CHEST

Critical Care of the Adult Patient With Cystic Fibrosis

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Cystic fibrosis (CF) is a multiorgan, genetic disease resulting from dysfunction of the CF transmembrane conductance regulator. The primary clinical manifestations are bronchiectasis, chronic pulmonary infections with recurrent exacerbations, and pancreatic insufficiency. Advances in CF care have led to improved survival, with more than one-half of those affected being adults. As a result, adult pulmonary and critical care physicians increasingly will be involved in the care of these patients. Patients with CF are at risk for numerous conditions that require ICU admission, including respiratory failure, massive hemoptysis, pneumothorax, hepatic failure, and bowel obstruction. Multiple aspects of the care of patients with CF benefit from specialized knowledge, including pancreatic enzyme replacement and nutritional support; airway clearance modalities; treatment of multiply resistant, polymicrobial infections, and unique drug metabolism. In extreme cases, patients may benefit from advanced therapies, including extracorporeal support and organ transplant. Optimal care of patients with CF requires a multidisciplinary care team that includes respiratory therapists, dieticians, social workers, psychologists, pharmacists, and physicians who have expertise in the treatment of this complex, multisystem disorder.

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Cystic fibrosis (CF) is an autosomal recessive, multisystem disease caused by reduced function of the CF transmembrane conductance regulator (CFTR), an apical membrane protein on the surface of epithelial cells, that acts as a channel for chloride and bicarbonate.[1] CFTR dysfunction impacts fluid and salt transport, resulting in viscous secretions that ultimately impair the function of multiple epithelial-lined organs. With advances in care, CF outcomes are improving rapidly and more than one-half of Americans with CF are now adults.[2] Despite these improvements, the median age of death is still younger than 30 years, and more than 600 patients died or required organ transplant in 2016.[2]

ABBREVIATIONS: APE = acute pulmonary exacerbation; ARF = acute respiratory failure; BAE = bronchial artery embolization; CF = cystic fibrosis; CFRD = CF-related diabetes mellitus; CFTR = CF transmembrane conductance regulator; DIOS = distal intestinal obstruction syndrome; ECMO = extracorporeal membrane oxygenation; HHHFNC = heated-humidity high-flow nasal cannula; HTS = hypertonic saline; IMV = invasive mechanical ventilation; MRSA = methicillin-resistant *Staphylococcus aureus*; NIV = noninvasive ventilation; PEEP = positive end-expiratory pressure; PERT = pancreatic enzyme replacement therapy

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Given the increasing life span and propensity for critical illness in patients with CF, adult critical care practitioners will encounter more patients with CF in the ICU. However, many intensivists have had limited exposure to the population with CF and are unfamiliar with the unique aspects of care for this population. Patients with CF differ from the general population in the ICU regarding many issues, including antibiotic selection and dosing, the need for aggressive airway clearance, and pancreatic enzyme replacement therapy (PERT) and nutritional support. Optimal CF care requires a multidisciplinary team at a center experienced in caring for this population with complex needs; however, access to care at an accredited center may not always be immediately available. An analysis of 1,249 ICU admissions of adult patients with CF in Texas from 2004 to 2013 found that only 50.5% were treated at teaching facilities and that a mere 6.2% were cared for at care centers accredited by the Cystic Fibrosis Foundation.[3] Although this experience may not be entirely representative of CF care around the country, it certainly highlights the fact that patients with CF often are cared for outside of expert care centers, particularly during unplanned hospital admissions. This review is designed to provide a focused overview of the approach to critical care for adult patients with CF.

Respiratory Failure in Patients With CF

The large majority of hospitalizations in patients with CF are respiratory in nature, accounting for 89% of admissions among patients with CF in the United States in 2013 in the National Inpatient Sample database.[4] Most patients do not require ICU admission; however, 13% of patients who are hospitalized required ICU-level care in the Texas analysis of CF admissions, with 17% of patients admitted to the ICU needing invasive mechanical ventilation (IMV).[3]

CF lung disease is characterized by airway obstruction and bronchiectasis. Patients with hypercapnia, resting hypoxemia, markedly reduced FEV_1, and pulmonary hypertension are at increased risk of respiratory decompensation.[5] Therefore, knowledge of baseline pulmonary function at the time of admission is helpful to risk stratify the likelihood of requiring and ability to liberate from IMV. Likewise, knowledge of a patient's past microbiologic culture history is also essential to ensure appropriate selection of antimicrobial therapy (Table 1).

The majority of respiratory failure episodes in patients with CF occur due to acute pulmonary exacerbations (APEs). These important events typically manifest as increased cough and sputum production, anorexia, weight loss, and lung function decline.[6] Additional features that may be present in some, but not all, adult patients include pleuritic chest pain, shortness of breath, hemoptysis, fever, and leukocytosis (Table 2). Exacerbation triggers commonly include acute viral infection or nonadherence to prescribed treatments but often occur without an obvious precipitant. Although patients with severely reduced baseline lung function have the greatest risk of respiratory failure, those with moderate impairment are at risk as well.[7] The same general tools for radiographically and functionally characterizing the lungs are used for the population with CF. Appropriate chest imaging should be performed, with chest radiography typically being sufficient. Chest CT scanning may be useful, however, when there is concern for allergic bronchopulmonary aspergillosis or infection with nontuberculous mycobacteria. In the setting of massive hemoptysis, multidetector CT scanning sometimes can be useful for the identification of aberrant, nonbronchial collateral vessels that may be the source of bleeding. Finally, CT angiography is indicated for the diagnosis of pulmonary emboli. Blood gas analysis is useful to assess for acute and chronic hypercapnia because impaired ventilation often predates hypoxemia in patients with CF. Bedside spirometry testing is helpful objectively to assess and compare lung

TABLE 1] Three Key Components of Cystic Fibrosis Assessment

• Lung function: FEV_1
• Weight and BMI
• Respiratory culture history

TABLE 2] Clinical Characteristics of Cystic Fibrosis Pulmonary Exacerbation

Major features
• Increased sputum production
• Increased sputum purulence
• Loss of appetite
• Weight loss
• Fatigue
• Lung function decline
Occasional features
• Fever
• Chest pain
• Shortness of breath
• Hemoptysis

function, specifically FEV_1, to baseline levels but should not be performed in patients with pneumothorax, massive hemoptysis, or frank respiratory distress.

Major Tenets of Care

The principle components constituting the treatment of severe CF APE are support of oxygenation or ventilation, airway clearance, antimicrobial therapy, and nutritional support. In addition, physical therapy or exercise therapy is an important adjunct to airway clearance and helps maintain cardiovascular fitness and muscle strength (Fig 1). Treatment with CFTR modulator therapy, although increasingly more important in routine CF care, is not always possible in the ICU setting because of the need for oral administration. The following sections provide a framework for the use of these interventions in the ICU setting.

Respiratory Support

The level of respiratory support should be tailored to the severity of the patient's respiratory insufficiency. Patients with hypoxemia without increased work of breathing or hypercapnia can be supported with supplemental oxygen alone.

Heated-Humidity High-Flow Nasal Cannula

Heated-humidity high-flow nasal cannula (HHHFNC) therapy may be useful in patients with CF with increased work of breathing who have not progressed to acute hypercapnic respiratory failure. HHHFNC has a number of positive physiologic effects, including reduction of nasopharyngeal resistance, washout of pharyngeal dead space, generation of positive end-expiratory pressure (PEEP), and alveolar recruitment, which reduce inspiratory effort and improve lung compliance.[8,9] Additionally, HHHFNC allows for oral intake and expectoration following airway clearance. Although not specifically validated as a means of support in patients with CF, HHHFNC has an established role in support of adults with hypoxemic respiratory failure and in the postextubation setting.[10-12] A clinical trial on use of HHHFNC in patients with CF is currently underway.[13] The use of HHHFNC in patients with mild acute hypercapnia who are intolerant of noninvasive ventilation (NIV) is reasonable; however, these patients require close monitoring for decompensation.

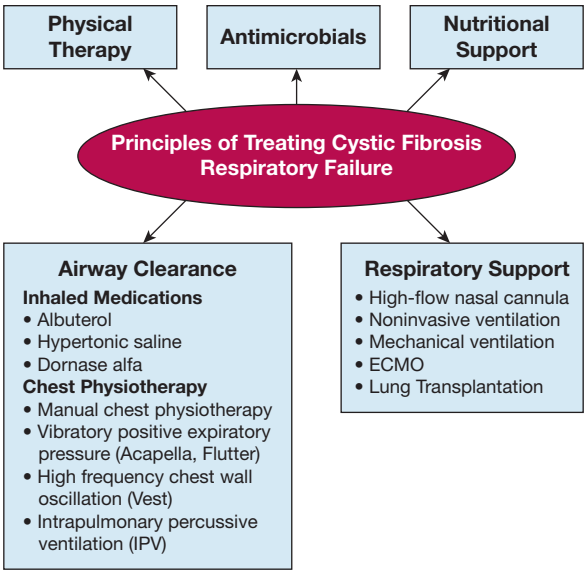


Figure 1 – *Diagram highlighting the principle components involved in the treatment of respiratory failure in patients with cystic fibrosis. ECMO = extracorporeal membrane oxygenation.*

Noninvasive Ventilation

Borrowing from the experience in COPD, NIV provides an additional level of support for patients with CF with acute respiratory failure (ARF).[14] Although no prospective studies have validated the use of NIV for ARF in patients with CF, a small retrospective study reported favorable outcomes.[15] Potential pitfalls related to the dependence on NIV for ARF in patients with CF include reduced ability to perform mucus clearance techniques, the need to modify delivery of inhaled treatments, and interference with sleep and eating. NIV has shown potential benefit as an adjunct to airway clearance techniques in the ambulatory setting; however, such evidence in the patient who is critically ill is lacking.[16] NIV also should be avoided in patients with CF with severe respiratory acidosis or mental obtundation. To optimize success, NIV should be initiated early in the course of acute hypercapnia. Patients should be monitored closely to assess for tolerance of the interface, patient-device synchrony, worsening hypercarbia, and other signs of clinical deterioration.

Invasive Mechanical Ventilation

On the basis of dismal outcomes from early reports, the use of IMV in patients with CF long was considered futile.[17] Newer data have led to evolution in the thinking about this topic. Sood and colleagues[7] reported on the experience at the University of North Carolina between 1990 and 1998. They reported on 32 episodes of respiratory failure requiring IMV in 30 patients. Of these, 12 patients (40%) died and 10 (33%) underwent lung transplant. The remainder survived to discharge without an immediate transplant. Patients who survived

without lung transplant were more likely to have an acute reversible process, such as pneumothorax or hemoptysis, rather than simply progressive respiratory failure. In Australia, a similarly specialized CF center showed a 40% 1-year survival rate in a cohort of 15 patients who received IMV for ARF between 1988 and 2003.[18] A more contemporary review of admissions of patients with CF in Texas between 2004 and 2013 reported a short-term mortality rate of 41.8% among 213 patients with CF requiring IMV.[3]

Prognosis and Advanced Directives

The appropriate use of IMV in patients with CF largely depends on the situation. Intubation for a procedure in a patient with only mild to moderately impaired lung function is likely to be uncomplicated. Conversely, use of IMV for ARF may result in the inability to liberate the patient from IMV and requires careful consideration of the reversibility of the clinical issue and prior health status. Patient preferences are crucial, but often complex, because of young age, heavy burden of disease, varying levels of psychosocial support, and high prevalence of depression. Only about 30% of adults with CF have advanced directives in place.[19] Patients with an $FEV_1 < 25\%$ predicted or severely compromised nutritional status have a low likelihood of liberation from IMV.[7,18] However, IMV as a bridge to lung transplant is reasonable in a candidate for this therapy and does not appear to affect posttransplant survival.[20] Ideally, patients should be referred for nonurgent transplant evaluation as their disease progresses. Should unanticipated decompensation occur in a patient who has not been evaluated previously for transplant, efforts should be made to transfer the patient expeditiously to a lung transplant center for urgent evaluation. Despite best care practices, many patients with CF will die during an ICU admission or in the following months. Because these patients are young, decision-making often is fraught with emotion for family, caregivers, and hospital staff. ICU admission, even when successful in reversing acute illness, provides an opportunity to initiate discussions about prognosis, lung transplant candidacy, and longitudinal goals of care, with introduction of palliative and hospice care options when appropriate.

Challenges With Mechanical Ventilation

Because of their obstructive pulmonary physiology, patients with CF can be challenging to treat with IMV. Patients with CF are prone to progressive air trapping and intrinsic PEEP, which, if left unmitigated, can result in ventilator dyssynchrony, barotrauma, and hemodynamic compromise. To allow adequate time for patient exhalation, physicians should adjust ventilator settings by decreasing respiratory rate, setting a prolonged expiratory time, and using high inspiratory flow rates. Patients should receive adequate sedation to prevent tachypnea and breath stacking. The strategy of permissive hypercapnia, with ventilator settings titrated to achieve a pH of approximately 7.25 to 7.4, rather than attempting to normalize Pco_2, may help to achieve the goal of avoiding ventilator-induced complications. Applied PEEP should be set at or just below (1-2 cm H_2O) intrinsic PEEP to reduce the effort required to trigger the ventilator while maintaining open airways during exhalation and reducing atelectasis.[21] Airway clearance during IMV is a major challenge because effective cough is eliminated in this setting and endotracheal suctioning addresses only trachea and tube patency. Results of a limited report showed the benefits of less commonly used modes of ventilation, such as high-frequency percussive ventilation with volumetric diffusive respiration; this mode purportedly assists with secretion clearance and oxygenation in patients with CF while potentially reducing the risk of barotrauma.[22] Further studies are required to validate the benefit of these ventilator modes in comparison with conventional ventilator support modes.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is being used increasingly as a bridge to recovery or transplant in numerous conditions.[23] A query of the Extracorporeal Life Support Organization data from 1998 to 2013 found reports of ECMO use in 73 patients with CF, with an associated rate of survival to discharge of 52%.[24] Improvements in ECMO technology, including the advent of dual-lumen bicaval cannulas, have resulted in the ability to perform ambulatory ECMO, thus combating deconditioning during the wait for organ transplant. This strategy is likely preferable to prolonged IMV alone, although firm evidence is lacking. Currently, ECMO in CF generally is reserved for candidates for lung transplant, although one could envision scenarios in which its use would be reasonable in the context of a potentially reversible process with mild or moderate underlying lung disease. When ECMO is used in the setting of massive hemoptysis, minimizing or avoiding the use of anticoagulation is advisable, when possible.

Sedation and Analgesia

The goals of sedation and analgesia in the patient with CF who is critically ill are essentially the same as those in the population without CF, albeit sometimes more difficult to achieve. As established by the Society of Critical Care Medicine, best practices for management of sedation and analgesia should be followed regarding daily interruptions of sedation, maintenance of light sedation through validated scales, and a protocolized approach to sedation and weaning.[25] In addition, early and aggressive mobilization of patients is advisable.

There are, however, a few considerations unique to the population with CF with respect to sedation and analgesia. A higher dose requirement to achieve adequate sedation may be encountered, which likely is due to alterations in drug metabolism.[26,27] Propofol is a reasonable first-line therapy for sedation. In patients who do not achieve adequate sedation with propofol, the addition of dexmedetomidine may be efficacious. Anecdotally, the use of a low-dose ketamine infusion may be helpful as an adjunctive agent in more challenging cases. Benzodiazepines generally should be avoided because of their association with delirium.[25] High-dose narcotic infusions also should be avoided because they may precipitate bowel obstruction due to the distal intestinal obstruction syndrome (DIOS), particularly in patients receiving IMV, given that immobility is an additional risk factor for DIOS. A multimodal, opiate-sparing approach to pain control to include nonnarcotic analgesics and other modalities is advisable. Patients receiving opioids should receive an aggressive bowel regimen with osmotic laxatives (polyethylene glycol) and appropriate IV hydration and should be monitored closely for the development of constipation and DIOS.

Airway Clearance

CFTR dysfunction results in dehydration of airway secretions and defective mucus clearance.[28] Optimal airway clearance requires the combination of inhaled therapies and physical modalities to enhance mucus transport. In the context of APE, the CF guidelines recommend increasing airway clearance therapy, which can be challenging to operationalize in a critical care environment.[6]

Inhaled Medications

Nebulized bronchodilators are a mainstay in the treatment of CF APE. In addition to reversing bronchospasm and improving the tolerability of other sometimes irritating inhaled therapies, these medications also may improve the deep lung deposition of subsequent treatments. As a result, they typically are used first in a series of treatments. Inhaled hypertonic saline (HTS) also is used widely in patients with CF to hydrate airway secretions and provide a sustained acceleration in mucociliary clearance in adults with CF.[29] Although 7% sodium chloride is the best studied HTS solution, 3% to 3.5% sodium chloride solutions are available for patients in whom 7% sodium chloride causes bronchospasm or airway irritation.[30] Recombinant human deoxyribonuclease (rhDNase, dornase alfa) is a mucolytic that acts by cleaving DNA released by airway neutrophils. Although both HTS and dornase alfa are established therapies in patients with stable CF, their efficacy is less well studied in those with APE.[31-33] Despite the lack of data, these agents generally are conceded to be critical elements in this setting. If well tolerated, HTS can be administered 2 to 4 times daily and dornase alfa once or twice daily. Multiple other inhaled mucolytics and mucokinetic agents (mannitol, N-acetylcysteine, inhaled unfractionated heparin) currently are in development but do not have evidence or approval for use.[34] The typical order of inhaled medication delivery is a bronchodilator followed by HTS, followed by chest physiotherapy, and then dornase alfa. Inhaled antibiotics then are administered last.

In the setting of IMV, the delivery of the amounts of medications by nebulizer systems is influenced by several factors, including the type of nebulizer, the treatment time, the duty cycle, the volume fill of the nebulizer, and the presence of a humidification device; thus, those factors should be assessed if airway clearance appears to be suboptimal.[35] Heat and moisture exchangers need to be inspected and exchanged routinely to prevent clogging both from respiratory secretions and from nebulized agents.

Chest Physiotherapy

Numerous devices have been developed to assist with airway clearance in patients with CF (Fig 2). Modalities include manual chest percussion and postural drainage, specific breathing techniques, and a wide range of device-based treatments. Studies have not shown clear superiority of one technique over another. Therapy should be tailored to the needs and preferences of the patient, as well as the expertise of the center. Additionally, patient mobilization and exercise serve as an important adjunct to formal airway clearance.

Mechanism	Examples	Special Considerations
Positive Expiratory Pressure (PEP) Therapy	 Acapella Flutter Valve	Patient Effort Dependent
High Frequency Chest Wall Oscillation		No Patient Effort Required Compatible with NIPPV or mechanical ventilation
Manual Chest Physiotherapy		Requires a trained individual to perform
Hand Held Chest Percussion		Limited availability in hospital setting
Intrapulmonary Percussive Ventilation (IPV)		Compatible with spontaneous breathing, NIPPV, or mechanical ventilation
Cough Assist Device		Helpful when component of muscular weakness

Figure 2 – *Various airway clearance devices used in cystic fibrosis care. NIPPV = noninvasive positive pressure ventilation.*

Facilitating airway clearance in the patient who has undergone intubation presents a particular challenge. Medications can be delivered via nebulization through the endotracheal tube but require careful consideration of the respiratory circuit configuration and drug dose required to ensure adequate lung delivery and deposition.[34] Chest physiotherapy can be performed via high-frequency chest wall oscillation vests or intrapulmonary percussive ventilation in-line with the ventilator. In patients with lobar collapse or substantial retained secretions that cannot be mobilized with chest physiotherapy, therapeutic bronchoscopy may be required. Deep sedation can impair the cough reflex and impair airway clearance; therefore, sedation should be lightened as much as possible to enhance it.

An optimal method for airway clearance in the patient who is critically ill cannot be determined according to the currently available literature. However, at our centers, patients who require intubation receive intrapulmonary percussive ventilation up to 4 times per day, therapy sessions lasting at least 20 minutes. We have had anecdotal success with this technique, particularly in patients who cannot be involved actively in their therapy because of heavy sedation or analgesia requirements. Pharmacologic therapy used includes maximal dosing frequency of HTS and dornase alfa as tolerated and in sequence with physiotherapy as detailed in Table 3. We do not perform bronchoscopy routinely unless there is substantial volume loss due to mucus plugging. Typically, if a patient does not require ventilation, we would increase the frequency of the individual home regimen.

Antimicrobials

Optimal antimicrobial coverage is essential to the treatment of CF APE. The two most commonly encountered organisms in adult patients with CF are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[2] Other commonly encountered bacteria include *Haemophilus influenzae*, *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia*, and the *Burkholderia cepacia* complex.[2] Nontuberculous mycobacteria (*Mycobacterium abscessus* and *Mycobacterium avium* complex) are also increasingly common and problematic. The increasing life expectancy of the population with CF and increasing exposure to antibiotics have resulted in high rates of multidrug-resistant organisms among adults.

Formulation of an antimicrobial treatment plan requires review of previous culture data. In the absence of prior cultures, coverage for both *Pseudomonas* and methicillin-resistant *S aureus* (MRSA) should be provided and then tailored as culture data become available. In general, treatment with two systemic antipseudomonal agents should be used, in concordance with the CF pulmonary guidelines, to provide potential antibiotic synergy and reduce the emergence of resistance in the setting of a chronic, incurable infection.[6] Traditionally, this treatment has been a beta-lactam or carbapenem plus an aminoglycoside or fluoroquinolone. Because fluoroquinolone resistance emerges fairly rapidly during treatment, patients who are hospitalized typically receive IV aminoglycosides, when appropriate, and generally tobramycin rather than gentamicin because of decreased nephrotoxicity.[36] Extended interval dosing of aminoglycosides largely has replaced the traditional intermittent dosing strategy and has been shown to have equal efficacy with less nephrotoxicity.[37] Conversely, extended or continuous infusion times for beta-lactams or carbapenems may have enhanced antipseudomonal killing because of their time-dependent effect on bacterial killing.[38]

Linezolid and vancomycin are the two first-line antimicrobial choices for the treatment of MRSA during serious CF APE. Concomitant use of IV vancomycin and IV tobramycin requires vigilant monitoring, given the increased potential for nephrotoxicity.[39,40] Inhaled agents active against MRSA are in development.[41]

TABLE 3] CF Critical Care Checklist

Category	Checklist Items
Respiratory support	• Determine baseline respiratory status • Clarify code status and lung transplant candidacy • Perform chest imaging, blood gas assessment, clinical assessment to determine severity of respiratory failure • Tailor respiratory support to clinical condition ◦ Supplemental oxygen (mild hypoxia, no CO_2 retention, or increased WOB) ◦ High-humidity high-flow nasal cannula (increased WOB, minimal or mild CO_2 retention) ◦ Noninvasive ventilation (increased WOB, moderate CO_2 retention) ◦ Invasive mechanical ventilation (altered mental status, hemodynamic instability, or severe respiratory acidosis) • Consider ECMO and expedited transfer to transplant center if the patient has undergone intubation
Airway clearance	• Inhaled therapy ◦ Albuterol ◦ Hypertonic saline ◦ Dornase alfa ◦ Consider inhaled antibiotics • Chest physiotherapy ◦ Numerous devices available; select based on clinical situation and patient preference • Typical treatment order ◦ Albuterol >> hypertonic saline >> chest physiotherapy >> dornase alfa >> inhaled antibiotic
Sedation and analgesia	• Sedation (if required) • Anticipate tolerance to sedatives • Propofol is first-line treatment • Consider dexmedetomidine or low-dose ketamine if propofol is inadequate • Use daily SAT or SBT • Analgesia • Multimodal approach to pain treatment • Caution with opiates because of risk of DIOS
Infectious disease	• Obtain prior culture data • Send new cultures on admission • Use dual systemic coverage of *Pseudomonas* • Ensure appropriate drug dosing for patients with CF (see Table 4)
Nutrition	• Provide nutrition consultation • Ensure adequate calorie and protein intake, lower carbohydrate content with severe hypercarbia • Consider metabolic cart testing when caloric requirements unclear • Provide enteral feeding if unable to meet needs with oral intake • Use TPN if unable to feed enterally • Ensure adequate pancreatic enzyme replacement therapy • Consider antacid therapy
Diabetes	• Do not restrict calories • Insulin is mainstay of therapy • Treatment can improve BMI and respiratory status
Physical therapy	• Mobilization with physical therapy and occupational therapy
Psychological issues	• Screen for depression and anxiety and treat if found • Consider palliative care consultation to assist in symptom management and goals of care discussions
Gastrointestinal issues	• Treat GERD if present • Monitor for constipation and DIOS • Use osmotic laxative-based bowel regimen
Miscellaneous	• Use appropriate VTE prophylaxis • Consider early transfer to CF care center

CF = cystic fibrosis; DIOS = distal intestinal obstruction syndrome; ECMO = extracorporeal membrane oxygenation; GERD = gastroesophageal reflux; SAT = spontaneous awakening trial; SBT = spontaneous breathing trial; TPN = total parenteral nutrition; WOB = work of breathing.

TABLE 4] CF-Specific IV Antibiotic Dosing Guidelines

Antibiotic	Dosing in Adults With CF	Dosing Considerations
Antipseudomonals		
Piperacillin-tazobactam	4.5 g IV q6h	Extended infusion
Ceftazidime	2 g IV q8h	Extended infusion
Cefepime	2 g IV q8h	Extended infusion
Meropenem	2 g IV q8h	Extended infusion
Ciprofloxacin	400 mg IV q8h	…
Levofloxacin	750 mg IV or po q24h	…
Tobramycin	8-10 mg/kg IV q24h	Preferred aminoglycoside because of less ototoxicity Check random levels after dosing and adjust based on pharmacokinetics Consider pharmacy assistance where available
Amikacin	20 mg/kg IV q24h	Primarily used in NTM infection Check random levels after dosing and adjust based on pharmacokinetics Consider pharmacy assistance where available
Reserved for highly resistant *Pseudomonas*		
Ceftazidime-avibactam	2.5 g IV q8h	2-h infusion time
Ceftolozane-tazobactam	3 g IV q8h	…
Colistimethate sodium	2.5 mg/kg IV q12h	…
Anti-MSSA		
Nafcillin	2g IV q4h	…
Ceftriaxone	2 g IV q12h	…
Anti-MRSA		
Vancomycin	Loading dose of 25-30 mg/kg IV, then 15 mg/kg IV q8-12h	Target trough: 15-20 mg/dL
Linezolid	600 mg IV q12h 600 mg po q12h	…
Ceftaroline fosamil	600 mg IV q12h	…

MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *S aureus*, NTM = nontuberculous mycobacterium. See Table 3 legend for expansion of other abbreviation.

Antibiotic selection commonly is tailored to prior resistance patterns, although studies have shown that in vitro sensitivities poorly predict clinical response to antimicrobial regimens.[42,43] Standard antibiotic dosages in patients with CF differ from those in the population without CF because of increased renal clearance and larger volume of distribution. Typical duration of treatment ranges from 10 to 21 days, with a median duration of 14 days at accredited CF centers.[44] The role of inhaled antibiotics, which are used commonly in the ambulatory setting, is somewhat limited in patients with CF who are critically ill. As with other nebulized therapies, the delivery of inhaled antibiotics in patients receiving IMV is influenced by several factors and may be suboptimal, although there are data to support the feasibility and possible benefits in the general population. However, on the basis of larger studies, optimization of nebulization techniques and standardization of nebulization procedures are required before the clinical use is expanded.[45] Table 4 lists antibiotics commonly used in CF APE and appropriate doses for patients with CF.

In addition to bacterial pathogens, *Aspergillus* commonly is seen on respiratory cultures in CF but usually indicate colonization or allergic bronchopulmonary aspergillosis rather than invasive fungal disease. For this reason, the use of antifungal therapy is not routinely necessary, unless patients are immunocompromised or have a diagnosis of allergic bronchopulmonary aspergillosis or in select cases in which patients are failing to improve with aggressive broad-spectrum antibiotics.

The need for multiple antimicrobials, as well as other agents with a high potential for drug interactions,

including the CFTR modulators, makes pharmacotherapy in patients with CF complicated. The risk of drug interactions is particularly high in the critical care setting in which multiple other drugs are required for treatment. A clinical pharmacist with a good knowledge of the pharmacologic agents used for CF would be valuable in patient care in this setting as can be extrapolated from studies on the benefit of having clinical pharmacists in the ICU in general.[46]

Nutrition

Maintenance of adequate nutritional status is essential to CF care. Longitudinal studies have demonstrated a strong correlation between BMI and both FEV_1 and survival.[47,48] Patients with CF are at risk for malnutrition for numerous reasons, including malabsorption from pancreatic exocrine insufficiency and bile salt abnormalities due to low duodenal pH, suboptimal glycemic control in those with CF-related diabetes mellitus (CFRD), and poor appetite.[49] The energy imbalance is compounded by increased energy expenditure due to work of breathing and cytokine-mediated catabolism in the setting of infection and inflammation.[50]

All patients who are hospitalized should undergo evaluation of nutritional status by a registered dietician, preferably with CF training. The assessment should take into consideration BMI, pulmonary status, and weight trend. Goal BMI is > 23 kg/m^2 for male patients and > 22 kg/m^2 for female patients.[50] Depending on multiple clinical factors, recommendations for estimated caloric needs range from 110% to 200% of that of individuals without CF.[51] Patients with adequate baseline nutritional status and low severity of illness who can maintain adequate oral intake can be treated simply with a high-calorie unrestricted diet.[51] Patients at greater baseline nutritional risk or those who are unable to meet caloric needs orally should receive enteral feeding, which is accomplished best with nasoenteral feeding in those who are critically ill, deferring percutaneous or surgical gastrostomy tube placement until clinical stability is achieved.[52] Parenteral nutrition should be reserved for cases where enteral feeding is not possible or sufficient.

Eighty-five percent to 90% of patients with CF require PERT.[50] Recommended dosing ranges from 500 to 2,500 units of lipase per kilogram per meal, with a maximum dose of 10,000 units of lipase per kilogram per day.[51] In patients receiving enteral feeding, PERT in capsule form can be administered at 4- to 6-hour intervals for those receiving continuous feeding and administration of three-fourths of a dose of PERT before and one-fourth of a dose of PERT near completion of nocturnal feeding.[53] PERT capsule contents should not be crushed and frequently will clog feeding tubes. A recent option for supplying PERT to patients receiving enteral feeding is the use of an immobilized lipase cartridge (RELiZORB; Alcresta Therapeutics), a digestive enzyme cartridge that is placed in-line with enteral feeding and eliminates the need for oral PERT.[53]

CF-Related Diabetes Mellitus

CFRD is a commonly encountered extrapulmonary complication of CF. It affects 40% to 50% of adults and can be a major contributing factor to poor nutritional status.[54] Poor glycemic control can complicate the course of CF and predispose patients to recurrent and severe APE, as well as weight loss. Because CFRD is primarily a deficiency of insulin production, insulin is the only recommended therapy for CFRD.[55] Dietary restriction is not advisable because high caloric intake is crucial for people with CF. In many cases, the use of even small doses of insulin with meals or enteral tube feeding can result in weight gain and potentially better response to treatment of APE. Insulin resistance during infectious exacerbations typically worsens glycemic control in patients with CF and can result in a new insulin requirement or greater insulin needs.

CFTR Modulator Therapy

Three CFTR modulator medications currently are approved by the FDA: ivacaftor, lumacaftor-ivacaftor, and tezacaftor-ivacaftor.[56-58] These medications partially restore CFTR function in patients with specific CF mutations. Although these medications are a major advance in CF care, the possibility of acute intolerability (eg, lumacaftor-ivacaftor) and multiple drug interactions dictates that these medications should not be initiated during an APE or other critical illness.[59] However, abrupt withdrawal of highly active CFTR modulators should be avoided to prevent a withdrawal syndrome that has been observed in patients with highly responsive mutations.[60] Of note, these medications require some dietary fat for optimal absorption, and tablets cannot be crushed for enteral administration. Ivacaftor is available as an oral granule packet that may be dissolved in liquid; however, there is no endorsement of administration through feeding tubes. For these reasons, CFTR modulators generally are not given to patients who are unable to eat or swallow medication.

Special Considerations

In addition to ARF due to pulmonary exacerbation, there are other circumstances that may require ICU-level care in patients with CF. Massive hemoptysis and pneumothorax are acute and potentially fully reversible conditions that can affect patients across the spectrum of lung function, although they occur more frequently in those with more advanced architectural distortion of the lungs.[61] Likewise, DIOS, the adult equivalent of meconium ileus, can affect patients regardless of pulmonary status and occurs more frequently following lung transplant.[62]

Massive Hemoptysis

Hemoptysis is a common complication of CF, affecting approximately 8% of patients.[61,63] Massive hemoptysis occurs in 4% of patients with CF and may be fatal, accounting for 8.5% of deaths in patients without lung transplant.[64,65] Adult patients with CF, particularly those with more severe lung disease, are at an increased risk.[61] Mild to moderate episodes of hemoptysis can be managed by treating infection and temporarily holding HTS.[66] Other airway clearance therapies should be withheld only if they appear to exacerbate or trigger bleeding.[66] Massive hemoptysis requires prompt control of the airway, antibiotic therapy, and correction of coagulopathy.[66] When intubation is required, selective intubation with a dual-lumen endotracheal tube may be helpful, when possible, to allow for split-lung ventilation and occlusion of the airway on the bleeding side. Alternatively, the patient can undergo intubation with a standard single-lumen endotracheal tube followed by placement of an endobronchial blocker under bronchoscopic guidance to facilitate isolation of the bleeding lung until stabilization is achieved. Many patients can lateralize bleeding on the basis of symptoms. In other cases, bronchoscopy or bronchial artery imaging with CT scanning with contrast material or angiography may be helpful but are not recommended universally because they may postpone treatment.[66]

The majority of episodes stop spontaneously; however, bronchial artery embolization (BAE) can be a life-saving intervention in patients with bleeding that results in airway compromise or hemodynamic instability or that does not slow with conservative interventions.[67] Despite the effectiveness of BAE in controlling hemoptysis in the short term, patients with CF who undergo BAE remain at increased risk for recurrent hemoptysis, deterioration of respiratory function, and death. Therefore, evaluation for lung transplant should be considered in patients with severe disease or recurrent, life-threatening hemoptysis after BAE.[67]

Pneumothorax

Pneumothorax is a well-known complication of CF, occurring in about 3.4% of all patients with CF during their lifetime.[66] The median age for pneumothorax is 21 years, with 72.4% occurring in the adult population with CF.[68] Severe airway obstruction; colonization with *Pseudomonas*, *Burkholderia* species, and *Aspergillus*; allergic bronchopulmonary aspergillosis; pancreatic insufficiency; and need for a feeding tube are risk factors for pneumothorax. The diagnosis often can be established

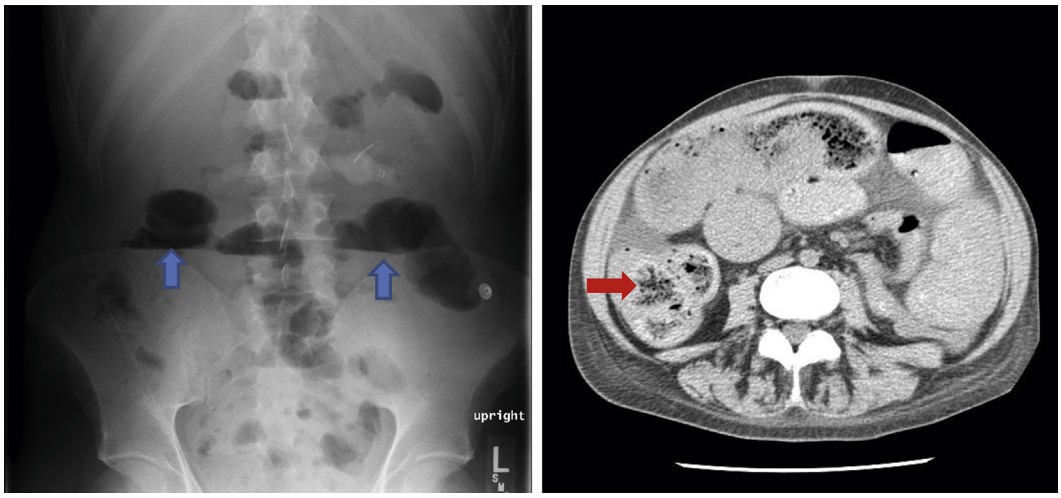


Figure 3 – *Radiographic findings in distal intestinal obstruction syndrome. A, Blue arrows show air-fluid level in distended loops of bowel on anterior posterior abdominal radiograph. Red arrow shows fluid- and stool-filled colon on axial abdominal CT scan.*

with chest radiography; however, pleural adhesions may prevent collapse of the lung away from the chest wall. In these cases, CT scanning readily can help establish the diagnosis.[68] Management of pneumothorax in patients with CF is similar to that in patients without CF and includes supplemental oxygen and chest tube placement (ideally with imaging guidance). In addition, airway clearance modalities that incorporate positive expiratory pressure and intrapulmonary percussive ventilation should be avoided, especially in those with large pneumothoraces.[66] Consideration of mechanical pleurodesis for recurrent episodes is reasonable.[69] Chemical pleurodesis (eg, talc) should be avoided in patients who may be candidates for lung transplant later in life.

Distal Intestinal Obstruction Syndrome

DIOS is an acute or subacute small-bowel obstruction, typically in the ileocecal region, caused by accumulation of badly digested food and mucus.[70] The diagnosis is based on suggestive symptoms of abdominal pain, nausea and vomiting, and signs of obstruction on plain radiographs or CT scans (Fig 3).[62] Patients with CF who are critically ill are at increased risk of DIOS because of immobility, dehydration, use of opiates, and potentially inadequate doses of pancreatic enzymes. Treatment consists of the patient receiving nothing by mouth, IV hydration, decompression with nasogastric tube placement, reduction or avoidance of opiates, and administration of osmotic agents such as polyethylene glycol electrolytes lavage solution by mouth or via nasogastric tube.[62] Enemas, including use of a hypertonic radiopaque contrast material, may be useful when bowel obstruction is more distal and not improving with enteral therapy.[62] Exploratory laparotomy is only a last resort for patients not responding to medical therapy, primarily because with each abdominal surgery, the risk for recurrent DIOS increases in the future.[71]

Conclusions

Patients with CF who are critically ill are a vulnerable population with a high risk for mortality. There is a paucity of data on the optimal ICU care of patients with CF. We believe that optimal care requires a multidisciplinary approach that addresses the unique needs of this population. Despite the challenges, favorable outcomes can be achieved in many of these patients. Early transfer to centers specializing in CF care should be pursued to optimize outcomes. Consolidation of care at CF centers also may facilitate much-needed research on the ICU care of this unique population.

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