Cystic Fibrosis: Improving quality of life

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ABSTRACT

Cystic Fibrosis (CF) or Mucoviscidosis is an inherited condition. In cystic fibrosis transmembrane conductance regulator (CFTR) protein does not function properly i.e regulation of fluids and salts outside the cells. Cystic fibrosis affects exocrine glands eg., the mucus-secreting and sweat glands in the respiratory and digestive systems. The frequency of common mutation F508del (deletion of phenylalanine residue at position 508) in children is between 19% and 34%. The estimate frequency of CF as 1:10,000 to 1:40,000 in children. There is no cure for cystic fibrosis, but treatment can reduce symptoms and complications to improve quality of life. Close monitoring and early, aggressive intervention is recommended to slow the progression of CF, which can lead to possible longer life.

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Table 1: Grades of cystic fibrosis

| Class | Mutation |
|-------|----------|
| Classic or typical CF | CFTR is not synthesized |
| Class I | CFTR is synthesized but in abnormal form |
| Class II | CFTR is synthesized but there is disruption at cell membrane |
| Class III | Reduced chloride conductance |
| Non Classic or Atypical CF | CFTR synthesis or processing is partly defective |
| Class IV | Impaired conductance of ions other than chloride |
| Class V | |
| Class VI | |

1. Introduction

Cystic fibrosis is a genetic, autosomal recessive disease that involves different organ systems with particular damage occurring to the respiratory and gastrointestinal tracts.1,2 The most common mutation worldwide, found in approximately 66% of patients with CF, is a class II mutation caused by a deletion of phenylalanine in position 508 (F508del) of CFTR. F508del CFTR is misfolded and trapped in the endoplasmic reticulum (ER) and subsequently proteolytically degraded.

The gene that encodes the CFTR protein, which is called CFTR, is located on chromosome 7. Mutations in this gene lead to CF. CFTR’s soluble domains, which include two nucleotide binding domains (NBF1 and NBF2) and a regulatory domain (R). The cystic fibrosis transmembrane conductance regulator (CFTR) is defective in cystic fibrosis (CF). The CFTR gene provides instructions for making a protein called the cystic fibrosis transmembrane conductance regulator. This protein functions as a channel across the membrane of cells that produce mucus, sweat, saliva, tears, and digestive enzymes. The channel transports negatively charged particles called chloride ions into and out of cells.
1.1. Symptomatology

CF is characterized by mucoviscid respiratory tract secretions that impair ciliary clearance. There is salty skin, persistent cough, frequent lung infections, wheezing, poor growth and weight gain, greasy bulky stools, and male infertility. Early colonization with Staphylococcus aureus, Haemophilus influenzae, and Streptococcus pneumoniae is followed by chronic infection of the lower respiratory tract due to Pseudomonas aeruginosa.3

Pancreatic insufficiency is the most common gastrointestinal complication of cystic fibrosis (CF), affecting approximately 85 percent of patients at some time in their lives. In rare cases, cystic fibrosis can manifest itself as a coagulation disorder.4

1.2. Differential diagnosis

Gastro-esophageal reflux (GERD), fibrosing colonopathy, Celiac disease, inflammatory bowel disease, strictures and adhesions after surgery, and short bowel syndrome can mimic CF gastrointestinal symptoms5

1.3. Pathogenesis

CF lung may be attributed to endogenously increased levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 8 (IL-8), and IL-1. According to some reports, the levels of these cytokines may be altered in CF subjects even before a bacterial infection can be documented. Intriguingly, reduced levels of the anti-inflammatory cytokine IL-10 have been recently reported in CF patients. Chronic bacterial airway infections are characteristically seen in the majority of individuals with CF. These infections are commonly polymicrobial and rarely can be eradicated with antimicrobial treatment.6,7

1.4. Associated conditions

1. Diabetes occurs in about 10% of adolescents with CF. Beginning at age 10, children should be tested annually with an oral glucose tolerance test to monitor for impaired glucose tolerance
2. Pancreatic insufficient patients may have recurrent episodes of pancreatitis.
3. Small bowel obstruction should be suspected anytime an individual with CF presents with abdominal pain.
4. Meconium ileus is reported in 10–15% of CF new born and is usually but not invariably related to exocrine pancreatic insufficiency. In most infants this intestinal obstruction can be successfully treated with hyperosmolar enemas
5. People with CF may have early aquagenic wrinkling of the skin, in which the palms wrinkle in less than 3 minutes of exposure to water, compared to 7 minutes in carriers and 11 minutes in controls.
2. Diagnosis

Sweat chloride: 60 mmol/l is considered diagnostic of CF. Values of sweat chloride of 40–60 mmol/l are considered highly suggestive of CF. Patients with CF usually have a sweat sodium: chloride ratio > 1. DNA testing for the more common CF transmembrane regulator (CFTR) mutations is a valuable diagnostic test. The identification of increased immunoreactive trypsinogen (IRT) levels in the blood of infants with CF has made neonatal screening for CF possible. Trypsinogen is one of the secretory products of the pancreas making its level in the blood a specific marker of pancreatic function. Immunoreactive Trypsinogen (IRT) \( \geq 120 \text{ ng/mL} \) is confirmatory.¹

3. Treatment

3.1. Preventing and controlling lung infections

Antibiotics are prescribed. These mainly consist of inhaled forms of azithromycin, tobramycin, aztreonam and levofloxacin. Other antibiotics recommended are ciprofloxacin, cephalaxin, amoxicillin and doxycycline depending on the sensitivity pattern.

Aztreonam inhalation solution is an alternative antibiotic for patients with chronic colonization of P aeruginosa. Aztreonam 75 mg is administered by nebulization route three times daily for 28 days on and then 28 days off.

For chronic use, Tobramycin is administered by nebulization (300 mg) or dry powder inhalation (112 mg) twice daily for 28 days on and 28 days off.

Azithromycin 22-30 mg/kg/week is the lowest recommended dose.

The treatment of multidrug-resistant gram-negative bacteria in patients with CF with advanced lung disease is challenging given the intrinsic resistance of these organisms to antimicrobials of several different classes.

3.2. Preventing adequate nutrition and electrolyte

Oral rehydration and osmotic laxatives (incomplete blockage) and hyperosmolar contrast enemas. Providing appropriate nutrition and preventing dehydration—a high-calorie-fat diet, supplemental vitamins ADEK, and minerals including fluoride and zinc are recommended. Additionally sodium chloride supplementation is given tailored to patient’s age and environmental conditions.

3.3. Pancreatic enzyme replacement therapy

As long been considered as a safe, well-tolerated. Consensus Committees recommend pancreatic enzyme replacement with approximately 1800 U lipase/g fat or 1000–3000 U lipase/kg body weight/meal with an upper limit dose of 10,000 U lipase/kg body weight/d. The amount of lipase prescribed ranges from 2,600 to 40,000 lipase units per capsule. (2,500 lipase units x weight in kilograms).

The main functions of enzymes are to:

1. Digest fat, protein and carbohydrate (to supply the body with energy)
2. Promote nutrition absorption
3. Help with weight gain and growth
4. Improve bowel motions

Pancreatic enzyme replacement products are generally well tolerated. Common adverse effects include headache, dizziness, abdominal pain, and flatulence.

Oral corticosteroids at a Prednisolone equivalent dose of 1-2 mg/kg alternate days appear to slow the progression of lung disease in CF but this benefit needs to be weighed against the occurrence of adverse events, in particular, development of cataracts and effect on linear growth.⁹,¹⁰

Megestrol acetate (MA) has been used in several controlled studies. MA 40-80mg seems to facilitate significant weight gain in treatment subjects. It has been successfully used in patients with CF who have failed conventional nutrition interventions. Appetite improvement is reported with significant weight gain consisting of both fat mass and lean body mass.¹¹

3.4. Cystic fibrosis transmembrane regulator replacement therapy

There are four CFTR modulators for population with CFTR mutations:

1. Ivacaftor: is a drug used to treat cystic fibrosis in people with certain mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (primarily the G551D mutation), who account for 4–5% cases of cystic fibrosis. The target CFTR-mutation of ivacaftor, G551D, is a Class III defect. Ivacaftor is a “potentiator” of CFTR, meaning it increases the probability that the defective channel will be open and allow chloride ions pass through the channel pore. Doses in 25, 75, or 150 mg were studied for 14 days followed by a dose of 150 or 250 mg for 28 days. It was concluded that ivacaftor was associated with few severe side effects.

2. Lumacaftor/ivacaftor: is a fixed-dose tablet (200mg of Lumacaftor and ivacaftor 150ng) containing a corrector (lumacaftor) and potentiator (ivacaftor) of the cystic fibrosis transmembrane conductance regulator (CFTR) and is the first therapy approved to treat the underlying cause of cystic fibrosis in patients (aged \( \geq 12 \) years) homozygous for the most common CFTR mutation, F508del. Lumacaftor improves the processing of F508del CFTR and its transport to the cell surface, while ivacaftor increases the channel’s open probability and transport of chloride. lumacaftor 400 mg plus ivacaftor 250 mg, administered every 12 h in combination with standard therapy, was associated
### Table 2: Antimicrobials preferred

| Organism | Antibiotic       | Child Dose | Adult Dose | Side Effects          |
|----------|------------------|------------|------------|-----------------------|
| Gram positive | Vancomycin      | 15mg/kg every 6 hour, IV 10mg/kg IV or Oral | 1gm, IV, 12 hourly 600mg, orally or IV, 12 hourly | Oto/ nephrotoxicity Optic/Peripheral neuropathy |
| MRSA     | Linezolid        | 600mg, orally or IV 12 hourly, hourly 600mg, orally | 6 hour, IV 10mg/kg IV or 50mg/Kg IV every 24 hour | Nephrotoxicity Oto and |
| Gram negative | Tobramycin      | 0mg/Kg IV every 24 hour | 10mg/kg IV | Optic/Peripheral neuropathy, Rash, hepatitis |
| PsAeruginosa | Meropenem     | 2g, 8 hourly, IV 400mg/kg IV | 12 hourly or 750mg BD | GI, Insomnia |
|          | Ciprofloxacin   | 2mg/kg, 8 hourly, IV 500mg-1g, IV, 6 hourly Same as above | 15mg/kg jg IV or 20mg/kg orally every 12 hour | GI, Neutropenia |
| Stenothrophomas maltophilia | Trimethoprim + Sulfamethoxazole | 4- 5mg/kg Orally or IV | 4- 5mg/kg orally | GI, Phototoxicity |
|          | Doxycycline     | 2mg/Kg orally or IV, every 12 | 100mg IV or orally, every 12 | GI, cholestasis |
|          | Tigecycline     | hours 1.2mg / kg every 12 hours | hours 50mg IV 12 hourly | GL, Seizures GI, Insomnia |
| Achromobacter species | Imipenem        | 15-25mg/kg IV, 6 hourly Same as above | 500mg-1g, IV, 6 hourly Same as above | GI, Photosensitivity |
|          | Ciprofloxacin   | 15-25mg/kg IV, 6 hourly Same as above | 100mg, 12 hourly | GI, Photosensitivity |
|          | Minocycline     | 2mg. kg. oral or IV 12 hourly | 100mg. 12 hourly | GI, Photosensitivity |

with an ≈3% statistically significant improvement in lung function relative to placebo

3. **Tezacaftor/ivacaftor**: is approved for individuals 12 years and older with two copies of the most common cystic fibrosis mutation, F508del, as well as for individuals who have a single copy of one of 153 specified mutations. 100 mg of tezacaftor once daily and 150 mg of ivacaftor twice daily or matched placebo for 24 weeks. The adverse events were mild or moderate in severity. None were serious or led to treatment interruption or discontinuation. Tezacaftor/ivacaftor was generally safe, well tolerated, and efficacious in people ≥12 years of age with cystic fibrosis homozygous for Phe508del-CFTR with ppFEV₁ of ≥25% and ≤90% who previously discontinued lumacaftor/ivacaftor due to treatment-related respiratory signs or symptoms. It was better than ivacaftor monotherapy

4. **Elexacaftor-tezacaftor-ivacaftor** is used for use is for persons 12 years of age and older with at least 1 F508del mutation for the CFTR gene. This drug combination provides potential therapy to many patients who had previously been excluded from CFTR modulation therapy due to the nature of their genetic mutations. Side effects were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, alanine aminotransferase raised, nasal congestion, rhinorrhea, rhinitis, influenza, sinusitis, and raised blood bilirubin.

The yearly cost CFTR group is expensive with some benefits.12–14

3.5. **Therapeutic strategies to manage cystic fibrosis**

3.6. **Supportive measures**

Airway clearance techniques — also called chest physical therapy (CPT) can relieve mucus obstruction and help to reduce infection and inflammation in the airways. These techniques loosen the thick mucus in the lungs, making it easier to cough up.
3.7. Corrector/modifier therapeutic agents in clinical pipeline

3.7.1. Andecaliximab
800mg dose of Andecaliximab binds to MMP9 at the junction between the propeptide and catalytic domains, distal to the active site, and acts by preventing the activation of inactive zymogen. It is under advanced stages phase III trial and expected to reduce inflammation and improve lung function. Side effects reported were anemia (20%), DIC, fatigue, anorexia, hypoglycemia, cholangitis, AST elevation and neutropenia.

3.7.2. Riociguat (also used in Pulmonary Hypertension)
Result in improved function of the CFTR protein as a chloride channel, moving salt and fluids in and out of cells. Side effects reported were headache, dizziness, indigestion, swelling of your hands, legs, feet, and ankles (peripheral edema), nausea, diarrhea, and vomiting.

3.7.3. Cavosonstat
An orally bioavailable inhibitor of S-nitrosglutathione reductase, promotes cystic fibrosis transmembrane conductance regulator (CFTR) maturation and plasma membrane stability, with a mechanism of action complementary to CFTR correctors and potentiators. Cavosonstat was well tolerated, with no dose-limiting toxicities.

3.7.4. Ataluren
Was developed for potential treatment of nonsense-mutation cystic fibrosis (CF). Trial results are not very encouraging. Ataluren is taken three times a day, and the recommended dose is 10 mg/kg (10 mg per kilogram body weight) in the morning, 10 mg/kg at midday and 20 mg/kg in the evening (for a total daily dose of 40 mg/kg). Granules (125, 250 and 1,000 mg) are available. Side effects of ataluren include vomiting, nausea, headaches, stomach aches, and flatulence.

3.7.5. Tezacaftor in combination with ivacaftor
The combination of tezacaftor and ivacaftor was efficacious and safe in patients 12 years of age or older who had cystic fibrosis and were homozygous for the CFTR Phe508del mutation.9–15

3.7.6. Lung transplantation
International Society for Heart and Lung Transplantation (ISHLT) Guidelines:

| Oxygen-dependent respiratory failure | Hypercapnia |
|-------------------------------------|-------------|
| Pulmonary hypertension              | FEV1 < 30% of baseline or rapid decline in FEV1, particularly if female |
| Recurrent haemoptysis not controlled by embolism | Refractory and/or recurrent pneumothorax |

For severe cystic fibrosis-related liver disease, such as cirrhosis, liver transplant may be an option. In some people, a liver transplant may be combined with lung or pancreas transplants.16

3.7.7. Oxygen therapy
Cystic fibrosis may cause hypoxia. Oxygen therapy may down-regulate inflammation, halting the catabolic effects of a pro-inflammatory state, and also reduce complications associated with hypoxia. High-flow nasal cannula oxygen therapy (HFOT) is an oxygen technique offering greater comfort and more efficient oxygenation than standard oxygen. HFOT is increasingly used, particularly in patients with acute hypoxemic respiratory failure.

People with cystic fibrosis (CF) suffer from breathing problems. Giving additional oxygen has long been a standard of care for people with chronic lung diseases. Participants receiving oxygen therapy were able to exercise for a significantly longer duration during exercise. Often,
patients who need oxygen therapy for 15 hours or more use a large oxygen tanks. High-flow nasal cannula oxygen therapy (HFOT). Is an oxygen technique offering greater comfort and more efficient oxygenation than standard oxygen. HFOT is increasingly used, particularly in patients with acute hypoxic respiratory failure. A large randomized controlled trial has found that mortality of patients with acute hypoxic respiratory failure was lower when they were treated with HFOT than with standard oxygen.17,18

4. Conclusion
Treatment for cystic fibrosis (CF) will depend on child’s symptoms, age, and general health. There is no proper for cystic fibrosis, and the disease generally gets worse over time. Maintenance treatments reduce the risk of pulmonary exacerbations. Antibiotics should be targeted against the common CF bacteria and these could be given orally, but i.v. antibiotics will be required for ongoing symptoms or severe pulmonary exacerbations. Management of comorbidities, like poor nutrition and diabetes, will be critical in improving outcomes. Four CFTR modulators for people with certain CFTR mutations are generally adopted. Management of comorbidities, like poor nutrition and diabetes, will be critical in improving outcomes.

5. Source of Funding
None.

6. Conflict of Interest
None.

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Cite this article: Chaudhry S. Cystic Fibrosis: Improving quality of life. J Community Health Manag 2021;8(2):91-96.