Review Article

CME Perioperative Management of the Adult with Cystic Fibrosis

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Since cystic fibrosis (CF) was first differentiated from celiac disease in 1938, the medical care of patients with CF has substantially improved. These improvements have resulted in a significant increase in median survival and the quality of life experienced by patients. The resultant increase in survival has caused the "average" CF patient to be a young adult and not a child. The gene that causes CF was first identified in 1989 and is the first gene discovered by positional cloning. Unfortunately, gene therapy for CF has not been successful, although it continues to hold great promise for future patient care. Although pulmonary disease is responsible for more than 90% of the morbidity and mortality in patients with CF, they also experience pancreatic disease, including diabetes mellitus, bone disease, hepatobiliary disease, and genitourinary disease. The optimal perioperative management of patients with CF requires an understanding of the relevant pathophysiology and the unique challenges presented by these patients. We reviewed these concepts, including special considerations such as liver and lung transplantation and pregnancy.

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A poem dating from the 18th century that reads "The child will soon die whose brow tastes salty when kissed" presumably referred to cystic fibrosis (CF) and suggests that people have long been aware of CF. Nevertheless, CF was first distinguished from celiac disease in 1938 when the autopsy studies of malnourished infants revealed "cystic fibrosis of the pancreas."[1] Since that time, substantial advances in the care of these patients have caused many clinicians to consider CF a chronic disease requiring active and continuous management. The median survival age of patients with CF is now 38 yr.[2] CF occurs in approximately 1 in 2500–3200 live Caucasian births. Approximately 1000 new cases of CF are diagnosed each year; however, the prevalence of CF is growing much faster as the median survival age continues to increase. In 1990, only 30% of patients with CF were adults (older than 18 yr); now, however, 45% of patients are adults.[2] Among adults with CF, more than two-thirds are 18–29 yr of age, 25% are 30–39 yr, 10% are 40–49 yr, and 2% are older than 50 yr.[3] The past 30 yr have witnessed CF change from a uniformly fatal childhood disease to a chronic, progressive disease of adults. At present, there are about 30,000 patients with CF in the United States with about 3000 patients living in Canada and 20,000 living in Europe.

As the median age continues to increase, more and more patients with CF will require anesthetic and surgical care. Although many of these patients have historically been treated in specialty centers (especially pediatric hospitals) that are familiar with the disease, the changing epidemiology of CF will undoubtedly result in more patients presenting for health care at nonspecialty centers.[4] Herein, we review relevant genetic, pathophysiologic, and treatment aspects of CF and perioperative concerns unique to these patients.

GENETICS

CF is caused by mutations in a 230-kB gene located on the long arm of chromosome 7 that encodes a 1480 amino acid protein named the CF transmembrane regulator (CFTR). The CFTR functions as an adenosine triphosphate- and cyclic adenosine monophosphate-dependent chloride channel that is found at the apical border of epithelial cells lining most exocrine glands.

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The gene that causes CF was first identified in 1989 and represents the first gene discovered by positional cloning whose function was entirely unknown.[5,6] To date, more than 1000 disease-causing mutations have been characterized. CFTR mutations can be grouped into 6 basic classes: 1) nonsense mutations, frame shift mutations, and splice site mutations that result in premature termination signals and a total lack of CFTR synthesis; 2) mutations that give rise to a translation product that is not able to attain the properly folded protease-resistant structure in the endoplasmic reticulum, resulting in defective processing; 3) mutations that interfere with phosphorylation and regulation of the CFTR; 4) mutations that affect amino acids located in the pore of the channel resulting in defective chloride-conductive properties; 5) partially defective production or splicing that results in a small amount of functional CFTR chloride channels and a mild phenotype; and 6) mutations that harbor nucleotide alterations that affect the regulatory properties of the CFTR protein on other channels.[7,8] The most common mutation is the Class 2 deletion of phenylalanine at position 508 (ΔF508) and is found on approximately 70% of the CF chromosomes in the United States with about 50% of American patients homozygous for the ΔF508 mutation.[1] Class 1–3 mutations are significantly more common and associated with pancreatic insufficiency, whereas Class 4–6 mutations are less common and not normally associated with pancreatic insufficiency.[9]

Although certain genotypes are clearly associated with normal pancreatic function, genotype is a poor predictor of pulmonary disease and eventual patient outcome[10] and attempts to correlate phenotypic clinical severity with genotype have been generally unsuccessful.[11] Indeed, the most common ΔF508 mutation is associated with tremendous variability in clinical severity in an ethnically diverse population in the United States.[12] The lack of association between disease severity and genotype reflects the importance of modifier genes at other, non-CF loci[13–15] and the importance of environmental and therapeutic factors. Exposure to tobacco smoke,[16] female gender,[17] certain geographic locations,[18] and low socioeconomic status[19] are associated with an accelerated clinical course. Gene therapy for CF continues to hold great promise.[20]

Although CF is the most common lethal genetic disease among Caucasians, the CF gene can be found in other patient populations. Commonly accepted approximate carrier rates in Hispanics and African Americans are 1:46 and 1:65 with an incidence of CF of 1 in 12,000 and 1 in 15,000 live births, respectively. The CF genotype is also variable between patient populations.[21] It is interesting to note that Native Americans, for example, may have a disease incidence of about 1 in 10,000 live births, but that ΔF508 has not been observed in this population.

PATHOPHYSIOLOGY

CF leads to pathologic changes of organs that express the CFTR in their epithelial cells, notably the airways (including the sinuses and lungs), the gastrointestinal tract (including pancreas and biliary system), the sweat glands, and the genitourinary system. The pathophysiologic changes are summarized in Table 1.

Pulmonary Manifestations

Pulmonary disease is responsible for more than 90% of the morbidity and mortality in patients with CF. The lungs are characterized by hypertrophy of the goblet cells, viscid mucous secretions with reduced mucociliary clearance leading to patchy atelectasias, airway inflammation, chronic hypoxia, and colonization with *Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenza, Stenotrophomonas maltophilia,* and a variety of other Gram-negative organisms.[22] *Burkholderia cepacia*[22] and the fungus *Aspergillus fumigatus*[22–24] have become increasingly important pulmonary pathogens associated with high morbidity and mortality. Pulmonary function tests (PFTs) most frequently reveal a pattern of obstructive airway disease with decreased forced expiratory volume in 1 s (FEV_1), decreased peak expiratory flow, and increased residual volume (RV). Airway obstruction may or may not improve with bronchodilators. Chronic pulmonary infection and inflammation, with episodes of acute exacerbation, are typical in patients with CF.

Despite tremendous advances in the understanding of the genetics of the disease, the mechanism by which defective chloride conductance leads to viscid secretions and bacterial infection remains incompletely understood. Several theories have been proposed to explain this process. The "inflammation-first" hypothesis suggests that inflammation is present in the airways of patients with CF before infection and that this inflammation leads to changes in airway anatomy and physiology that lead to chronic infection.[25,26] The epithelial cells of patients with CF produce less of the antiinflammatory cytokine interleukin 10.[27] The "cell-receptor" hypothesis suggests that altered intracellular pH leads to the reduced sialylation of glycoconjugates. This results in the overexpression of asialo GM1, which serves as a receptor for *P. aeruginosa and S. aureus*.[28] The "salt defensins" hypothesis proposes that CF airway cells have higher luminal salt concentrations, similar to those of sweat glands. The increased salt inactivates substances called defensins, allowing bacterial multiplication and infections on airway surfaces.[29] The preceding theories do not explain the presence of mucoid *S. aureus* or mucoid-type *P. aeruginosa*. Indeed, although providing an important glimpse into various lung-defense alterations in CF, the preceding theories only explain lung susceptibility to infection from a specific organism. None of the above theories provides a unitary hypothesis that

Table 1. Manifestations of Cystic Fibrosis

Pathophysiology	Treatment
Pulmonary	
Hypertrophy of goblet cells, viscid mucous secretions with reduced mucociliary clearance	Comprehensive care at adult subspecialty centers decreases hospitalization, and improves morbidity and mortality
Atelectasis, airway inflammation, and chronic hypoxia	Chest physiotherapy: breathing exercises, flutter valves, and chest percussion
Ineffective cough leads to mucous plugging and airway hypoxia	Chronic suppressive antibiotic therapy with aerosolized tobramycin
Colonization with *Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenza, Stenotrophomonas maltophilia*, and other Gram negative organisms	Mucolytic agents such as DNase
Burkholderia cepacia and *Aspergillus fumigatus* associated with high morbidity and mortality	β-adrenergic agonists such as albuterol for bronchial hyperreactivity
Obstructive airway disease pattern with decreased FEV1 and peak expiratory flow, increased residual volume	Oral or inhaled glucocorticoids
Apical blebs and pneumothorax	IV antibiotics for pulmonary exacerbations targeted to organisms
Increased PVR, pulmonary hypertension, and cor pulmonale	Oxygen therapy
	Noninvasive positive pressure ventilation (BiPAP)
Upper airway	
Nasal polyps	Ventilation and drainage of sinonasal passages
Hypertrophy and hyperplasia of nasal/sinus mucosa	Decongestants, topical glucocorticoids, and saline irrigation
	Consideration of surgical resection
Pancreas	
Exocrine pancreatic deficiency: decrease in volume and pH of secretions, retention of digestive enzymes, pancreatic autodigestion leads to protein and fat malabsorption, especially fat-soluble Vitamins E and K	Dietary supplementation with enteric-coated, microencapsulated enzyme supplements
Endocrine pancreatic disease: CF-related diabetes mellitus (CFRD) due to pancreatic fibrosis and destruction of β cells plus insulin resistance	Blood glucose monitoring and therapies including oral hypoglycemic agents and insulin as needed
Hepatobiliary	
Abnormal liver function tests	Surgical treatment of gallbladder disease
Fatty infiltration of liver	Care and caution with medications metabolized by hepatic system
Cirrhosis and portal hypertension	Possible liver transplantation for end stage liver disease
Associated with hepatocellular carcinoma	
Cholelithiasis and cholecystitis are common	
Altered hepatic metabolism of drugs	
Gastrointestinal tract	
Distal intestinal obstruction syndrome (DIOS): recurrent episodes of intestinal obstruction, abdominal pain, distention, nausea, vomiting, and failure to pass stool	Avoidance of dehydration and agents that suppress GI motility (i.e., opiates)
	Adherence to pancreatic enzyme replacement therapy
Bone disease	
Low bone mineral density	Growth hormone replacement, calcium and Vitamin D supplementation, bisphosphonates, and sex steroid replacement therapy
Increased incidence of fractures especially rib and vertebral fractures	
Genitourinary	
Late onset of puberty common both for men and women	No surgical correction available for male infertility although sperm can be harvested from epididymis or testes and assisted reproduction techniques used to combine oocytes from female partner
Male infertility due to congenital bilateral absence of vas deferens and obstructive azoospermia	
Normal female anatomy but tenacious cervical mucus may result in decreased fertility	
Normal or near-normal menstrual cycles	

FEV_1 = forced expiratory volume in 1 s; PVR = pulmonary vascular resistance; BiPAP = Bilevel positive airway pressure, CF = cystic fibrosis; GI = gastrointestinal.

explains the generalized susceptibility to lung colonization in patients with CF.

The "isotonic fluid depletion/anoxic theory" proposes that defective chloride secretion, increased sodium and water absorption, and diminished mucociliary clearance lead to increased mucus viscosity. An inadequate cough to clear the airways leads to mucous plugging and airway hypoxia. Bacteria are trapped within the thick, viscous airway fluid, and colonization occurs because the hypoxic conditions do not provide adequate oxygen stores to maintain oxidative killing by neutrophils.[30] Bacterial multiplication occurs within the anaerobic growth conditions by changing from a nonmucoid to a mucoid type of organism. The transformation of these bacteria to a biofilm-encased form protects the bacteria from normal host defenses and antibiotics, making eradication difficult.

In addition to inflammation and infection, many patients with advanced pulmonary disease have apical blebs. In some patients with CF, these blebs can rupture, leading to pneumothorax. In a review of 28,858 patients studied over a 10-yr period, pneumothorax occurred with an annual incidence of 0.64% and in 3.4% of patients overall.[31] It occurs more frequently in older patients with more advanced lung disease. The mechanism is poorly understood.[31,32] The prognosis for the patient after a spontaneous pneumothorax is poor, with an attributable mortality between 6.3% and 14.3% within 2 yr of their first spontaneous pneumothorax.[31]

The combination of chronic hypoxia and hypercarbia leads to increases in pulmonary vascular resistance (PVR), pulmonary hypertension, and cor pulmonale.[33,34] Supplemental oxygen may reduce the PVR and improve right ventricular performance in patients with CF.[35] Regardless, clinically significant cor pulmonale occurs in the terminal stages of CF with a mean survival time of 8 mo.[34] Pulmonary hypertension increases the risk of death among patients with CF awaiting lung transplantation.[36]

Curative treatment to restore CFTR function with gene therapy has proven elusive.[20,37] "Comprehensive care" at adult subspecialty centers has been shown to decrease the incidence of hospitalization and improve morbidity and mortality. Symptomatic treatment of pulmonary manifestations is complex and multifactorial. Chest physiotherapy including breathing exercises, flutter valves, and chest percussion is effective in preserving lung function.[3] Chronic suppressive antibiotic therapy with aerosolized tobramycin improves pulmonary function, decreases the density of *P. aeruginosa* in the sputum, and decreases hospitalization.[38] Mucolytic agents such as *N*-acetylcysteine have not been shown to improve mucous clearance. However, DNAase reduces air trapping,[39] improves FEV_1, and decreases pulmonary exacerbation rate.[40] Nebulized hypertonic saline acutely increases mucociliary clearance and has emerged as a safe and inexpensive adjunct therapy.[41] Patients with bronchial hyperreactivity benefit from β-adrenergic agonists such as albuterol. Many patients have a significant inflammatory component with asthma or asthma-like symptoms and benefit from oral or inhaled glucocorticoids.[42]

Manifestations in the Upper Airway

Although it is associated with considerably less morbidity and mortality, the upper airway is also involved in CF.[43] Pedunculated nasal polyps are observed in 6%–48% of patients.[44] Polyposis does not usually occur before the age of 5 yr or after the age of 20 yr,[45] and the histopathology[46,47] and pattern of involvement[48,49] differ from polyps associated with atopy. The exact mechanism by which patients with CF develop polyps remains poorly understood; however, as in the lungs, theories centered upon inflammation and alterations in mucociliary clearance have been advocated.[44] Indeed, nasal cyclooxygenase enzymes 1 and 2 are significantly upregulated in patients with CF.[50] Although hypertrophy and hyperplasia of the mucosa result in a high incidence of chronic sinusitis, fewer than 10% of patients complain of sinonasal symptoms.[51] This observation has been explained by the lack of a healthy baseline status for comparison and the adaptation of patients to their symptoms. Regardless, clinicians must remain alert to the possibility of sinonasal disease, even in asymptomatic patients.

The reestablishment of ventilation and drainage of sinonasal pathways are the goals of conventional treatment of CF. Decongestants, topical treatment with glucocorticoids, and saline irrigation may be effective in most patients. However, some patients will require surgical resection.[44] Nasally inhaled DNAase can be effective in patients with CF and sinonasal disease who do not respond to conventional therapy after surgical treatment.[52] Sinonasal manifestations of posttransplant lymphoproliferative disorder have also been observed in patients after lung transplantation, particularly in children with CF and associated nasal polyposis.[53] If indicated, nasotracheal intubation should always be undertaken cautiously. The role of surgery for chronic sinusitis in CF is controversial.[43]

Manifestations in the Pancreas Including Diabetes Mellitus

Absence of the functional CFTR in the apical membranes of pancreatic ductal epithelial cells results in impaired secretion of bicarbonate secondary to dysfunction of the chloride-bicarbonate exchanger. This leads to a decrease in the volume and pH of pancreatic secretions, which results in the retention of digestive enzymes and proenzymes and pancreatic autodigestion, destruction, and reactive fibrosis.[54] Exocrine pancreatic deficiency is present in >90% of all patients with CF, and all patients are at risk for acute or recurrent pancreatitis.[3] Exocrine deficiency can lead to

protein and fat malabsorption, including the malabsorption of fat-soluble vitamins, especially vitamins A, D, E, and K. Furthermore, vitamin K malabsorption may be exacerbated secondary to antibiotic-induced suppression of vitamin K synthesis by intestinal bacteria. Vitamin K deficiency with resulting coagulopathy and bone disease (see below) is frequently noted among patients with CF.[55] Pulmonary disease and infection lead to increased metabolic requirements that may worsen the malnourished state induced by pancreatic insufficiency.[56] Dietary supplementation with enteric-coated, microencapsulated enzyme supplements improves patient nutrition and quality of life.

Pancreatic β cells are initially spared and pancreatic endocrine function is initially preserved. Nevertheless, the prevalence of CF-related diabetes mellitus (CFRD)[57] increases with patient age and approaches 30% at the age of 30 yr.[58] Indeed, the actual prevalence may be much higher as the implementation of routine screening of adult patients at 1 major CF center in the United States revealed a prevalence of >43% in patients older than 30 yr.[57] Although the pathogenesis of CFRD is primarily related to pancreatic fibrosis and destruction of pancreatic β cells, insulin resistance is also observed.[59] CFRD has significant associated morbidity and mortality and deterioration of pulmonary function.[57] Microvascular complications including retinopathy, nephropathy, and neuropathy are frequently observed. However, macrovascular complications, such as atherosclerosis and coronary artery disease, seem to be rare.[3]

Hepatobiliary Disease

CFTR is expressed in the cells of the biliary tract, and at least one-third of patients have abnormal liver function tests. Fatty infiltration is reported in up to 70% of adult patients, whereas cirrhosis and portal hypertension may complicate up to 10% of all CF cases.[9,60,61] CF has been associated with hepatocellular carcinoma.[62] Indeed, cirrhosis is the second most common cause of death after respiratory failure. As patient survival continues to increase, liver disease and its manifestations will likely become more important. A so-called "micro-gallbladder" occurs in up to 30% of patients with CF, and cholelithiasis is also noted in approximately 10% of patients.[63] Pancreatic fibrosis may lead to common bile duct stenosis with resultant cholecystitis.

Whereas the pathological increase of liver enzymes and fatty infiltration is frequently observed, it is unclear why only certain patients progress to cirrhosis. Indeed, certain genotypes are clearly associated with liver dysfunction and an increased incidence of cirrhosis.[64] There is also an increased incidence of liver disease in patients with certain major histocompatibility complex genotypes,[65] genetic polymorphisms,[66] male gender, coexisting liver disease, and poor nutrition (especially fatty acid deficiency).[61] The diagnosis of CF at a young age is associated with greater hepatobiliary and pancreatic compromise than is a later diagnosis.[63] It is interesting to note that major liver disease is rarely noted in the absence of pancreatic insufficiency. Although cirrhosis would be expected to reduce hepatic metabolism, the metabolism of some drugs is increased in patients with CF.[67,68]

Manifestations in the Gastrointestinal Tract

Abnormally viscid intestinal contents lead to the syndrome of meconium ileus in neonates and infants, which presents with abdominal distention, failure to pass stool, and vomiting. In adults, as many as 16% of patients present with a syndrome characterized by recurrent episodes of intestinal obstruction.[69] The syndrome used to be known as meconium ileus equivalent syndrome. However, it is now termed distal intestinal obstruction syndrome (DIOS) as the obstruction may occur in the colon and the terminal ileum.[3] DIOS can present the physician with significant diagnostic difficulties given its nonspecific presentation (abdominal pain and distention, nausea, vomiting, and failure to pass stool) and its ability to mimic many medical and surgical conditions. Although the pathogenesis of DIOS is thought to be similar to that of meconium ileus, no significant association between DIOS and a history of meconium ileus has been established.[69] DIOS does not present in most patients until adulthood[69] and occurs almost exclusively in patients with pancreatic insufficiency. Dehydration, the use of medications that suppress intestinal motility (e.g., narcotics), and noncompliance with pancreatic enzyme replacement may be precipitating factors. There is an increased risk of DIOS after gastrointestinal surgery, especially lung transplantation.[70,71]

Bone Disease

Low bone mineral density (BMD) is common in adults with CF.[72] The pathogenesis of the bone disease seems to be multifactorial. Contributing factors include pancreatic insufficiency and associated poor nutritional status and malabsorption of vitamin D, physical inactivity, glucocorticoid therapy, and sex hormone insufficiency. Additionally, chronic pulmonary inflammation increases serum cytokine levels, which probably stimulates increased bone resorption and decreased bone formation.[72] As may be inferred from the contributing factors, bone disease is associated with pulmonary disease, pancreatic insufficiency, and malnutrition. Indeed, "healthy" patients with CF may have normal BMD, suggesting that the bone disease is not intrinsically related to the CFTR mutation.[73] As would be expected, the incidence of fractures in patients with CF is approximately twice that of the general population.[74] Rib fractures and vertebral compression fractures are particularly common.[72,74] In addition, the prevalence of scoliosis and kyphosis increases with patient age. One report found kyphosis angles of >40° in 77% of the female and 36% of the male patients aged 15 yr or older.[75] In addition

to causing pain and debilitation, rib and vertebral fractures produce chest wall deformities that reduce lung function, inhibit effective cough, hinder airway clearance, and, ultimately, accelerate the course of CF.[72] Growth hormone,[76] calcium, and vitamin D supplementation, bisphosphonates,[77] and sex steroid replacement therapy have been used to improve BMD.[72]

Genitourinary Manifestations

Late onset of puberty is common in both males and females. More than 95% of men are infertile because of the congenital bilateral absence of the vas deferens with resultant obstructive azoospermia. Absence of the vasa deferentia cannot be surgically corrected; however, with the advent of assisted reproductive techniques, sperm can be harvested from either the epididymis or the testes and combined with oocytes retrieved from the female partner.[78] Women have normal anatomy but tenacious cervical mucus that fails to thin during menses that may result in decreased fertility. The majority of women with CF develop a normal or near-normal menstrual cycle, although the incidence of menstrual problems is high. As the number of adults with CF increases and the number who are sexually active increases, it can be expected that more patients will become pregnant.[79] Pregnancy has significant physiologic effects on female patients, which will be discussed in detail below.

PREOPERATIVE ASSESSMENT

Before addressing specific preoperative issues, it is important to consider the anesthesiologist's role in the life of the adult patient with CF. These patients typically have established long-term relationships of trust with their CF specialist(s). Furthermore, they tend to be very savvy in their understanding both of CF and health care systems and to have great insight into their own health. The consulting anesthesiologist can partner with the patient and use these strengths first and foremost by embracing the CF specialist's involvement in appropriate management decisions throughout the perioperative period. The anesthesiologist can also gain credibility by demonstrating an understanding of the multiple aspects of living with CF and the individual fluctuations experienced by the patient. Respecting the concerns and life experience of patients battling this terrible and pervasive disease is an important part of gaining confidence from these chronically ill patients. Finally, adult patients with CF frequently meet their anesthesiologists during crises, and a frank discussion of advanced directives and end-of-life issues is often warranted.

As the number of adults living with CF as a chronic illness increases, more adult patients with CF will present for preoperative evaluation before surgical procedures and should undergo a comprehensive history and physical examination. Of paramount importance in planning the anesthetic care for a patient with CF is a thorough pulmonary evaluation. Patients should be questioned regarding the history of their CF diagnosis and course of the disease progression as a whole but especially with attention detailing their respiratory manifestations, exercise tolerance, and lung function testing.

The presence of cough, quality and quantity of mucous production, respiratory infections, and airway reactivity are vital aspects of the preoperative interview. Airway reactivity is common in younger patients with CF and wheezing may be persistent and even increase into adolescence and adulthood. There is a positive correlation between hyperresponsivity of the airways and the severity of disease. Airway reactivity is responsive to β-adrenergic agonist drugs, but adults may have worsening of expiratory airflow in response to β-agonists.[22] This worsening of expiratory airflow may be attributable to progressive loss of airway cartilaginous support, and patients are thus more reliant on muscle tone for maintenance of airway patency. Therefore, muscle relaxation may cause "floppy" airways and lead to increased airflow obstruction.

The ability to exercise and increase physical activity is a good prognostic indicator for any patient with pulmonary disease and those with CF are no exception to this rule. Physical activity augments airway clearance, enhances deep breathing and cough efforts, and may produce some bronchodilation.[80] Exercise training in patients with CF may be associated with some small but important clinical improvements such as improved nutritional status, improved or delayed worsening of PFTs, and better quality of life.[81] Thus, the preoperative interview for the patient with CF should assess functional exercise capacity, which may help determine patients at higher risk for postoperative pulmonary complications.

A radiographic pulmonary evaluation begins with a chest radiograph with attention to hyperinflation of the lungs as evidenced by flattening of the diaphragm, prominence of the retrosternal space, and in late disease, kyphoscoliosis. Also important to note on the chest radiograph are bronchovascular markings, which are initially present in the upper lobes but progress to the lower lobes later in the disease process. With bronchiectasis and cyst formation, peribronchial cuffing and "tram tracks" are able to be delineated on the chest radiograph, which appear as parallel lines as a result of thickening of the bronchial walls in longitudinal section. Chest computed tomography is helpful to delineate the degree of bronchiectasis, but this does not always correlate with exercise tolerance and may actually appear worse than the patient is physically doing from a pulmonary perspective.[82] Although pulmonary imaging may be used to document disease progression and to assess the degree of air trapping, hyperinflation, and bronchiectasis, further evaluation is necessary to determine a patient's pulmonary function.

PFTs may be especially helpful in the preoperative evaluation of the patient with CF. As noted above, an

obstructive pattern to airflow is typically observed, and the most sensitive early signs of airway obstruction include an increase in the ratio of RV to total lung capacity and a decrease in the forced expiratory flow at 25%–75% of lung volume (FEF 25%–75%). With progression of CF, FEV_1 and the ratio of FEV_1 to forced vital capacity (FVC) declines. Lung volumes such as total lung capacity and RV also increase with hyperinflation. Generally, as patients with CF age, their baseline pulmonary function decreases, but the pattern of change observed as they get older is unpredictable and can vary. Most patients are in 1 of 3 categories as far as the progression of pulmonary disease. They experience either a linear decrement in FVC and FEV_1 or may exhibit near-normal pulmonary function for years followed by a rapid decline or may have a stepwise decrease in pulmonary function, with each step being separated by periods of stability at the new level of function. Among children and adolescents with CF, FEV_1 has been shown to correlate with subsequent survival. Predictors of the rate of decline in FEV_1 according to a large, observational study include poor nutritional status, infection with *P. aeruginosa*, crackles on lung examination, and the frequency of respiratory exacerbations.[83] Thus, patients presenting for preoperative evaluation should have recent PFTs, and the anesthesiology team caring for the patient should plan their anesthetic care based on the understanding that patients with a severely reduced FEV_1 are at a more advanced stage of their CF disease process and steps should be taken accordingly to protect their limited pulmonary function and reserve as much as possible.

As CF progresses with worsening bronchiectasis and airflow obstruction, ventilation-perfusion mismatch leads to the development of hypoxemia and the ultimate late development of hypercarbia. Chronic hypoxemia and hypercarbia may lead to increasing PVR, right ventricular hypertrophy, and possibly eventual cor pulmonale with right heart failure. It is important for anesthesiologists to recognize these late signs as they indicate advanced and decompensated CF. Patients with advanced CF may require home oxygen therapy during exertion or at night while sleeping and may also benefit from noninvasive positive pressure ventilation (such as bilevel positive airway pressure [BiPAP]) to help ameliorate the effects of hypoxemia and hypercarbia. The chronic use of BiPAP has implications for patients presenting for surgery and anesthesia in that the patient may display more carbon dioxide (CO_2) retention in response to volatile anesthetics and opioid pain medications. For this reason, if patients are receiving BiPAP preoperatively, they should have access to their positive pressure ventilation support as early in the postoperative course as possible (e.g., in the postanesthesia care unit). Baseline arterial blood gas measurements before surgery are a reasonable addition to the laboratory assessment of patients who retain CO_2 or are hypoxemic, require home oxygen, or positive pressure ventilation therapy as they are at a more advanced stage of their disease and are likely to have postoperative pulmonary complications. For patients whose respiratory disease is mild or stable with no recent hospitalizations or infections, arterial blood gas measurement may be deferred.

Aside from the assessment of the pulmonary system for patients with CF, the preoperative assessment must also evaluate the other complications associated with CF. As noted above, nearly all patients with CF have sinus inflammation and disease that can act as a bacterial reservoir for pulmonary infectious exacerbations. Sinus inflammation may be a trigger for bronchospasm.[80]

As mentioned previously, pancreatic insufficiency is a hallmark complication associated with CF, and the degree of pancreatic endocrine and/or exocrine dysfunction must be delineated before surgery. Most patients with CF will have their pancreatic complications managed by an experienced endocrinologist, but it is important to know and understand their treatment regimens and return to those baseline regimens as soon as possible after surgery. CFRD is caused by insulin deficiency and worsened by insulin resistance. Rarely do patients display ketoacidosis and sometimes are asymptomatic with respect to hyperglycemia and hypoglycemia. Thus, in the perioperative setting, it is important to maintain patients with CF as close to their baseline, "normal" glucose as possible by frequent blood glucose monitoring, although the stress of surgery and anesthesia may impose a requirement for increased treatment with insulin.

The preoperative evaluation for liver disease in the setting of CF should include not only history and physical examination for stigmata of liver disease but also the laboratory assessment of liver function and liver function tests (LFTs). If the liver enzymes increase >1.5 times normal, further hepatic evaluation should be considered because CF may lead to progressive biliary fibrosis and cirrhosis. Patients experiencing hepatic involvement may require altered anesthesia management techniques because of coagulopathy and altered metabolism of medications and anesthetic drugs. Thus, it is important for the anesthesia care team to be aware of and understand the hepatic complications associated with CF. Patients with known biliary and hepatic complications often need to undergo multiple endoscopic retrograde cholangiopancreatography procedures, which may require general endotracheal anesthesia.

For patients who present for emergency surgery in whom there is not adequate time for a full preoperative workup, a thorough history and physical examination remain necessary. It is vital to delineate the recent time course of the pulmonary manifestations of the patient's CF disease, current exercise tolerance, recent hospitalizations, pulmonary infections, and requirement for IV antibiotics. These 4 items should

assist the anesthesiologist caring for a patient with CF in an urgent or emergent situation to stratify the pulmonary risk. The patient with stable disease, able to perform physical exertion, and without recent infection is likely to tolerate the rigors of surgery and anesthesia without postoperative pulmonary complications. However, the patient who has been sedentary and recently hospitalized or requiring IV antibiotics is at higher risk of pulmonary complications after surgery and general anesthesia. Secondary questions include a brief investigation into other CF-related manifestations, such as CFRD, pancreatic insufficiency, and hepatic disease, which will help the anesthesia team caring for the patient plan intraoperative and postoperative interventions, such as blood glucose and coagulation management.

INTRAOPERATIVE MANAGEMENT

The anesthetic plan of care should be tailored to each individual patient with regard to the history and course of CF disease. A common goal, however, should be for the anesthetic to produce minimal ventilatory depression. All patients should be managed such that airway reflexes are fully recovered at the end of the surgical procedure. Early tracheal extubation is of paramount importance as prolonged intubation and mechanical ventilation of the patient with CF may lead to increased pulmonary morbidity and possibly mortality. Monitoring should consist of the American Society of Anesthesiologists' recommended routine monitors and invasive monitors appropriate for each patient's physical condition and type of surgery. Given the increased frequency of impaired glucose control in patients with CF, frequent intraoperative and postoperative monitoring of blood glucose is indicated. Because patients with CF often have significant sinus disease and nasal polyps, nasopharyngeal airways should be avoided. Early use of oral airways after induction may prevent further airway obstruction. Gases should be humidified and warmed before administration to avoid further inspissation of airway secretions. If reactive airways and bronchospasm are significant components of a CF patient's disease, bronchodilators should be considered before induction, throughout the anesthetic, and before extubation.

When positive pressure ventilation is required, a dilemma often arises when higher than desired airway pressures are required because of the baseline pulmonary disease. High airway pressures and tidal volumes have been shown to decrease the need for cardiopulmonary bypass during lung transplantation[84] but obviously entail the risk of lasting injury in nontransplant surgery. Frequent suctioning of the viscous mucus (both blindly and/or by bronchoscopy) and even segmental lavage may be required to maintain adequate oxygenation and ventilation. At the end of a general anesthetic, it may be helpful to provide chest physical therapy, lung recruitment maneuvers, and endotracheal suction to help with mobilization of secretions and to avoid atelectasis. Extubation should not take place until adequate spontaneous ventilation is established, and the patient has met criteria for extubation, such as maintenance of oxygenation and ventilation, is warm, and is hemodynamically stable.

Although there is a paucity of data available as to which anesthetics to choose for patients with CF, it is reasonable to consider that with the variety of choices available, many anesthetic regimens might be appropriate for an individual patient. If general endotracheal anesthesia is required, using a volatile anesthetic, such as sevoflurane in oxygen and/or air mixture, should likely be well tolerated because volatile anesthetics are potent bronchodilators, which should prove helpful in patients with CF. In patients requiring general anesthesia, total IV anesthesia may be considered but does not have the bronchodilating qualities associated with volatile anesthetics.

Intraoperatively, opioid analgesics should be administered carefully. The type of surgical procedure and expected postoperative pain can be used to guide titration of opioids. Obviously, although it is important to avoid respiratory depression, it is equally important to avoid the potentially deleterious effects of pain on respiratory mechanics. To provide optimal analgesia and avoid respiratory depression, other adjunctive techniques should be considered: nonsteroidal antiinflammatory medications, IV lidocaine (by infusion if possible) to decrease inflammation,[85] ketamine for blockade of the *N*-methyl-D-aspartate receptor,[86] and regional anesthetic techniques such as peripheral nerve blocks and neuraxial analgesia.

The decision to use neuromuscular blockade should include consideration of the type and length of surgery, surgical requirement for muscle relaxation, and patient physical status. Patients with CF have progressive loss of airway cartilaginous support and are thus more reliant on muscle tone for maintenance of airway patency. Therefore, muscle relaxation may cause "floppy" airways and lead to increased airflow obstruction. For surgeries not requiring muscle relaxation, it seems reasonable to avoid long-lasting neuromuscular blockade.

If surgical anesthesia can be provided by a neuraxial or regional technique such as spinal, epidural, or peripheral nerve block, it may be advantageous for CF patients because airway manipulation may be eliminated with its attendant risks of postoperative pulmonary complications, such as respiratory failure and infection.[87,88] Indeed, these techniques will provide not only surgical anesthesia but also postoperative analgesia, thus reducing the amount of systemic opioid pain medications that are required.

POSTOPERATIVE MANAGEMENT

Postoperative pain management is critically important in the CF patient population. As noted above, opioid

medications may be combined with adjunctive techniques to control pain. Pain control is especially important in patients with CF to encourage coughing, deep breathing, and minimize pulmonary complications. Patients should have early access to chest physical therapy and early activity and mobilization as well.

Patients requiring home oxygen or noninvasive positive pressure ventilation such as BiPAP must be monitored carefully postoperatively for respiratory failure as evidenced by increased work of breathing, retention of CO_2, and hypoxemia. Patients requiring BiPAP should have immediate access to their equipment. Although there is a lack of evidence-based data for patients with CF undergoing surgery, patients with moderate to severe pulmonary disease should be admitted for overnight monitoring of their recovery from surgery and anesthesia. Depending on the nature of the surgery, intraoperative course, and postoperative recovery in the recovery room, patients with mild disease may be discharged home with the care of a responsible adult after an appropriate time of monitoring. The perioperative management of the patient with CF is summarized in Table 2.

SPECIAL CONSIDERATIONS

Lung Transplantation

Advances in the treatment for CF have delayed progression of disease but have not eliminated the premature death that occurs in the majority of patients due to respiratory failure and pulmonary complications. Lung transplantation, although an imperfect solution, provides a management option for respiratory failure. Patients with CF require double-lung transplantation because leaving a native lung *in situ* threatens the health of the transplanted lung with spillage of infectious secretions and sputum. Between 1995 and 2006, 29% of lung transplants were performed for a diagnosis of CF.[89] Patients may be referred for lung transplantation for any of the following indications: progressive pulmonary function impairment as evidenced by FEV_1 <30% predicted, severe hypoxemia and/or hypercarbia, increasing functional impairment manifested by increasing frequency and duration of hospitalization-requiring treatments for pulmonary exacerbations, and major life-threatening complications such as major hemoptysis.[36,90] Outcomes of lung transplantation for CF show a clear survival benefit for patients who have a predicted 5-yr survival rate of 30% without transplant.[91] For patients with a 5-yr survival in the 30%–50% range, the survival benefit is more difficult to demonstrate. Patients who are transplanted with a 5-yr expected survival >50% without the transplant have a lower survival compared with their nontransplanted counterparts.[91,92] Thus, lung transplantation is typically reserved for patients with severe disease. The timing of the transplant is further complicated by recent data showing that older CF recipients have decreased infection, bronchiolitis obliterans, and graft rejection.[93] A 2008 review of lung transplantation from the United Kingdom revealed a continued beneficial effect of lung transplantation.[92]

Whereas the rate of deterioration of lung function in CF is sometimes predictable, the timing of donor lung availability is not. Furthermore, the number of donor organs is inadequate. Bridging devices,[94] analogous to ventricular assist devices for heart failure, may allow patients to survive longer with end-stage failure while awaiting transplantation.

Lung transplantation does not address the myriad of nonpulmonary issues with which most patients with CF are afflicted. Chronic sinusitis and upper airway disease, pancreatic insufficiency, cholelithiasis, hepatic cirrhosis, diabetes mellitus, osteoporosis, and DIOS remain significant problems for patients with CF.

Liver Transplantation

For patients with CF who have decompensated cirrhosis but relatively well-preserved pulmonary function, liver transplantation is an option and has a relatively high 1-yr survival rate of 75%–80%.[95] The United Network for Organ Sharing reports that 255 US patients with the primary diagnosis of CF received liver transplants in the years 1988–2008.* It seems that CF patients with cirrhosis can undergo the rigors of liver transplantation and the postoperative course, including immunosuppression, when patients are very carefully selected. Those with the lowest morbidity and mortality are patients with well-preserved pulmonary function, good performance status, and a low incidence of pulmonary infections.[96]

Pregnancy

Some of the normal physiologic changes associated with pregnancy may have untoward effects on women with CF. For example, the patient may be unable to meet the required increases in minute ventilation and oxygen uptake secondary to their already impaired respiratory system.[97,98] Pregnancy is also associated with an increase in blood volume and cardiac output that increase dramatically by the end of pregnancy because of placental circulation and systemic vasodilation. These effects may cause right heart strain or even right heart failure for women with CF who have moderate to severe pulmonary disease.[98] Regardless of the severity of CF, pregnancy in a patient with CF should be considered of high risk. Factors associated with poor outcome in pregnant CF patients are weight gain <4.5 kg, FVC <50% predicted, pulmonary colonization with *B. cepacia*, frequent pulmonary infections, diabetes mellitus, and pancreatic insufficiency.[99,100] The incidence of preterm labor and delivery is increased for women with CF, and those most at risk seem to be the patients with the worst pulmonary function and nutritional and pancreatic function.[99]

*Available at: http://optn.transplant.hrsa.gov/latestData/advancedData.asp. Accessed June 11, 2009.

Table 2. Perioperative Management of the Patient with Cystic Fibrosis

- Preoperative assessment
  - Pulmonary evaluation
    - Thorough history and physical examination
    - Presence of cough and quality and quantity of mucous production
    - Frequency of respiratory infection
    - Airway reactivity and wheezing and response to bronchodilators
    - Exercise and functional capacity
    - Chest radiograph: hyperinflation of lungs, kyphoscoliosis, and bronchovascular markings
    - Chest CT: evaluate for bronchiectasis (does not always correlate with exercise tolerance)
    - Pulmonary function testing: obstructive pattern (increased ratio of residual volume to total lung capacity; decreased FEV_1; decreased FEV_1/FVC
    - Baseline arterial blood gas analysis for CO_2 retention
    - Ventilation-perfusion mismatching leads to chronic hypoxia and hypercarbia
    - Late findings include increased PVR, right ventricular hypertrophy, and cor pulmonale
    - Advanced disease patients require home oxygen therapy and noninvasive positive pressure ventilation
    - Consider presence of sinus disease and nasal polyps as may be trigger for bronchospasm
  - Pancreatic evaluation
    - Delineate presence of CFRD and patient's current management
    - Consider need for perioperative insulin therapy to manage hyperglycemia
    - Consider nutritional deficiencies related to pancreatic exocrine disease such as vitamin deficiencies and coexistent coagulation problems
  - Hepatobiliary evaluation
    - History and physical examination for stigmata of liver disease
    - Liver function testing; if elevations >1.5 times normal, need further evaluation
    - Considerations of coagulopathy and altered metabolism of medications related to cirrhosis
    - Need for frequent ERCP
  - Considerations for patients presenting for emergency surgery
    - Not usually adequate time for full workup of CF-related issues
    - Thorough history and physical examination
    - To assist in risk stratification for postoperative pulmonary complications need attention to pulmonary manifestations and present physical status including: exercise tolerance, recent hospitalizations, pulmonary infections, and need for IV antibiotics
    - Secondary questions target CFRD, pancreatic exocrine deficiency, and hepatic disease
- Intraoperative management
  - Anesthetic plan
    - Routine ASA monitors
    - Invasive monitors as appropriate for each patient's condition and type of surgery
    - Tailor the anesthetic plan of care to each patient
    - Common goal: minimal respiratory depression and full recovery of reflexes at end of surgery and anesthetic
    - Avoid nasopharyngeal airways (sinonasal disease) but early use of oral airways important to prevent airway obstruction
    - Humidify and warm airway gases
    - Bronchodilators for reactive airways and bronchospasm
    - Before extubation, consider chest physiotherapy, lung recruitment maneuvers and endotracheal suction to mobilize secretions, and avoid atelectasis
    - Extubation important but assure adequacy of ventilation first along with extubation criteria
    - Early extubation is vital to avoid prolonged intubation and mechanical ventilation, which increases morbidity and mortality
    - Volatile anesthetic agents produce some bronchodilation, which may be advantageous in patients with CF versus total IV anesthesia
    - Titrate intraoperative opioids based on type of surgical procedure and expected postoperative pain
    - Balance need for pain medication and avoiding deleterious effects of pain on respiratory mechanics with potential for respiratory depression caused by opioids
    - Consider adjunctive pain management medications and techniques: NSAIDs, IV lidocaine, ketamine, and peripheral nerve blocks/neuraxial analgesia
    - Neuromuscular blockade may not be advantageous in patients with CF with loss of airway cartilaginous support who rely on muscle tone for airway patency
    - If airway manipulation and instrumentation can be avoided by using a neuraxial or regional anesthesia technique, risks of postoperative pulmonary complications may be eliminated
- Postoperative management
  - Pain management
    - Consider advantages and disadvantages of opioid pain medications
    - Use adjunctive techniques as able to decrease requirement for opioids
  - Postoperative pulmonary complications
    - Monitor patients requiring home oxygen or noninvasive positive pressure ventilation for longer time in recovery room to assure recovery from anesthetic and surgery
    - Provide for use of noninvasive positive pressure ventilation as soon as possible in the recovery room
    - Consider overnight hospitalization for longer monitoring time period for patients with moderate to severe pulmonary disease
    - Patients with mild pulmonary disease may be discharged home in the care of responsible adult once stable

FEV_1 = forced expiratory volume in 1 s; PVR = pulmonary vascular resistance; CF = cystic fibrosis; CO_2 = carbon dioxide; CFRD = cystic fibrosis-related diabetes mellitus; ERCP = endoscopic retrograde cholangiopancreatography; NSAIDs = nonsteroidal antiinflammatory drugs; CT = computed tomography; ASA = American Society of Anesthesiologists; FVC = forced vital capacity.

For women with mild to moderate pulmonary disease (FEV_1 >60% predicted), there have not been documented adverse maternal outcomes related to pregnancy. Nevertheless, for women with severe pulmonary disease with coexisting right heart dysfunction and/or pulmonary hypertension, pregnancy should be considered contraindicated, as it is associated with worsening of cardiopulmonary function, respiratory failure, and significant risk of mortality.

Anesthesia and analgesia for patients with CF with well-compensated pulmonary disease who are laboring and expected to have successful spontaneous vaginal delivery can usually be provided by lumbar epidural analgesia. Although there is a paucity of evidence-based literature on anesthetic management of parturients and only case reports to review,[101,102] anesthesiologists must consider each patient presenting for cesarean delivery individually, particularly with regard to pulmonary status. General anesthesia is usually avoided because of the usual maternal airway concerns. Additionally, general anesthesia in the patient with CF increases the risk of exacerbating respiratory difficulties and may pose a risk of delayed weaning from mechanical ventilation and inadequate postoperative analgesia. Neuraxial techniques are preferred, and a combined spinal epidural anesthesia for cesarean delivery would provide for a denser, more predictable surgical block while allowing for postoperative pain relief with epidural infusion. However, compromise of respiratory muscle function is undesirable in patients with severe obstructive disease. One must weigh the risks and benefits of neuraxial versus general anesthesia for the parturient with CF presenting for cesarean delivery.

CF is an example of a chronic progressive pulmonary disease in which pregnancy may produce huge challenges in both the medical management of the patient and the ethics of how to best care for both mother and fetus. With increasing numbers of patients with CF living and thriving into their adult years, decisions surrounding the issues of fertility and pregnancy require cooperation and understanding on the parts of potential parents and physicians of the principles of autonomy, beneficence, and nonmaleficence.[103]

CONCLUSION

CF is a chronic multisystem disease involving primarily the pulmonary and gastrointestinal systems and may present along a spectrum of mild to severe. As the medical management of CF has improved over the past few decades, more patients with CF are surviving and thriving into adulthood. This creates not only a need for health care practitioners to care for adult patients with CF but also should alert anesthesiologists to the fact that CF is no longer solely a pediatric disease. Anesthesiologists and anesthesia care providers need to understand the medical issues and pathophysiology of CF when caring for a patient with CF presenting for surgery and anesthesia.

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