Pathophysiology of Cystic Fibrosis
Implications for Critical Care Nurses

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CFTR, the gene associated with cystic fibrosis, encodes the protein cystic fibrosis transmembrane conductance regulator (also abbreviated CFTR, but not italicized). The gene was identified in 1989 and is found at 7q31.2, the long arm (q) of chromosome 7 at position 31.2. Survival has increased for patients with cystic fibrosis from late teens to mid-30s because of the many advances in diagnosis and treatment, and in some instances, lung transplantation. As a result, critical care nurses are increasingly likely to provide care for patients who have this disease.

Etiology

More than 1000 possible changes can occur in CFTR to cause cystic fibrosis, but approximately 70% of all patients with cystic fibrosis have the same defect: F508. This defect is a deletion of 3 bases that causes the loss of the protein phenylalanine. Patients who have a complete loss of the CFTR gene have a clinical phenotype representative of pancreatic disease, severe pulmonary disease, gastrointestinal problems, and infertility (in men) or, sometimes, fertility problems (in women). Other patients have a partial loss of the gene, so their phenotype may be less severe (Table 1). Type I and type II errors in the production of the protein CFTR yield a more classic cystic fibrosis, whereas types III through V errors tend to be less problematic.

Gene defects are also classified in 4 or 5 categories depending on the production and function of the gene. Typical clinical manifestations of cystic fibrosis usually do not occur in patients who have 10% or more CFTR function. Patients with 1% or less functioning of CFTR generally have a more classic type of cystic fibrosis; however, no definitive correlation exists between the genotype and the phenotype. In patients with 1% or less functioning of the gene, the patients' cells have very defective CFTR; therefore, chloride, sodium, and water flow is faulty. In about 70% of patients, cystic fibrosis is diagnosed before the patients are 1 year old.

Most patients with manifestations of cystic fibrosis have parents who do not have cystic fibrosis but are heterozygotes or carriers of the disease. A heterozygote has 1 dominant allele and 1 recessive allele. If 2 persons who are heterozygous for CFTR have a child, the child can have cystic fibrosis. According to Mendelian inheritance theory, matings between carriers will generate approximately 25% affected offspring (25% chance of having a child with cystic fibrosis) and 75% unaffected offspring (50% chance of having a child who is a carrier and 25% chance of having a child with no cystic fibrosis alleles). If a cystic fibrosis carrier and a homozygote-dominant (no cystic fibrosis alleles) person have a child, the child will not have cystic fibrosis.

According to estimates, approximately 7 to 10 million cystic fibrosis carriers exist in the United States who are totally unaware that they carry a mutated CFTR gene. In addition, some persons have 2 mutations of the cystic fibrosis gene and are actually affected with cystic fibrosis and are unaware that they have the disease. A white American couple with no
family history of cystic fibrosis has a 1 in 2500 chance of having a child with cystic fibrosis.

As mentioned earlier, the gene for cystic fibrosis is on the long arm of chromosome 7. Genes are composed of strands of nucleotides, which are made up of base pairs. When the sequence of nucleotides changes, the CFTR gene becomes mutated and the CFTR protein produced is defective. The CFTR protein can be a chloride ion channel regulated by cyclic adenosine monophosphate and therefore can act as a regulator of other electrolyte channels.9

The CFTR protein has different roles in different types of epithelial cells. Normally, this protein allows chloride ions to exit the mucus-producing cells. After chloride leaves the cells, water follows and thins the mucus. However, if the CFTR protein has been damaged, as in cystic fibrosis, the chloride ions are not allowed out of the mucus-producing cells. As a result, the mucus thickens and becomes sticky and obstructs the various pathways. This obstructive process also prevents bacteria from being cleared from the cells and thus increases the potential for infection.10

Pathophysiology
The types of complications in patients with cystic fibrosis differ depending on the degree of mutation of CFTR. Also, some patients do not experience pathological changes in all the systems usually affected by cystic fibrosis.

Respiratory System
Typically, critically ill patients who have cystic fibrosis experience acute respiratory failure due to pneumonia or acute hemoptysis. The most common infecting organisms in patients with cystic fibrosis who have pneumonia include Staphylococcus aureus, Haemophilus influenzae, and Pseudomonas aeruginosa. Of note, patients with cystic fibrosis also tend to have nasal polyps that can trigger sinus infections. Thus, these patients may need longer and different antibiotic treatments than do patients who have solely pneumonia. It is hypothesized that the pH level in the cells of patients with cystic fibrosis differs from the level in patients without the disease. This difference leads to increased numbers of asialoGM1 molecules, which are receptors for bacterial respiratory organisms, and thereby results in increased binding of P aeruginosa and S aureus.11 The decrease in the amount of CFTR to bind with the bacteria leads to colonization of the airways.11 In a few patients with cystic fibrosis who have pneumonia, the pneumonia is due to Burkholderia cepacia (previously known as Pseudomonas cepacia), which is very resistant to most antibiotics.

As obstruction of the airway increases, it becomes more difficult for air to pass during exhalation. This condition leads to expansion of alveoli, where air trapping occurs and, over time, causes the barrel-shaped chest that is also common in patients with emphysema. Destruction of the pulmonary parenchyma leads to increased pulmonary arterial pressure that, in turn, causes right-sided heart failure or cor pulmonale.

Pulmonary function testing is a method that may be helpful in establishing data that will assist in predicting deterioration in clinical status in patients with cystic fibrosis. One parameter, forced expiratory volume in 1 second (FEV_1), is often used as an indicator of deterioration. The lower the FEV_1, the more the work of breathing increases; this increase is correlated with further problems in gas exchange.13 The increased work of breathing can include any of the following: tachypnea, irregular breathing pattern, diaphoresis, flared nares, pursed lip breathing, intercostal muscle retractions, and use of accessory muscles. Patients with lower FEV_1 also tend to be in a chronic state of respiratory acidosis and, like other patients with chronic obstructive pulmonary disease, may need lower PaO_2 levels to trigger the hypoxic ventilatory drive, although they still need adequate oxygenation. Clubbing or enlargement of the last joints of the toes and fingers, which has no definite cause, also occurs in patients with cystic fibrosis.

Typically, patients with cystic fibrosis have decreased levels of

<table>
<thead>
<tr>
<th>Table 1 Types of errors in production of the protein cystic fibrosis transmembrane regulator (CFTR) in patients with cystic fibrosis</th>
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<td>Type</td>
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interleukin-10, a cytokine that has anti-inflammatory properties, especially in the lungs. The decreased levels predispose the patients to severe lung inflammation after infection. Sometimes the pulmonary inflammation persists and becomes a chronic inflammatory condition. Chronic inflammation can cause hypertrophy of the bronchial arteries and ultimately hemoptysis. This life-threatening situation is further exacerbated by coagulopathies often caused by malabsorption of vitamin K and repeated use of some antibiotics. The manifestation of hemoptysis varies from blood-tinged sputum to massive hemorrhaging. It is thought that 5% to 7% of patients with cystic fibrosis actually have massive hemoptysis.

Patients with cystic fibrosis, who have increased levels of thick and tenacious mucus in their airways, are often admitted to the intensive care unit because of airflow limitation. The most severe respiratory signs and symptoms are due to the production of increased levels of thickened mucus that cause inflammation and swelling and thus obstructed airways. The obstruction causes consolidation that leads to pneumonia and respiratory failure. Often, patients have increased retention of mucus in the right upper lobe, which is indicated by evidence of hyperinflation on chest radiographs.

Approximately 10% of patients with cystic fibrosis also have infection caused by the fungus Aspergillus fumigatus, which can cause allergic bronchopulmonary aspergillosis and results in a dramatic increase in secretions and a definitive downward spiral in lung function. Patients with sino-bronchial allergic mycosis and/or allergic bronchopulmonary mycosis have very thick secretions and are resistant to antibiotics. They often do not manifest any signs or symptoms of cystic fibrosis before sino-bronchial allergic mycosis and/or allergic bronchopulmonary mycosis develops but when tested are found to have mutation(s) in the CFTR gene. In many patients, cystic fibrosis is misdiagnosed as celiac disease, asthma, or chronic bronchitis.

Hematopoietic System

Patients with cystic fibrosis who have iron deficiency anemia generally have the anemia as a result of chronic hemoptysis and/or colonization of resistant *P. aeruginosa*. Bleeding often comes from the hypertrophied and tortuous bronchial arteries as a result of chronic inflammation. *Pseudomonas aeruginosa*, a frequent antibiotic-resistant bacterium in the lungs and/or upper airways of patients with cystic fibrosis, robs iron from the host for its own growth. In addition, sputum and bronchial airway lavage fluid of patients with cystic fibrosis who have *P. aeruginosa* infection has a high iron content.

Gastrointestinal System

Some gastrointestinal problems in patients with cystic fibrosis are due to the inability of the pancreas to supply digestive enzymes to the intestine. Because the volume of pancreatic enzymes secreted decreases, the pancreas secretes thick mucus that obstructs the pancreatic ducts and the volume of enzymes that can be secreted becomes even smaller. This change causes malabsorption of proteins and influences absorption of the fat-soluble vitamins A, D, E, and K. The pancreatic enzyme supplements that many patients with cystic fibrosis take may impair iron absorption. It is recommended that patients with cystic fibrosis take supplements and vitamins separately.

The distal part of the intestine is commonly dilated and filled with fecal content in patients with cystic fibrosis. This change is manifested as vomiting, abdominal distention, anorexia, pain in the right lower quadrant of the abdomen, and cramping with a decrease or no change in bowel movements. Distal intestinal obstruction syndrome (DIOS) is a result of faulty secretion of salt and water from the intestinal epithelium, a situation that causes dehydration of the intestinal material.

Some patients with cystic fibrosis also have gastroesophageal reflux disease due to hypersecretion of gastric acid and hyposecretion of bicarbonate. Postural drainage can exacerbate gastroesophageal reflux disease, as can the negative pressures generated by vigorous coughing. Gastroesophageal reflux disease can likewise aggravate bronchial reactivity.

Endocrine System

About 13% of all patients who have cystic fibrosis have cystic fibrosis–related diabetes, which is most often diagnosed after the patients are 30 years old. Studies indicate that assays of glycated hemoglobin (hemoglobin A1c) are not an accurate diagnostic test for cystic fibrosis–related diabetes because the turnover of red blood cells is more rapid in patients with cystic fibrosis than in patients without cystic fibrosis. The primary problem in cystic fibrosis–related diabetes is insulin deficiency due to obstruction of the pancreatic duct.
Patients with cystic fibrosis–related diabetes still require a high-energy diet, which is contrary to the diet that others with diabetes mellitus must follow. Glucose metabolism is influenced by many factors specific to cystic fibrosis, such as severe dehydration, administration of corticosteroids, malabsorption, frequent infection, poor nutrition, increased energy expenditure, slowed gastrointestinal transit time, and liver dysfunction.22

Sweat Glands

Because of the decreased levels of the protein CFTR, which helps regulate salt in sweat, patients with cystic fibrosis can experience excessive salt loss from intense heat or even after extreme exercise. Some patients experience dehydration or heat prostration manifested by lethargy, weakness, and loss of appetite.

Reproductive System

Most men with cystic fibrosis are sterile because they have no vas deferens or it is malformed. Women tend to be fertile but often require more time to become pregnant than do women without cystic fibrosis. Mucus plugs in the oviduct and thicker cervical mucus that decreases sperm movement have been detected.1 Puberty seems to be delayed for both men and women who have this disease.

Detection and Management of Cystic Fibrosis in Critically Ill Patients

Critical care nurses who know that hemoptysis, increased work of breathing, and decreased FEV1 are clinical features of cystic fibrosis may help detect unrecognized cases of this disorder. For example, hemoptysis is often an indicator of pulmonary embolism, and most critically ill patients do not generally experience hemoptysis. Recognizing that a critically ill patient may have a mutation in the CFTR gene can help in focusing the patient’s treatment. If a patient has several of the indicators in Table 2, a nurse may be the first person to suggest use of genetic diagnostic tests. If a patient has a change in the results of tests of pulmonary function, such as a decrease in FEV1, the healthcare team may manage the patient’s pulmonary hygiene more aggressively or use alternative ventilator settings. Knowing that a patient has cystic fibrosis and may be infected or colonized with P. aeruginosa could trigger a change in antibiotics to include a β-lactam. If a critically ill patient has clubbing of the fingers and/or toes, critical care nurses probably would assume that the patient has cardiac disease. However, patients with cystic fibrosis often have clubbing without any cardiac disease.

Table 2  Clues for recognizing cystic fibrosis in patients in intensive care units

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Thick tenacious sputum and mucus</td>
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<tr>
<td>Cultures positive for <em>Pseudomonas aeruginosa</em></td>
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<tr>
<td>Chronic sinusitis</td>
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<tr>
<td>Nasal polyps</td>
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<tr>
<td>Cultures positive for <em>Burkholderia cepacia</em></td>
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<tr>
<td>Poor resolution of respiratory infections</td>
<td></td>
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<tr>
<td>Barrel-shaped chest in young adults</td>
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<tr>
<td>Increased work of breathing</td>
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<tr>
<td>Decreased forced expiratory volume in 1 second</td>
<td></td>
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<tr>
<td>Hemoptysis</td>
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<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Clubbing of fingers and toes</td>
<td></td>
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<tr>
<td>Iron deficiency anemia</td>
<td></td>
</tr>
<tr>
<td>Infertility in men and fertility problems in women</td>
<td></td>
</tr>
<tr>
<td>Crampy abdominal pain</td>
<td>Steatorrhea</td>
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</table>

Pharmacological Treatment

Pharmacogenetics involves studying how genetic differences affect a patient’s response to drugs.23 Because of the multiple mutations associated with cystic fibrosis, only gene therapy for the most common mutations has been explored.24 The goal is to transfer the healthy, functional CFTR protein to the cell membrane via protein repair therapy. Some researchers think that gene therapy should be administered in utero to prevent the respiratory and gastrointestinal consequences of cystic fibrosis.2 Certain drugs, transport modifiers such as amiloride (Midamor), are being studied. One aerosolized substance being used for mucolytic therapy is recombinant human deoxyribonuclease (dornase alfa; Pulmozyme). According to a meta-analysis,27 therapy with recombinant human deoxyribonuclease is associated with increased lung function after 6 months of use of the drug; however, it is not known whether this effect is long term.

Respiratory System

Lung Transplantation

Transplantation of either cadaveric or living lobes from 2 donors is becoming more common treatment in patients with cystic fibrosis. At this time, results of pulmonary function tests, specifically FEV1, are predictors of a successful lung transplantation. In addition, height-corrected FEV1, minimum oxygen saturation during...
exercise, hemoglobin and albumin levels, age, sex, and age-adjusted resting heart rate are predictors of prognosis in patients with cystic fibrosis who undergo lung transplantation. Liou et al described a model in which 9 variables and a worksheet are used to help clinicians and patients determine the most appropriate candidates for lung transplantation.

Some transplant centers intubate terminally ill patients who are awaiting lung transplantation, whereas other centers use noninvasive mask ventilation. Patients and families should be aware of the futility of mechanical ventilation for patients with cystic fibrosis who experience acute respiratory failure who are not interested in or are not deemed candidates for lung transplantation. End-of-life issues should be addressed collaboratively with patients and their families.

Postural Drainage Postural drainage requires a specific amount of time (3-15 minutes) for each position drained, otherwise the treatment is not effective in mobilizing secretions in patients with cystic fibrosis. Fink found that proper postural drainage along with exercise, for patients who were mobile, and routine scheduled repositioning, for patients who were in bed, was effective and imperative for sputum clearance in critically ill patients who had cystic fibrosis.

Depending on the reason a patient with cystic fibrosis is in the intensive care unit, either traditional chest physiotherapy techniques or other airway clearance techniques, which simulate traditional percussion and vibration maneuvers, may be used. Critical care nurses must advocate for rigorous pulmonary toilet for critically ill patients who have cystic fibrosis.

Use of noninvasive positive-pressure ventilation in patients who have severe but stable lung dysfunction gave peace of mind to patients with cystic fibrosis who were awaiting lung transplantation but did not significantly influence standard objective measurements such as arterial blood gas levels, pulmonary function, respiratory muscle strength, or exercise tolerance.

Research supports the notion that recurrent hemoptysis may decrease patients’ compliance with rigorous chest physiotherapy and also predispose patients to exacerbations of acute respiratory failure. Therefore, nurses should be aware that hemoptysis of greater than 240 mL of blood in 24 hours is considered life threatening and will require surgery or bronchial artery embolization. Careful suctioning and monitoring of the suctioned secretions is imperative. Patients with cystic fibrosis who have hemoptysis will require stabilization of their hemodynamic status. Patients still require aggressive airway clearance maneuvers after bronchial artery embolization. It is recommended that patients with any hemoptysis have bronchial artery embolization as an early preventive treatment to avoid massive hemorrhaging.

Critically ill patients who have cystic fibrosis can experience pneumothorax and require chest drainage to reexpand lung tissue. They also should continue receiving chest physiotherapy and suctioning to maintain meticulous airway clearance.

Hematopoietic System

Patients with cystic fibrosis who have hemoptysis may be treated with vitamin K and should have the results of coagulation studies monitored frequently, especially if the patients are receiving anticoagulation therapy. Red blood cell indices should also be monitored carefully because patients may be experiencing iron deficiency. Iron supplementation may be indicated. Some pancreatic enzyme supplements may impair iron absorption, so need for an iron supplement should be considered.

Gastrointestinal System

Bowel Obstruction Critically ill patients with cystic fibrosis have a much greater risk than patients without the disease for bowel obstruction due to inactivity, changes in diet, stress, or possibly pain medications or sedation. DIOS can lead to complete bowel obstruction, so patients should be monitored carefully and adequate fluid and electrolyte balance should be ensured. Administration of lactulose, 15 to 45 mL twice a day, and/or polyethylene glycol 3350 (MiraLax) along with a prokinetic drug is also an important intervention for patients with DIOS. If a patient has a change in bowel habits or abdominal bloating or tenderness, DIOS must be ruled out. Patients with complete obstruction require parenteral hydration and nutrition as well as diagnostic radiological tests. Often hyperosmolar contrast enemas administered during fluoroscopy can be used instead of surgical intervention to manage the obstruction.

Malabsorption Patients must understand the need for 100% compliance with their pancreatic supplements, especially patients who have DIOS. A total of 80% of patients with cystic fibrosis have adequate absorption if they take these supplements. During acute pulmonary exacerbations of cystic fibrosis, malabsorption prob-
lems can be life threatening and require aggressive intervention. **Other Problems** Because of the frequent need for antibiotic therapy, patients with cystic fibrosis often experience diarrhea. If diarrhea is a problem, *Clostridium difficile* may be the causative organism.

Patients with cystic fibrosis often have nasal polyps. Nurses should be aware of this possibility if any resistance is encountered during insertion of a nasogastric tube or during any nasal intervention. The levels of liver transaminases and alkaline phosphatase should be monitored because they tend to be elevated in patients with cystic fibrosis. Generally, no symptoms or signs of liver failure occur in patients who have these elevations.2

**Endocrine System**

Older patients with cystic fibrosis tend to have glucose intolerance because of frequent stress, infection, and treatment with steroids. Nurses need to account for the elevated levels of blood glucose when these patients are critically ill. Diagnosis of cystic fibrosis–related diabetes is followed up by doing a 2-hour glucose tolerance test after a patient’s overall clinical condition is stabilized.

**Summary**

Even though a specific gene associated with cystic fibrosis has been identified, patients who have this disease are still experiencing life-threatening problems. Understanding the multisystem pathophysiology of the disease greatly helps nurses provide holistic care for these patients when pulmonary exacerbations occur. Clues to assist in detecting and managing patients with cystic fibrosis mutations are discussed. Critical care nurses will always manage the inherent ethical, social, and legal issues that confront patients with cystic fibrosis even when genetic testing and interventions are more fully implemented.

Studies of the clinical, psychological, quality-of-life, and genetic issues associated with cystic fibrosis are needed. Knowledge of the information in this article can assist critical care nurses in managing patients with cystic fibrosis who have these challenging clinical problems.

Because patients with cystic fibrosis are living longer than before, more of them experience signs and symptoms of multiple organ dysfunction. Critical care nurses need to advocate for these patients during the patients’ acute exacerbations.

**Acknowledgment**

This article is in appreciation of Shep and Cindy Tye and in memory of Kenny and Pamela Tye, who fought and continue to support the fight against cystic fibrosis.

**References**

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