CHEST

Pulmonary Complications in Cystic Fibrosis: Past, Present, and Future

Adult Cystic Fibrosis Series

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[1]Cystic fibrosis (CF) is an autosomal recessive genetic condition with multisystemic disease manifestations, the most prominent of which occur in the respiratory system. Despite significant developments in disease understanding and therapeutics, each contributing to improved lung function and survival in patients with CF, several pulmonary complications, including pneumothorax, massive hemoptysis, and respiratory failure, continue to occur. In this review, we briefly describe each of these complications and their management and discuss how they impact the care and disease trajectory of individuals in whom they occur. Finally, we discuss the evolving role that palliative care and CF transmembrane conductance regular modulator therapies play in the natural disease course and care of patients with CF.

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Cystic fibrosis (CF) is a genetic disease with an autosomal recessive inheritance pattern affecting nearly 32,000 individuals in the United States and even more individuals worldwide.[1] Although CF is a multisystemic condition, mediated through abnormalities in the CF transmembrane conductance regulator (CFTR) protein, the most prominent disease manifestations are found in the respiratory system with infectious and noninfectious complications each contributing to reduced quality of life as well as increased morbidity, mortality, and health care use.[1-4] The complications related to infection are discussed elsewhere in this series[5]; herein, we review the pulmonary complications that result from the longstanding airways infection and inflammation and the progressive obstructive airways dysfunction (as measured by FEV_1 % predicted). These include pneumothorax, hemoptysis, and respiratory failure, which long have been known to be associated with older age and more severe airways disease.[1,3,4] The development of new therapies, especially CFTR modulators, has led to improvements in the overall health and survival of patients with CF.[1,6-9] Although these medications have led to great improvements in lung health, they are not curative, and a large number of patients with CF remain who have advanced lung disease and in whom these pulmonary complications continue to

ABBREVIATIONS: ACFLD = advanced cystic fibrosis lung disease; BAE = bronchial artery embolization; CF = cystic fibrosis; CFF = Cystic Fibrosis Foundation; CFTR = cystic fibrosis transmembrane conductance regular; NIPPV = noninvasive positive pressure ventilation; PH = pulmonary hypertension

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TABLE 1] Frequency of Pulmonary Complications in the Population With CF

Variable	2015	2016	2017	2018	2019
Patients with FEV_1 < 40% predicted, % of population	5.3	4.0	4.0	3.9	2.6
Patients using supplemental oxygen	11.1	10.4	11.0	10.8	10.9
Patients using noninvasive ventilation	2.9	2.8	3.1	3.2	3.1
Cause of death, % of total deaths					
Respiratory	64.5	66.8	62.9	59.3	62.2
Transplantation	19.2	13.9	16.1	17.1	16.4
Total respiratory and transplantation	83.7	80.7	79.0	76.4	78.6
Hemoptysis (any)					
< 18 y of age	0.4	0.7	0.8	0.7	0.8
≥ 18 y of age	4.1	5.9	5.9	5.3	5.8
Total	2.3	3.3	3.4	3.0	3.4
Hemoptysis (massive)					
< 18 y of age	0.1	< 0.1	< 0.1	< 0.1	< 0.1
≥ 18 y of age	1.8	0.8	0.7	0.6	0.7
Total	0.9	0.4	0.4	0.3	0.4
Pneumothorax (with chest tube placement)					
< 18 y of age	0.1	< 0.1	0.1	0.1	< 0.1
≥ 18 y of age	0.8	0.4	0.4	0.3	0.4
Total	0.5	0.2	0.2	0.2	0.2

Data are presented as percentage, unless otherwise indicated. Source: Cystic Fibrosis Foundation. Cystic Fibrosis Foundation patient registry. Annual data report to the center directors. 2016-2020. CF = cystic fibrosis.

occur (Table 1). Given the improved health overall, these complications are much more common in adults, but they do occur in pediatric patients as well. This review presents updates to the recommendations about the most common noninfectious pulmonary complications encountered in patients with CF.

Pneumothorax

Pneumothorax is the accumulation of air within the pleural space. Previous analyses have shown it to occur in 1 in 167 patients with CF (0.64%) each year,[3] although perhaps a slight decrease in the number of events has occurred in recent years (Table 1). Risk factors for pneumothorax include colonization with *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex, use of enteral feeding, FEV_1 of < 30% predicted, history of massive hemoptysis, and colonization with *Aspergillus*, among others.[3] Presentation of pneumothorax is manifested by the acute onset of chest pain, dyspnea, tachypnea, hypoxemia, or a combination thereof, with diagnosis confirmed via chest imaging.

Recommendations for management of pneumothorax in this patient population have been outlined in a set of consensus guidelines[10] and are summarized in the following statements. The initial management of all individuals with large pneumothorax (measuring > 3 cm from the cupola) or pneumothorax of any size with clinical instability should include admission to the hospital and treatment with tube thoracostomy placement. Recommendations regarding management of clinically stable individuals with small pneumothorax are more variable, ranging from outpatient monitoring to hospital admission for closer observation. Regardless of the size of the pneumothorax, it is recommended that positive pressure therapy should be withheld in the presence of pneumothorax and that certain activities (eg, flying, weight lifting, and spirometry) should be restricted for a period after treatment of pneumothorax. All other chronic therapies, including nebulized mucolytics and antimicrobials, should be continued. No consensus exists regarding administration of oral or IV antibiotics in the absence of other findings consistent with a pulmonary exacerbation.[10]

In situations where a pneumothorax may not resolve with tube thoracostomy alone, alternate therapies may need to be considered. The most commonly encountered situation is the case of persistent air leak, defined as ongoing air leak after 4 days of tube thoracostomy placement.[11] Patients in this situation may be referred for pleurodesis, preferably performed surgically.[3,10] Pleurodesis also should be considered for recurrent ipsilateral pneumothorax, although this is not recommended after the first presentation.[10] It should be noted that although pleurodesis is a not an absolute contraindication to lung transplantation, concern exists that pleurodesis could be associated with increased risk of complications both during and after lung transplantation,[12] and this should be taken into consideration when creating care plans.

More recently, the use of endobronchial valve therapy has been reported for the treatment of persistent air leak in individuals with a variety of underlying pathologic features, including postoperative bronchopleural or bronchoalveolar fistula, iatrogenic injury, and those occurring as a sequela of underlying pulmonary disease, including CF.[13-16] Case reports detail the successful use of this method as a bridge to lung transplantation in patients with CF.[14,15] Given reports of success, this novel therapy may be considered more widely in centers with appropriate expertise as an alternative for patients deemed high risk for surgery or in those for whom concern exists that pleurodesis may unnecessarily increase risk of complications of lung transplantation.

Hemoptysis

Hemoptysis in the patient with CF is defined based on the volume of expectorated blood and is classified as follows: scant (< 5 mL), mild to moderate (5-240 mL), and massive (> 240 mL in a 24-h period or > 100 mL per day over several days), with the source of bleeding arising from the bronchial arterial circulation in the vast majority of patients.[4,17] This complication has been reported to occur in 1 of 115 patients with CF (0.87%) each year,[4] and although no reduction in the frequency of hemoptysis overall seems to have occurred, a reduction in the frequency of massive hemoptysis may have occurred in more recent years (Table 1). Overall, hemoptysis rates are greater among adults compared with children, those with lower FEV_1 % predicted, and patients infected with *P aeruginosa*,[18] whereas massive hemoptysis is associated with FEV_1 of $< 40\%$ predicted, *Staphylococcus aureus* infection, and diabetes.[4] As might be expected, hemoptysis causes significant psychologic distress for patients.[19]

Management of hemoptysis in this population has been outlined in a set of consensus guidelines.[10] A patient should contact their provider, be admitted to the hospital, or both, dependent on the degree of hemoptysis, with the exception of massive hemoptysis, in which case all patients should be hospitalized for observation and treatment, including the initiation of IV antibiotics and discontinuation of airways clearance and other aerosolized therapies that may exacerbate the condition. Procoagulant therapies (eg, tranexamic and aminocaproic acid) for the treatment of hemoptysis in patients with and without CF have shown benefit with reduced need for hospitalization, shorter length of stay for those patients who are hospitalized, and less need for invasive therapeutic procedures; however, their efficacy has not been evaluated fully.[20-22] Given the nature of the cause and pathogenesis of massive hemoptysis in patients with CF, strategies used to localize bleeding in other patients with hemoptysis, such as chest imaging and bronchoscopy, are not recommended because they can delay more definitive therapy without providing additional clinical information.[10]

Bronchial artery embolization (BAE) is the therapy of choice for patients with massive hemoptysis that persists or if clinical instability occurs.[10] An identified vessel proven or suspected to be the culprit of the bleeding should be embolized, but other abnormal vessels should be embolized if the source cannot be identified readily.[4,10,23] Several cases series and retrospective reviews have demonstrated the effectiveness of BAE in the population with CF with 24-h and 30-day clinical success rates, defined as absence of the need for repeat embolization and death from any cause, reported as 96.6% and 82%, respectively.[23,24] In these cohorts and another cohort of patients, episodes of recurrent hemoptysis were not uncommon; however, the need for repeat embolization was reported in only a proportion of these patients (25%-37%).[23-25]

Unfortunately, despite encouraging short-term results, BAE is not without risk, and clinicians must consider possible procedural complications and impact on future disease trajectory. Reported rates of procedural complications resulting from BAE in patients with CF vary, although they have been reported from 0% to 60.8%.[23-25] Although most reported adverse events are minor, including transient and typically self-limiting chest, esophageal, or thoracic back discomfort, or a combination thereof, more significant complications including transverse myelitis, spinal cord ischemia, vascular injury, and vascular access site thrombosis have

been reported.[23,25-27] Massive hemoptysis (with and without need for BAE) has been associated with increased risk of mortality and the need for lung transplantation, as demonstrated in registry data and more recently in cohort analyses.[4,23,24,28] These findings highlight the prognostic implications of massive hemoptysis and support early consideration for appropriate referral and evaluation for lung transplantation.

Respiratory Failure

The most common cause of death for people with CF remains respiratory failure (Table 1). The improvements in overall health of the population with CF have raised not only the mean predicted survival, but also the actual median age of death; in 2003, the median age of death was 25.7 years and increased to 30.8 years in 2018.[1] This increase means that fewer pediatric patients experienced advanced lung disease; in 1988, 24.2% of the pediatric population showed an FEV_1 of < 40% predicted, whereas only 3.9% met this severity of lung impairment in 2018.[1] Along with improved survivorship in the general population with CF, we have seen similar improvements among those with severely reduced lung function, with the most recent cohort study in this domain showing median survival of 6.6 years (range, 5.9-7.0 years) in patients with FEV_1 of < 30% predicted and an approximate 10% risk of death annually.[29] Even with these improvements, the natural history of CF disease remains progressive, and patients are at risk of the development of hypoxemic or hypercarbic respiratory failure, or both, which regardless of FEV_1 % predicted, are features of advanced lung disease; other criteria to define advanced CF lung disease (ACFLD) are shown in Table 2.[30]

TABLE 2] Defining Advanced CF Lung Disease

Any of the following criteria
• FEV_1 < 40% predicted
• Referral for lung transplant evaluation
• ICU admission for respiratory failure
• Resting hypercarbia ($Paco_2$ > 50 mm Hg or $Pvco_2$ > 56 mm Hg)
• Resting daytime hypoxemia
• Pulmonary hypertension (pulmonary arterial systolic pressure > 50 mm Hg on echocardiogram)
• Severe functional impairment (NYHA functional class IV)
• Severely reduced 6-min walk distance (< 400 m)

Criteria adapted from Kapnadak et al.[30] CF = cystic fibrosis; NYHA = New York Heart Association; $Pvco_2$ = partial pressure of co_2 in venous blood.

Guidelines recommend that all individuals with ACFLD should be evaluated for hypoxemia, hypercarbia, and pulmonary hypertension with the 6-min walk test, arterial or venous blood gas analysis, and transthoracic echocardiography, respectively.[30,31] Although supplemental oxygen and noninvasive positive pressure ventilation (NIPPV) are prescribed to qualifying individuals, no consistent evidence exists to support that these therapies improve survival or pulmonary function. Yet, Cochrane reviews suggest that implementation of these technologies can lead to significant improvement in quality of life, including improved exercise capacity and, in the case of NIPPV, even improved airway clearance.[32,33]

Unfortunately, studies investigating the long-term use of NIPPV in individuals with CF are difficult to design and conduct. Despite challenges, over the last few years, new evidence has emerged providing insight into the use of this treatment method. For example, in 2019 a prospective longitudinal study investigated the use of NIPPV vs standard oxygen therapy in a cohort of 29 patients with CF with documented nocturnal hypoxemia and demonstrated the benefit of NIPPV, with significant reduction in the end points of therapy failure (defined as worsening of hypercapnia), need for lung transplantation, and death.[34] Another, more recent single-center retrospective review of 56 patients over 10 years suggests a reduced rate of decline of lung function in patients with longer-term use of NIPPV[35]; however, this result has not been replicated elsewhere. Furthermore, it did not demonstrate any meaningful difference in the rate of other pulmonary complications, such as pulmonary exacerbations. Although these are just two examples in relatively small study populations, they provide a foundation for future investigation in this area.

Pulmonary Hypertension

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure of > 20 mm Hg (previously mean pulmonary arterial pressure of > 25 mm Hg) and can be the consequence of a wide variety of clinical conditions, including chronic lung disease and hypoxemia.[36] The gold standard for diagnosis of PH is made via right heart catheterization; however, guidelines recommend transthoracic echocardiography be used as a noninvasive screening tool to stratify likelihood of the condition and to determine need for further invasive testing.[37] Although it may be difficult to distinguish clinical symptoms of CF from those of PH, it is

important diagnostically to consider PH, because studies in the CF population have demonstrated poorer outcomes when it is present.[38-40] For example, in one study, patients with CF with mean pulmonary arterial pressure of > 25 mm Hg showed an increased risk of death compared with both matched patients with CF without PH as well as those with PH secondary to other chronic lung diseases.[38] Another study reported PH as measured by transthoracic echocardiography to be an independent risk factor for death for patients awaiting lung transplantation.[39] Despite the increased risks associated with PH in CF, no PH-specific therapies are proven to be effective in patients with CF, and recommendations are to treat the underlying condition and to consider referral and evaluation for transplantation in appropriate individuals.[41,42]

Management of Acute Illness and Considerations for the Intensivist

For patients experiencing acute illness resulting in acute or acute-on-chronic, hypoxemic, hypercarbic, or mixed respiratory failure, medical interventions and technologies may be available that could be used if they are consistent with the patient's goals of care.[30] These might include supplemental oxygen, high-flow nasal cannula, NIPPV, invasive mechanical ventilation, and even extracorporeal life support, recognizing that some options may not be appropriate or available in all health-care settings. The important point is that critical illness in patients with CF does not always mean the end of life, and use of these technologies can be of particular importance if the patient is deemed to be an acceptable candidate for lung transplantation.[12,30] Nonetheless, given the risk of death and poor prognosis for some individuals with acute critical illness, particularly those with more severe disease, despite the use of advanced medical technology,[43,44] active involvement of the patient's primary CF care team and palliative care specialists should be considered strongly.

Goals of Care

Each of these pulmonary complications is associated with increased health care use as well as increased risk of mortality.[1,3,4,45] Because the occurrence of each of these complications is also associated with poor prognosis, care teams should engage in conversation to determine appropriate goals of care such as consideration of lung transplantation and palliative care.

Recommendations for referral of patients with CF for lung transplantation evaluation include consideration of these pulmonary complications, as outlined in Table 3.[12,45] Open lines of communication between CF providers and transplant teams are crucial for success.[45] Despite these guidelines, a recent survey evaluating physicians' perspectives on timing of lung transplantation referral in the United States demonstrates wide variety in practice that is inconsistent with guideline recommendations.[46]

Palliative Care

As defined by a working group of patients with CF, providers, and palliative care specialists, "palliative care focuses on reducing physical and emotional symptoms and improving quality of life for people with CF throughout their lives. Palliative care occurs alongside usual treatments and is individualized according to the unique goals, hopes and values of each person with CF."[47] Although consensus guidelines recommend the introduction of palliative care services for individuals with ACFLD, evidence suggests that such services may be underused with significant variability in clinical practice.[30,47-50] For example, a recent survey of 164 adults with CF reports that 78% of participants identifying at least one unmet palliative care need in a wide range of domains.[50] These needs (in descending order of prevalence) include physical, psychological, health system or information, patient care and support, and sexual.[50]

Given advancements in medical technology and therapeutics that have improved survivorship in patients with CF, it is important now more than ever that we as providers recognize barriers to fulfilling the unmet need of palliative care. The introduction and use of palliative care in the population with CF poses unique challenges for patients, providers, and caregivers alike. These challenges include a relatively younger patient population with chronic illness, high caregiver burden, and long-term established professional and personal relationships with providers. Although these conversations are difficult and can even be uncomfortable, it is important to recognize their importance and to engage all members of the care team in therapeutic patient-provider partnerships. Consensus guidelines recently developed by the CFF provide recommendations for recognition of need, training, and implementation of primary palliative care by CF teams in collaboration with patients, caregivers, and associated care teams as well as indications for screening and referral to specialty palliative care providers.[51]

TABLE 3] Recommendations for Timing of Transplantation Referral in Adults With CF

Metric	International Society for Heart and Lung Transplantation	Cystic Fibrosis Foundation
FEV_1 % predicted	• < 30 • Rapidly declining lung function despite maximal medical therapy with special pathogens, diabetes, or both	• < 50 with rapidly declining pulmonary function, defined as relative decline of FEV_1 > 20% predicted within 12 mo • < 40 with markers of shortened survival • < 30 Note: The above recommendations refer to people 18 y of age and older. For those < 18 y of age, the recommendations are as follows: • < 50 with rapidly declining pulmonary function, defined as relative decline of FEV_1 > 20% predicted within 12 mo • < 50 with markers of shortened survival • < 40
6MWT distance	< 400 m	< 400 m
Pulmonary hypertension	In absence of exacerbation • PASP > 35 mm Hg by TTE • Mean PAP > 25 mm Hg by RHC	• PASP > 50 mm Hg by TTE
Special considerations	Increased number of pulmonary exacerbations with any of the following: • Acute respiratory failure requiring NIPPV • Antimicrobial resistance • Nutritional impairment despite supplementation • Pneumothorax • Life-threatening hemoptysis despite bronchial artery embolization Special pathogens: Nontuberculous mycobacteria *B cepacia* complex	Markers of shortened survival regardless of FEV_1 • 6MWT distance < 400 m • Hypoxemia • Hypercarbia ($Paco_2$ > 50 mm Hg) • Pulmonary hypertension (PASP > 50 mm Hg by TTE) • ≥ 1 exacerbation requiring NIPPV FEV_1 < 40% predicted and the following • BMI < 18 kg/m^2 and concurrently working to improve nutrition • > 2 exacerbations requiring IV antibiotics • Massive hemoptysis (> 240 mL) requiring ICU admission or bronchial artery embolization • Pneumothorax Additional special considerations for • Younger age • Female sex • Short stature • Special pathogens ○ Nontuberculous mycobacteria ○ *B cepacia* complex ○ Scedosporium

Source: Summary recommendations per consensus guidelines by the International Society for Heart and Lung Transplantation[12] and the Cystic Fibrosis Foundation.[45] 6MWT = 6-min walk test; CF = cystic fibrosis; NIPPV = noninvasive positive pressure ventilation; PAP = pulmonary artery pressure; PASP = pulmonary artery systolic pressure; RHC = right heart catheterization; TTE = transthoracic echocardiogram.

CFTR Modulator Therapy in Advanced CF Lung Disease

CFTR modulator therapy, first introduced in 2012 in the form of ivacaftor, followed by several combination therapies and most recently with elexacaftor-tezacaftor-ivacaftor in November 2019, is available for use in increasing proportions for the population with CF. Clinical trials investigating these drugs included patients with FEV_1 of 40% to 90% predicted,[6-9] but subsequent reporting of their effects in patients with advanced lung disease consistently demonstrate improvements in both pulmonary function and nutritional end points[52-54] and are summarized in a recent review.[55] Consistent with these findings, use of elexacaftor-tezacaftor-ivacaftor also has been shown to have benefits in patients with advanced lung disease. A single-site observational study including 14 patients showed statistically significant improvement in FEV_1 % predicted and BMI along with a reduction in both sweat chloride levels and pulmonary exacerbations.[56] A short-term single-center retrospective review of 11 patients showed improvement in pulmonary function, BMI, and patient-reported quality of life.[57] A larger retrospective cohort study evaluating outcomes in 64 patients with advanced lung disease in three large academic centers in the Southeast reported improvement in FEV_1 % predicted and BMI, as well as reduced need for focused discussions and referrals for lung transplantation.[58] Most robustly, a prospective cohort study of 245 French patients showed improved lung function and weight as well as significant reductions in need for supplemental oxygen therapy, NIPPV, supplemental enteral nutrition, and lung transplantation.[59]

Improvement in lung function is important, but that alone does not make a therapy disease modifying. Evidence suggests that the CFTR modulators also may offer additional benefit. Registry-based studies, comparing ivacaftor-treated patients with matched controls in participants with a wide range of lung function, demonstrated reductions in rate of lung function decline, pulmonary exacerbations, need for lung transplantation, and death.[60,61] Also, a nominal reduction was found in noninfectious pulmonary complications, including allergic bronchopulmonary aspergillosis, asthma, massive hemoptysis, and pneumothorax requiring chest tube.[60] Similar results with respect to reduced rate of lung function decline have been demonstrated with both lumacaftor-ivacaftor and tezacaftor-ivacaftor.[62,63]

These therapies still are not a cure and may only delay, but not eliminate, the eventual progression to advanced-stage lung disease. We must remain vigilant of these complications and be prepared to treat them in an efficacious and expeditious fashion should they arise.

Conclusions

The natural history of CF airways disease includes persistent infection, exaggerated inflammation, and progressive loss of lung function with obstructive airways disease. These pathophysiologic features allow for pulmonary complications including pneumothorax, hemoptysis, and eventual respiratory failure. CF airways therapies treating the consequences of CF airways disease have improved survival, and the recent advent of highly effective CFTR modulators is expected to have an even greater impact on the health of the CF population. Although no changes seem to have occurred in the proportion of patients with ACFLD, defined as the need for supplemental oxygen or NIPPV, a slight reduction in the proportion of patients with FEV_1 of $< 40\%$ predicted has occurred (Table 1). Also, a slight reduction in the proportion of patients with massive hemoptysis, pneumothorax, and even death resulting from respiratory causes has been observed, perhaps offering early evidence that CFTR modulators are having an impact on these complications. The addition of even more effective modulators may influence these complications further, although they are not curative, so we anticipate that the risk of pulmonary complications will remain in those who demonstrate advanced stages of lung disease.

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