Parker A, Prasad A, Pryor J, Kennedy N, eds. *Clinical Guidelines for the Physiotherapy Management of Cystic Fibrosis.* Bromley, United Kingdom: Cystic Fibrosis Trust; 2002.
22. Boyle MP. Update on maintaining bone health in cystic fibrosis. *Curr Opin Pulm Med*. 2006;12(6):453-458.
23. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33(12)(PMC2992215):2697-2708.
24. Kern AS, Prestridge AL. Improving screening for cystic fibrosis-related diabetes at a pediatric cystic fibrosis program. *Pediatrics*. 2013;132(2):e512-e518.
25. Standards of medical care in diabetes--2012. *Diabetes Care*. 2012;35 Suppl 1:S11-S63.
26. Bruznell C, Hardin DS, Moran A, Schindler T. *Managing Cystic Fibrosis-Related Diabetes (CFRD)*. Bethesda, MD: Cystic Fibrosis Foundation; 2011. http://www.cff.org/UploadedFiles/LivingWithCF/StayingHealthy/Diet/Diabetes/CFRD-Manual-5th%20Edition-05-2012.pdf. Accessed May 15, 2012.
27. Hypoglycemia. National Institute of Diabetes and Digestive and Kidney Disease. http://diabetes.niddk.nih.gov/dm/pubs/hypoglycemia/#points. Accessed May 10, 2012.
28. *Pancreatitis.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; NIH Publication No. 04-1596. http://digestive.niddk.nih.gov/ddiseases/pubs/pancreatitis/. Accessed May 7, 2012.
29. Cystic Fibrosis Foundation. *Nutrition for Your Child with Cystic Fibrosis*. Bethesda, MD: Cystic Fibrosis Foundation; 2006. http://www.cff.org/UploadedFiles/treatments/Therapies/Nutrition/ForChild/Nutrition%20-%20For%20Your%20Child%20w%20CF%2002-06.pdf. Accessed September 1, 2007.
30. Turcios NL. Cystic fibrosis: an overview. *J Clin Gastroenterol*. 2005;39(4):307-317.
31. Creon (pancrelipase) delayed-release capsules [package insert]. North Chicago, IL: Abbott Laboratories; June 2011.
32. Zenpep (pancrelipase) delayed-release capsules [package insert]. Milan, Italy: Eurand S.p.A.; June 2011.
33. Ultresa (pancrelipase) [package insert]. Birmingham, AL : Aptalis Pharma US, Inc ; March 2012.

34. Pancreaze (pancrelipase) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; September 2011.
35. Viokace (pancrealipase) [package insert]. St. Hubert, Canada: Confab Laboratories, Inc.; March 2012.
36. Ferkol T, Fosenfeld M, Milla CE. Cystic fibrosis pulmonary exacerbations. *J Pediatr*. 2006;148(2):259-264.
37. Kalydeco [package insert]. Cambridge, MA: Vertex Pharmaceuticals Incorporated; December 2014.

