Cystic Fibrosis: A Systems Review

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Cystic fibrosis (CF) is a fatal genetic disorder that affects many organ systems in the body. Historically, few patients with CF lived beyond early childhood, but with continuous improvement in treatment modalities, quality of life and the life span of persons with CF has greatly improved. As the surviving population of people with CF increases, a greater chance of encountering them in anesthesia practice exists. Comorbidities associated with the disease, such as diabetes mellitus and osteopenia, may also contribute to an increased frequency of surgical and anesthetic encounters. An understanding of the pathophysiology of the disease, as well as anesthetic implications and management, is crucial to the safe administration of anesthesia in this population.

Cystic fibrosis is traditionally thought of as a childhood disease affecting the lungs and pancreas, which does not accurately describe the disease in its entirety. Many organ systems are affected, from the heart and lungs to the reproductive system, and may warrant alterations in an anesthetic plan. This review highlights the pathologic conditions associated with multiple systems, therapy regimens, and potential complications and suggests anesthetic implications.

Keywords: Anesthesia, cystic fibrosis, systemic effects.

Objectives
At the completion of this course the reader should be able to:
1. Understand the pathophysiological mechanisms of cystic fibrosis.
2. Describe multisystem involvement in cystic fibrosis.
3. Identify common and appropriate pharmacologic management of cystic fibrosis.
4. Recognize common procedures and appropriate anesthetic interventions when caring for patients with cystic fibrosis.
5. Identify appropriate preoperative testing and common pathologic conditions related to cystic fibrosis.

Introduction
Cystic fibrosis (CF) is a fatal genetic disorder that affects many organ systems in the body. It is estimated that CF affects 30,000 adults and children in the United States, with approximately 1,000 new cases diagnosed each year.1 Cystic fibrosis is most prevalent among whites but affects all ethnic groups. Cystic fibrosis results from an autosomal recessive gene mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) protein located on chromosome 7.2 The normal CFTR protein acts as a chloride channel and ensures proper electrolyte and water movement across epithelial membranes. Normally, secretions from the body’s exocrine glands (sweat, tears, saliva, digestive juices, and mucus) are thin and slippery. The mutation causes abnormal chloride ion transport across epithelial cells, with disturbances in sodium and water transport, resulting in dehydrated viscous secretions.3 Thick secretions prevent proper functioning of several organs. Although pulmonary complications are the most common cause of death, many other organ systems are also affected. At least 1,000 genetic mutations have been identified; hence, the severity of the disease may range from asymptomatic or mild forms to severe symptoms, affecting activities of daily living.4

Historically, few patients with CF lived beyond early childhood, but with continuous improvement in treatment modalities, quality of life and the life span of persons with CF have greatly improved. The median survival age has been reported to be as high as the early 40s, thus increasing the likelihood that people with CF will be candidates for procedures requiring anesthesia.2 The patients may undergo anything from lung transplantation...
to cesarean section (assuming a functional adulthood). An understanding of the pathophysiology of the disease and of anesthetic implications and management is crucial to the safe administration of anesthesia in this population. The complexity of CF requires a thorough understanding of how each organ system is affected.

**History**

Retrospective analyses of cases describing people who had most likely died of CF date as far back as 1595. Afflicted people were commonly described as being bewitched during this era. Cystic fibrosis F was first clearly pathologically described as CF of the pancreas in 1938 by Dorothy Andersen, a pathologist, clinician, and chemist at the Babies Hospital at the Columbia Presbyterian Medical Center, New York, New York. Major advances in CF medicine occurred in the 1950s. Increased salt content in the sweat of patients with CF was recognized by Paul di Sant’Agnese in 1953, and the standardized sweat test for diagnosis of the disease evolved. Surprisingly, genetic involvement was suggested, and inhaled antibiotics were being implemented even then. Important advances in the late 1970s and 1980s revealed the basic defect to be altered membrane electrolyte transport, specifically chloride impermeability. A great milestone was the identification of the *CFTR* gene mutation in 1989 by Canadian scientists. From this point, the progress of research and therapy has been steady, with focus on gene replacement and pharmacological therapy.

**Diagnosis**

Most cases of CF are recognized during childhood; two-thirds of the cases of CF are diagnosed by the time the children are 1 year old. Prenatal genetic testing, ultrasound, and amniocentesis may be used if there is a suspicion of CF. Newborns may have meconium ileus, which indicates CF in 98% of cases. The sweat test is the “gold standard” for the diagnosis of CF. Sweat glands on the forearm or thigh are stimulated by using pilocarpine. The sweat collected is analyzed for high chloride concentration; levels greater than 60 mmol/L are usually indicative of CF in children. A positive sweat test result should initiate further genetic testing.

**Pulmonary Manifestations and Management Considerations**

The pulmonary system is rarely spared in CF; complications in this organ system are commonly the cause of death in patients with CF. Normally, thin salt-containing mucus in the respiratory tract traps and neutralizes inhaled bacteria and foreign substances, while the cilia on the surface of the airway cells carry the debris out of the lungs. Mucociliary clearance is the primary defense mechanism protecting the lungs from infection. The airways of a patient with CF exhibit decreased chloride and excess sodium transport from the mucus. Water follows the sodium, resulting in volume depletion and dehydrated secretions. Viscous mucus is difficult to clear from the respiratory tract and creates a medium for various pathogens to grow, leading to infections. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the 2 most common pulmonary pathogens. These bacterial infections induce neutrophil recruitment that leads to tissue damage and ciliary dysfunction, creating increased susceptibility to further infection.

Bronchiectasis describes abnormally dilated and thick-walled bronchi that are chronically inflamed and infected. It occurs after sustained inflammatory injury, leading to structural damage with loss of elasticity, muscle integrity, and cartilage. In patients with CF, bronchiectasis and symptoms of airway obstruction will eventually develop. Chronic inflammation of the airways also leads to enlarged and tortuous bronchial arteries, which are at risk for spontaneous rupture. Hemoptysis is possible and, if severe, may require airway protection and pulmonary artery embolization or lobectomy to control hemorrhage.

Altered ventilation-perfusion and gas exchange are common due to chronic obstruction. In advanced disease, decreased arterial oxygen tension and normal or elevated carbon dioxide tension typically lead to respiratory acidosis. Chronic airway obstruction may lead to air trapping and emphysematous bullae, which have the potential to rupture resulting in pneumothorax.

Airway hyperreactivity is due to viscid secretions, chronic inflammation, and bronchitis and may predispose patients to bronchospasm. Histamine-releasing drugs, such as morphine and thiopental, increase bronchial reactivity and should be avoided.

Early effective management of CF has led to great improvements in the quality of life and longevity in affected people. Airway clearance is one of the primary goals of therapy. Chest percussion and drainage with vibration techniques are time-consuming and often require assistance. Mucolytics such as dornase alfa (Pulmzoyme), an inhaled mucolytic, are often used in the management of CF. Dornase alfa initiates breakdown of extracellular DNA present in the thick secretions of the lower airway. A 7% hypertonic saline may also be inhaled to liquefy secretions, but it may induce bronchospasm. A new drug in phase 3 trials, Bronchitol, is an inhaled powder form of mannitol aimed at loosening secretions to enhance expectoration. Oral, intravenous, or inhaled antibiotics such as tobramycin (TOBI) are used to manage acute and chronic pulmonary infections. Colistin (Coly-Mycin M, Polymixin E) is an inhaled antibiotic that may also induce bronchospasm. Bronchodilators augment therapy and prove crucial in the management of airway hyperreactivity. Pulmonary exacerbations should be treated with antibiotics, aggressive chest physiotherapy, breathing treatments, and, potentially, hospitalization.
Lung transplantation for CF was first performed in the 1980s. This procedure might be considered for patients with CF and very poor lung function. Although transplanted tissues will not develop CF, sinuses, upper airways, and other involved systems will remain diseased. The 5-year survival rate is reported to be around 50% after lung transplantation. Each year, approximately 120 to 150 patients with CF undergo lung transplantation (frequently bilateral).

Anesthesia considerations concerning the pulmonary status of a patient with CF are numerous. Pulmonary function tests and arterial blood gas levels may help determine the progress of the disease. Increased functional residual capacity, decreased forced expiratory volume in the first second (FEV₁), decreased peak expiratory flow rate, and decreased vital capacity are expected findings of pulmonary function tests. Aggressive pulmonary therapy, including chest percussion and postural drainage, should be used during the preoperative and postoperative periods. Sputum culture and sensitivity tests should be included in preoperative preparation, with administration of appropriate antigen-specific antibiotics initiated well before the procedure. Elective cases should be avoided in patients with active pulmonary infections. Baseline room air pulse oximeter–measured oxygen saturation levels may provide realistic expectations and help guide oxygen therapy during anesthesia.

Glucocorticoids or corticosteroids are often used to manage lung disease in patients with CF. Administration of “stress-dose” corticosteroids may be considered perioperatively. Adrenal function is commonly suppressed with exogenous corticosteroid treatment leading to a decrease in the release of cortisol in the response to the stress of surgery. Respiratory depression should be minimized; therefore, preoperative sedatives should be administered cautiously. Although ketamine (Ketalar) may preserve spontaneous ventilation, it also increases secretions, which may lead to airway irritation. Anticholinergics may further dry secretions, and their use is controversial. Bronchodilators should be continued and administered preoperatively, if warranted.

The effects of positive pressure ventilation on the fragile airways may be detrimental. Suppressing cough and airway reflexes will compound the already compromised secretion-clearance mechanisms; therefore, spontaneous ventilation should be maintained if possible. An endotracheal tube allows for suctioning, although deep anesthesia should be obtained before intubation to avoid coughing and dislodgement of the thick mucus secretions that may further irritate the airway. Volatile agents, with the exception of desflurane, may decrease airway resistance and hyperreactivity. Humidification of inspired gases is encouraged to avoid further drying of secretions. Aggressive suctioning should be used to clear the airway secretions, especially before extubation. Nitrous oxide should be avoided due to the potential for rupture of the bullae and pneumothorax. In chronic obstructive pulmonary disease, carbon dioxide may be the stimulus for respiration; therefore, hyperventilation should be avoided to optimize postoperative ventilation status. Anesthesia providers need to be able to recognize and manage potential pulmonary complications such as massive hemoptysis, pneumothorax, and bronchospasm in patients with CF.

**Cardiovascular Considerations**

Cardiac involvement is typically secondary to chronic pulmonary infections, destruction of lung parenchyma, and hypoxemia. Pulmonary hypertension secondary to hypoxemia and bronchiectasis will eventually lead to cor pulmonale and is often an ominous complication of the disease. In advanced disease, an electrocardiogram or echocardiogram may be necessary for preoperative evaluation of cardiac function. Chronic hypoxemia may also lead to polycythemia and digital clubbing, which are frequently present in patients with CF. Diabetes may result from pancreas destruction, leading to the potential for autonomic neuropathy with abnormal heart rate control, orthostatic hypotension, and silent myocardial infarction. Atropine may be ineffective in patients with autonomic neuropathy, and early treatment with epinephrine may be required for successful management of bradycardia.

**Gastrointestinal, Pancreatic, and Nutritional Considerations**

The inability to secrete sodium bicarbonate and water by the exocrine glands in the pancreas lead to abnormal production of enzymes and thick secretions blocking the pancreatic ducts. Pancreatic enzymes are continually secreted despite the obstructed ducts and ultimately destroy the pancreatic tissue, finally impeding the production of the essential digestive enzymes. Pancreatic enzymes are necessary for the absorption of fat, protein, and fat-soluble vitamins in the intestine. Steatorrhea may be a clinical sign of fat malabsorption secondary to pancreatic insufficiency. Patients with CF are often malnourished despite administration of exogenous enzymes and vitamins. Patients often require enteral feeding devices for which anesthetic management may be requested. Malnourished patients with CF are susceptible to heat loss, resulting in increased oxygen consumption. Patients should be protected against hypothermia to avoid increased workload on an already compromised respiratory system. Patients may be excessively thin and require appropriate padding in addition to careful positioning.

Destruction and fibrosis result in functional impairment of the endocrine and exocrine glands of the pancreas. Damage to the insulin-producing beta cells in the pancreas, along with long-term corticosteroid therapy,
often leads to glucose intolerance or diabetes mellitus.\textsuperscript{7,9} Frequent blood glucose monitoring and insulin therapy should be instituted, as appropriate.

The intestinal epithelium is also subject to faulty secretion of chloride and water.\textsuperscript{2} Desiccate intraluminal contents and mucous plugs in the intestine frequently cause constipation or bowel obstruction in patients with CF. Meconium ileus often is the initial sign of CF in a newborn. Prophylactic laxative medications should be considered if opioids are given. Obstruction may manifest as mucus or feces in the terminal ileum, cecum, or right colon.\textsuperscript{7} Patients with bowel obstruction will likely have electrolyte imbalances that should be assessed and optimized preoperatively in all patients with CF. Significant gastroesophageal reflux is common among people with CF. Pretreatment with a histamine-2 receptor antagonist agent and rapid-sequence induction of anesthesia should be used to protect against aspiration of gastric contents.\textsuperscript{9}

**Hepatic Considerations**

The hepatic system is also subject to defective salt and water secretion. The gallbladder produces viscous and acidic bile, potentiating bile duct obstruction, cirrhosis, and damage to the small intestine. Cholelithiasis occasionally contributes to liver damage and may result in end-stage liver disease in a small percentage of patients with CF.\textsuperscript{2,7,9} Fatty liver may affect up to 60% of patients with CF.\textsuperscript{4} Synthesis of vitamin K–dependent coagulation factors may be impeded in a damaged liver. Prolonged prothrombin time, partial thromboplastin time, international normalized ratio, hemoptysis, bruising, or bleeding tendencies might alert providers to possible a vitamin K deficiency–related coagulopathy. Liver function tests and coagulation studies are necessary preoperatively, especially when considering regional anesthesia techniques. Correction with vitamin K may be appropriate in selected cases. Portal hypertension and hepatomegaly from right-sided heart failure are late consequences of the disease.\textsuperscript{9}

**Genitourinary Considerations**

The kidneys are not primarily affected by CF, although in people with chronic diarrhea, nephrolithiasis may develop due to altered absorption of oxalate. Increased uric acid and decreased citrate levels in the urine may also contribute to stone formation.\textsuperscript{4} Nephrotoxic effects from aminoglycoside antibiotic administration for *Pseudomonas* infections may be a valid concern.

As the age of a patient with CF increases, comorbidities, including renal compromise, may develop. Nephrotic syndrome and diabetic nephropathy have also been described in patients with CF and may be encountered in the surgical setting.\textsuperscript{14} Stress incontinence may develop due to frequent stress on the bladder muscle from chronic coughing.

**Considerations Related to the Ears, Nose, and Throat**

Upper respiratory infections are common among patients with CF. Chronic sinusitis and nasal polyps with epistaxis often require corticosteroid treatment and surgical removal.\textsuperscript{2} Nasal polypectomy is the most common procedure requiring anesthesia in patients with CF.\textsuperscript{15} Nasopharyngeal airways may disrupt polypoid tissue, resulting in significant bleeding, and are probably best avoided in patients with CF. Long-term corticosteroid use may lead to decreased adrenal function, which necessitates the need for stress dosing of corticosteroids perioperatively. Purulent nasal drainage is common and may be present even when patients are in optimal physiologic condition. Ototoxic effects of aminoglycoside antibiotic administration for the treatment of frequent *Pseudomonas* pulmonary infections are also possible.\textsuperscript{9}

**Neurological Effects**

Primary neurological consequences related to CF have not been reported in the literature. Theoretically hypoxia, hypercarbia, and encephalopathy due to liver involvement may alter neurological status. Neurologic sequelae are not typically of concern in a patient with CF.

**Reproductive Considerations**

Boys and girls with CF typically have a late-onset of puberty.\textsuperscript{2} Infertility in males with CF occurs at a rate of 95% to 99% due to obstruction or absence of the vas deferens and incomplete epididymis.\textsuperscript{2,16} Female infertility is less frequent (approximately 20%) but is related to an altered menstrual cycle secondary to chronic lung disease. Thick mucus blocks the fallopian tubes and impedes sperm transport through the cervix.\textsuperscript{2} The ovaries are not affected because they do not express the *CFTR* gene.\textsuperscript{17} An estimated 4% of females with CF become pregnant each year. Pregnancy does not exacerbate the disease, although ethical concerns about the mother’s long-term prognosis should be addressed before conception.\textsuperscript{17} If the mother’s FEV\textsubscript{1} is at least 70% of expected, pregnancy should be well tolerated. Lung function and nutritional status should be monitored closely throughout gestation.\textsuperscript{17}

Pregnant patients with CF may require anesthesia for epidural labor or cesarean section delivery. Coagulation studies must be obtained before considering regional anesthesia. As with any pregnant patient, edematous airway and decreased functional residual capacity are of concern to anesthesia providers. CF predisposes patients to a more precipitous oxygen desaturation during induction of anesthesia, making adequate preoxygenation imperative for patients with CF.

**Musculoskeletal Considerations**

Osteopenia, osteoporosis, and arthropathies may occur in...
Pulmonary infections—acute and chronic\textsuperscript{2}
Airway hyperreactivity\textsuperscript{7,9}
Hypoxemia\textsuperscript{8}
Pneumothorax, hemothorax, and hemoptysis\textsuperscript{8,9}
Pulmonary hypertension
Cor pulmonale\textsuperscript{9,17}
Malnutrition, growth retardation, low body mass index
Diabetes mellitus and glucose intolerance\textsuperscript{2,9}
Intestinal obstruction\textsuperscript{7,9}
Gastroesophageal reflux\textsuperscript{9}
Hepatobiliary disease\textsuperscript{2,7}
Coagulopathy\textsuperscript{9}
Acute and chronic sinus infections\textsuperscript{8}
Nasal polyps\textsuperscript{8}
Urinary stress incontinence
Delayed onset of puberty, azospermia, and infertility\textsuperscript{2,7,8,16}
Osteopenia and osteoarthritis\textsuperscript{2,7,8}

Table 1. Common Conditions Associated With Cystic Fibrosis

patients with CF\textsuperscript{2,7,8}. Metabolic bone disease is thought to be linked to malnutrition and decreased lung function. Accelerated bone resorption, reduced bone formation, vitamin D deficiency, and reduced calcium absorption are seen in CF\textsuperscript{7}. Rheumatoid arthritis, amyloidosis, and drug-induced arthritis have all been described in patients with CF. It is quite possible that a patient with CF will undergo orthopedic procedures requiring anesthetic intervention. The disease process precludes a straightforward anesthetic plan. Avoidance of muscle relaxants, as appropriate, or low doses of short-acting agents is recommended to prevent residual weakness and further postoperative respiratory compromise.

Conclusion

Cystic fibrosis is traditionally thought of as a childhood disease affecting the lung and pancreas, which does not accurately describe the disease in its entirety. Many organ systems are affected, from the heart and lungs to the reproductive system. Improving treatment modalities have increased the life span well into adulthood. Anesthesia providers must have a comprehensive understanding of the disease process and the systems affected in order to appropriately plan and provide care for patients with CF. A summary of conditions and anesthetic considerations for the patient with CF are provided in Tables 1 and 2.

REFERENCES


AUTHORS
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