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Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease

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ABSTRACT

Background: Advanced cystic fibrosis lung disease (ACFLD) is common, is associated with reduced quality of life, and remains the most frequent cause of death in individuals with cystic fibrosis (CF). These consensus guidelines provide recommendations to the CF community on management of both common and unique issues that arise when individuals reach a state of ACFLD.

Methods: The CF Foundation assembled a multidisciplinary expert panel consisting of three workgroups: Pulmonary management; Management of comorbid conditions; Symptom management and psychosocial issues. Topics were excluded if the management considerations did not differ in ACFLD from in the overall CF population or if already addressed in other published guidelines. Recommendations were based on a systematic literature review combined with expert opinion when appropriate.

Results: The committee formulated twenty-three recommendation statements specific to ACFLD that address the definition of ACFLD, pulmonary and intensive care unit management, management of selected comorbidities, symptom control, and psychosocial issues.

Abbreviation: ABPA, allergic bronchopulmonary aspergillosis; ACFLD, advanced cystic fibrosis lung disease; ACP, advance care planning; CF, cystic fibrosis; CKD, chronic kidney disease; ECLS, extracorporeal life support; ECFS, European Cystic Fibrosis Society; FEV_1, forced expiratory volume in one second; GER, gastroesophageal reflux; ICU, intensive care unit; ISHLT, International Society for Heart and Lung Transplantation; NIV, noninvasive ventilation; P_aCO_2, arterial partial pressure of carbon dioxide; P_vCO_2, venous partial pressure of carbon dioxide.

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Conclusions: These recommendations are intended to be paired with previously published management guidelines for the overall CF population, with the objective of reducing practice variability and improving overall care, quality of life, and survival in those with ACFLD.

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1. Introduction

While the quality of life and survival of individuals with cystic fibrosis (CF) are improving, advanced CF lung disease (ACFLD) remains common and the most frequent cause of death. CF Foundation Patient Registry data show that the forced expiratory volume in one second (FEV_1) is less than 40 percent predicted in 18% of patients who are age 30 years, and nearly 25% of those age 45 years. ACFLD is associated with reduced quality of life, worsening clinical symptoms, increased exacerbations, and increased healthcare utilization [1,2].

ACFLD-specific outcomes are improving for individuals with a FEV_1 < 30% predicted, but there remains an approximately 10% per year risk of death in this subset [3]. While lung transplantation may represent a key life-extending treatment, some with ACFLD may choose to forgo the option. In addition, many potential candidates are not referred [4,5], and among those referred approximately 27% die without transplant due to barriers to candidacy, waiting list mortality, or other issues [3].

Despite its prevalence and importance, there is limited literature directed specifically at the unique medical and psychosocial challenges facing individuals with ACFLD. Furthermore, clinical experience suggests variability in practice patterns pertaining to ACFLD management, with some aspects of recommended care shown to be inconsistently applied [4-6]. The goal of these Consensus Guidelines is to provide guidance for management of ACFLD. Recognizing that care must be customized to each individual, these recommendations aim to reduce practice variability, improve the quality of life and survival of those with ACFLD, and identify gaps in clinical knowledge where future research is needed.

2. Methods

The Cystic Fibrosis Foundation assembled a multidisciplinary team including pediatric, adult, and transplant pulmonologists, a gastroenterologist, palliative care specialist, pharmacist, respiratory therapist, nurse coordinator, social worker, dietitian, methodologist, one parent, and two individuals with CF. The panel included 20 members from the United States, one from Canada, and one from Switzerland. The committee met in October 2017 to outline the scope of the guidelines and divide into three working groups: (1) Pulmonary management; (2) Management of comorbid conditions; (3) Symptom management and psychosocial issues. PICO (Population, Intervention, Control, Outcome) questions were developed to address important aspects of care unique to individuals with ACFLD. Importantly, the committee recognized that many aspects of ACFLD management overlap with care that takes place during the process of referral for lung transplantation. For example, early discussions regarding transplant and screening for markers of disease severity such as hypoxemia were recently recommended in transplant referral guidelines [7], but addressing these issues also represent critical aspects of ACFLD care itself. Therefore, the committee developed these guidelines to be used in parallel and consistent with the transplant referral guidelines of Ramos et al. [7]. Topics were otherwise not included if the management considerations did not differ in ACFLD from in the overall CF population or if the topics were addressed in previously published guidelines.

Workgroups conducted literature searches in PubMed for each PICO question between January-August 2018 (Supplement) and reviewed the literature to inform their draft recommendation statements. For some topics, searches failed to identify high quality clinical studies, and in these cases recommendations were based largely on workgroup consensus. The committee reconvened in December 2018 to vote on statements. Although a formal Delphi method did not take place, each statement was presented and discussed among the entire committee during which language could be modified prior to formal voting. Voting on all recommendation statements met the (a priori) voting threshold of 80% agreement. In May 2019 the guidelines were distributed to the European Cystic Fibrosis Society (ECFS), the International Society for Heart and Lung Transplantation (ISHLT), the CF Foundation's medical listserv, and the CF Foundation's Community Voice for a two-week public comment period, after which the committee responded to all feedback and revised the manuscript as appropriate. To provide additional perspective from outside of the U.S., an "International Considerations" section was composed using input from the international committee members (Switzerland, Canada), as well as the Healthcare Advisory Council of CF Canada, who also approved the final version of the guidelines in its entirety.

3. Definition of advanced CF lung disease

The committee sought to create a pragmatic definition of ACFLD encompassing non-transplanted individuals whose disease has progressed to a level where alterations in care or increased attention to certain aspects of standard care are warranted (Fig. 1).

A systematic literature search identified CF articles that: (1) explicitly defined "advanced" or "severe" lung disease; (2) addressed unique aspects of care that were felt by the respective authors to apply to more severe disease; or (3) identified characteristics associated with worse outcome. An FEV_1 < 40% predicted was the most common defining criterion [8-10], including its use to define "severe" disease in many CF Registries globally [1,2,11,12]. Based on this and other considerations found in the literature search, ACFLD is defined as: FEV_1 < 40% predicted when "stable" (not during a pulmonary exacerbation), OR referred for lung transplantation evaluation, OR one or more of the following characteristics: previous intensive care unit (ICU) admission for respiratory failure, hypercarbia, daytime oxygen requirement at rest (excluding nocturnal use only), pulmonary hypertension, severe functional impairment from respiratory disease (New York Heart Association Class IV), six-minute walk test distance <400 m (Table 1). This definition yielded 100% voting consensus among members of the committee. The committee also recognizes that individuals who lose significant lung function as children likely have more aggressive disease than adults with similar decrements [7,13]. Although the committee concluded that its definition of ACFLD should apply to all ages, some providers may choose to apply some of the recommendations earlier in children.

Importantly, there may also be individuals with FEV_1 approaching 40% predicted who do not meet the above criteria but manifest other characteristics associated with more rapid progression to severe disease (Table 2). These individuals may also benefit from selective application of the guidelines. Table 3

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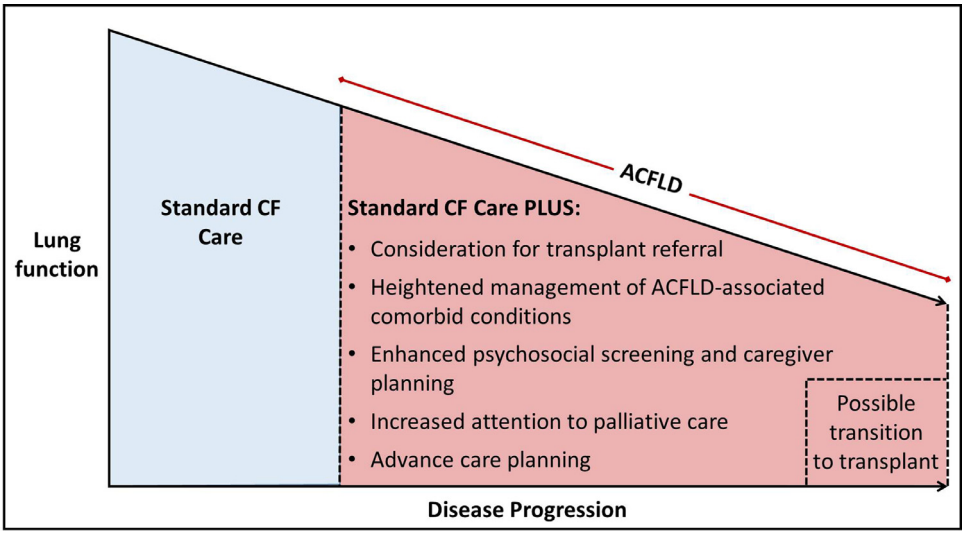


Fig. 1. Alterations in care when an individual progresses to ACFLD. CF = cystic fibrosis; ACFLD = advanced cystic fibrosis lung disease.

Table 1
Definition of advanced cystic fibrosis lung disease.

1) Forced expiratory volume in one second < 40% predicted when stable
OR
2) Referred for lung transplantation evaluation
OR
3) One or more of the following characteristics:
A) Previous intensive care unit admission for respiratory failure
B) Hypercarbia (P_aCO_2 > 50 mmHg on arterial blood gas OR P_vCO_2 > 56 mmHg on venous blood gas)
C) Daytime oxygen requirement at rest (excluding nocturnal use only)
D) Pulmonary hypertension (pulmonary artery systolic pressure > 50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of a tricuspid regurgitant jet)
E) Severe functional impairment from respiratory disease (New York Heart Association Class IV)
F) Six-minute walk test distance < 400 m

Table 2
Additional clinical manifestations associated with worse prognosis and/or disease progression in cystic fibrosis.

Frequent pulmonary exacerbations
Rapid rate of decline of forced expiratory volume in one second
Supplemental oxygen requirement with exercise or sleep
Worsening malnutrition despite supplementation
Infection with difficult to manage organisms
Cystic fibrosis-related diabetes
Pneumothorax
Massive hemoptysis (>240 mL) requiring intensive care unit admission or bronchial artery embolization

4. Discussion of consensus statements

1. When individuals with CF meet criteria for ACFLD, the CF Foundation recommends routine advance care planning (ACP) conversations with them and their caregiver(s), including communication about prognosis and goals of care, documentation of advance directives, and decision-making surrounding lung transplantation.

Palliative care concerns are often underestimated in lung disease. Although individuals with CF and caregivers report willingness and desire for earlier discussions, most ACP conversations occur during acute illness and frequently near the end of life [6]. Some unique barriers to ACP exist in CF and especially ACFLD including variable disease progression among those with advanced disease, the potential for rapid deterioration in some individuals, and the perceived conflict between advanced planning and pursuit of lung transplantation. Early introduction of palliative care in pulmonary disease is associated with more consistent ACP conversations, reduced healthcare utilization, and improved symptoms without reducing survival [14-16]. Literature supports early ACP for individuals with CF even before or while pursuing transplant [16-19], emphasizing that ACP conversations and aggressive treatments should not be mutually exclusive (Fig. 1). Discussions should review goals of care, preferences for palliative interventions, and decision-making pertaining to potential ICU admission, mechanical ventilation, tracheostomy, and lung transplantation. Early discussions also stand in accord with ECFS best practice recommendations [20], where preemptively outlining goals of care is recommended and allows individuals to carefully consider their wishes pertaining to future treatment options (including those discussed in Recommendation Statements 6, 7, 9, 10). Advance directives may include a durable power of attorney/health care proxy or living will. Care planning conversations should ideally involve the patient's chosen caregiver(s).

2. The CF Foundation recommends that individuals with ACFLD undergo screening for hypoxemia on exertion and sleep, hypercarbia, and pulmonary hypertension (also see related Recommendation Statements 3–5).

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Table 3
Recommendation statements.

Number	Recommendation
1	When individuals with CF meet criteria for advanced CF lung disease, the CF Foundation recommends routine advance care planning conversations with them and their caregiver(s), including communication about prognosis and goals of care, documentation of advance directives, and decision-making surrounding lung transplantation.
2	The CF Foundation recommends that individuals with ACFLD undergo screening for hypoxemia on exertion and sleep, hypercarbia, and pulmonary hypertension.
3	The CF Foundation recommends supplemental oxygen for individuals with advanced CF lung disease and exercise induced or nocturnal hypoxemia.
4	The CF Foundation recommends consideration of nocturnal noninvasive ventilation for individuals with advanced CF lung disease and chronic hypercarbia.
5	The CF Foundation found insufficient evidence to make a recommendation regarding the use of pulmonary vasodilator therapy in individuals with advanced CF lung disease and pulmonary hypertension.
6	The CF Foundation recommends lung transplantation as a treatment option for individuals with advanced CF lung disease if congruent with goals of care.
7	The CF Foundation recommends that individuals with advanced CF lung disease and acute respiratory failure be considered eligible for intensive care unit management regardless of transplant status if congruent with goals of care.
8	The CF Foundation recommends that individuals with advanced CF lung disease and acute respiratory failure be considered for a trial of high flow nasal cannula oxygen and/or noninvasive ventilation.
9	For individuals with advanced CF lung disease and acute respiratory failure requiring invasive mechanical ventilation, the CF Foundation recommends consideration of early tracheostomy when anticipated need for mechanical ventilation is more than 5–7 days and support remains congruent with goals of care.
10	The CF Foundation recommends that individuals with advanced CF lung disease who develop refractory respiratory failure requiring invasive mechanical ventilation be considered for early transition to extracorporeal life support if congruent with goals of care.
11	For individuals with advanced CF lung disease, the CF Foundation recommends a trial of continuous alternating inhaled antibiotics as dictated by bacterial pathogens identified in respiratory culture.
12	The CF Foundation recommends that individuals with progressive advanced CF lung disease undergo screening for fungal pathogens in addition to standard microbiological screening.
13	The CF Foundation recommends that individuals with advanced CF lung disease participate in a pulmonary rehabilitation program.
14	The CF Foundation found insufficient evidence to make a recommendation regarding the use of systemic corticosteroids in individuals with advanced CF lung disease.
15	The CF Foundation found insufficient evidence to make a recommendation regarding routine screening for gastroesophageal reflux in individuals with advanced CF lung disease.
16	The CF Foundation recommends the use of enteral tube feeds for individuals with advanced CF lung disease and malnutrition after consideration of procedural risks versus benefits.
17	For individuals with advanced CF lung disease with frequent prior and continuing exposure to nephrotoxic and ototoxic agents, the CF Foundation recommends increased monitoring for accumulating toxicity.
18	The CF Foundation recommends that women with advanced CF lung disease contemplating pregnancy carefully consider the risks in consultation with high-risk obstetrics and CF providers.
19	For individuals with advanced CF lung disease with indications for opioids, the CF Foundation recommends treatment in accordance with established Center for Disease Control guidelines; this should include monitoring for adverse effects, and consultation with pain and/or palliative care specialists as appropriate.
20	For individuals with advanced CF lung disease and anxiety, the CF Foundation recommends management in accordance with the International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety, reserving benzodiazepines for refractory symptoms or end of life symptom palliation.
21	When individuals with CF meet criteria for advanced CF lung disease, and with subsequent changes in clinical or social status, the CF Foundation recommends a formal care conference involving caregiver(s) and selected team members to develop a plan for ongoing psychosocial support.
22	In individuals with advanced CF lung disease, the CF Foundation recommends assessing the adequacy of financial resources at least biannually, and with changes in clinical or social status.
23	For pediatric patients with advanced CF lung disease nearing the age of transition to an adult CF care program, the CF Foundation recommends formally outlining a transition plan that provides flexibility in timing and coordination of transfer.

3. The CF Foundation recommends supplemental oxygen for individuals with ACFLD with exercise induced or nocturnal hypoxemia.

Screening for markers of severity in ACFLD can identify individuals at higher risk for poor outcomes, help determine the timing of lung transplant referral, and may direct specific therapies. Among these markers, nocturnal and exertional hypoxemia are associated with worse prognosis [3,21-23]. Screening for hypoxemia in advanced lung disease is advised in recently published CF lung transplant referral guidelines as well as ECFS best practice recommendations [7,20]. Nocturnal and/or exertional supplemental oxygen in CF improves oxygenation with potential for slight worsening of hypercarbia [24]. Oxygen use in ACFLD also improves exercise capacity [25-27] and reduces absenteeism from school or work [28], although no studies demonstrate improvements in mortality or exacerbations. A Cochrane review corroborated these findings [29], with the authors commenting that the risk of hypercarbia is likely clinically inconsequential. Consistent with lung transplant referral guidelines [7], annual screening for hypoxemia using six-minute walk test and nocturnal oximetry is thus advised. In accordance with U.S. Center for Medicare and Medicaid Services and most third party payer requirements [30], supplemental oxygen should be prescribed for those who desaturate to $\leq$ 88% with ambulation or to $\leq$ 88% for $\geq$ five minutes with sleep.

4. The CF Foundation recommends consideration of nocturnal noninvasive ventilation (NIV) for individuals with ACFLD and chronic hypercarbia.

Like hypoxemia, chronic hypercarbia is also associated with mortality in CF, can be detected on screening, and its presence in CF is cited as an indication for lung transplant referral [7,22,23,31]. Nocturnal NIV for chronic hypercarbia in CF was shown in one high-quality randomized crossover trial to improve partial pressure of carbon dioxide, dyspnea, and exercise tolerance [32]. Other series similarly demonstrate improvements in symptoms, lung function, or utility in bridging to lung transplant [33-36]. A Cochrane review corroborated these findings, also suggesting NIV as a use-

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ful adjunct to airway clearance [37]. Based on these observations and consistent with lung transplant referral guidelines [7], it is recommended that individuals with ACFLD undergo annual screening for hypercarbia using a venous blood gas. In accordance with U.S. Center for Medicare and Medicaid Services and most third party payer requirements [38], if P_vCO_2 is > 56 mmHg on venous blood gas a confirmatory arterial blood gas should be obtained. Nocturnal NIV should be considered in individuals with symptoms consistent with hypercarbia (including dyspnea, fatigue, morning headaches) AND:

- $P_aCO_2 \geq 55$ mmHg

OR

- P_aCO_2 50–54 mmHg AND nocturnal desaturation

OR

- P_aCO_2 50–54 mmHg AND ≥ two hospitalizations in the preceding year for hypercarbic respiratory failure.

Additional studies are necessary to define the optimal carbon dioxide thresholds and specific modalities for NIV in individuals with ACFLD and hypercarbia.

5. The CF Foundation found insufficient evidence to make a recommendation regarding the use of pulmonary vasodilator therapy in individuals with ACFLD and pulmonary hypertension.

Although the exact incidence is unknown due to varying definitions, pulmonary hypertension is also associated with increased mortality in ACFLD [39-41]. Its detection by screening echocardiography in CF is an indication for lung transplant referral [7,42]. Also consistent with transplant referral guidelines [7], a baseline screening echocardiogram is therefore recommended for individuals who develop ACFLD. Repeat echocardiogram should be considered if clinical status worsens. Despite its importance, there is limited literature on treatment of pulmonary hypertension in ACFLD. Sildenafil appears to be safe in CF and improves vascular endothelial function without impairing ventilation [43,44], but no data exist on its clinical efficacy. Further studies are needed to evaluate the physiologic and clinical effects of pulmonary vasodilators in ACFLD.

6. The CF Foundation recommends lung transplantation as a treatment option for individuals with ACFLD if congruent with goals of care.

Although outcomes have improved [3], ACFLD is associated with significant morbidity and reduced quality of life, and remains the most common cause of death in CF [1,2]. Lung transplant outcomes have also improved and multiple cohort studies demonstrate improved quality of life and survival with transplant for individuals with ACFLD [45-47]. In fact, ISHLT data show that adults with CF have a median survival after lung transplant of 9.9 years, with nearly 30% surviving twenty years after transplant and post-transplant survival in CF exceeding that of the other commonly transplanted diagnoses [48]. The benefits of lung transplant are likely most pronounced in those who are severely impaired and have additional predictors of mortality. Thus, while not all individuals with ACFLD will be eligible, lung transplant should be considered as a treatment option in ACFLD in conjunction with published referral guidelines [7,20,42].

7. The CF Foundation recommends that individuals with ACFLD and acute respiratory failure be considered eligible for ICU management regardless of transplant status if congruent with goals of care.

Survival in CF after an ICU admission has improved compared to previous decades. Survival to hospital discharge is reported as high as 55% when lung transplant is an option [49], and 10–55% when transplant is not an option [49-52]. Despite improvement from the 1970s, prognosis after admission to the ICU remains guarded in individuals requiring mechanical ventilation, especially those with non-reversible conditions [53]. Careful discussion between patients, families and healthcare teams is needed when ICU care is considered, particularly when lung transplant is not an option [54].

8. The CF Foundation recommends that individuals with ACFLD and acute respiratory failure be considered for a trial of high flow nasal cannula oxygen and/or NIV.

There is little evidence to assess the value of high flow oxygen or NIV in acute respiratory failure in CF. However, endotracheal intubation for mechanical ventilation leads to immobility, loss of gag reflex, sedation, and many secondary complications, which can potentially be mitigated with less invasive support. High flow oxygen and NIV are feasible and well tolerated as shown in a small study in CF patients [55]. Their benefit is also supported by literature in other diagnoses, including high flow oxygen for hypoxemic respiratory failure [56], and NIV for hypercarbic exacerbations of chronic obstructive pulmonary disease [57]. These modalities should therefore be considered in individuals with ACFLD and acute respiratory failure prior to endotracheal intubation for mechanical ventilation.

9. For individuals with ACFLD and acute respiratory failure requiring invasive mechanical ventilation, the CF Foundation recommends consideration of early tracheostomy when anticipated need for mechanical ventilation is more than 5–7 days and support remains congruent with goals of care.

The role for early tracheostomy in respiratory failure remains unclear [58]. However, early tracheostomy for patients anticipated to have prolonged mechanical ventilation may decrease sedation needs while improving airway clearance and mobilization. Based on this and collective experience among CF clinicians, early tracheostomy should be considered for individuals with ACFLD who are anticipated to require ventilatory support beyond 5–7 days. Communication with the pertinent transplant team(s) is advised for those pursuing or considering lung transplantation.

10. The CF Foundation recommends that individuals with ACFLD who develop refractory respiratory failure requiring invasive mechanical ventilation be considered for early transition to extracorporeal life support (ECLS) if congruent with goals of care.

Outcomes with ECLS have improved with modern-era technology including “awake” single-cannula techniques that allow for reduced sedation, increased mobility, and improved mucus clearance. Several case series that include a large percentage of patients with CF describe ECLS as a bridge to lung transplant, with post-transplant survival after ECLS now exceeding earlier reports utilizing mechanical ventilation for bridging [59-61]. Additionally, although data are limited, ECLS has the potential to provide a bridge to recovery in rare patients with CF and acute respiratory failure. In view of these reports and clinical experience, individuals with ACFLD and refractory respiratory failure should be considered for ECLS as a bridge to lung transplant or recovery. Preceding discussion with the pertinent transplant team(s) and review of goals of care are mandatory.

11. For individuals with ACFLD, the CF Foundation recommends a trial of continuous alternating inhaled antibiotics as dictated by bacterial pathogens identified in respiratory cultures.

Intermittent (28-day on/off) inhaled antibiotics are standard of care for individuals with CF and chronic airways infection [62]. A

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continuous regimen (often alternating between two different antibiotics, as dictated by organisms identified in respiratory cultures) may provide additional benefit to those with more severe disease. One randomized double-blind placebo-controlled trial in patients with CF and *Pseudomonas aeruginosa* failed to enroll enough patients as many centers were already using continuous regimens in some patients. Despite being underpowered, rates of total exacerbations and hospitalizations trended lower with continuous regimens [63]. Another retrospective study showed deterioration in lung function before initiation of continuous antibiotics that improved after their introduction. ACFLD patients in this study were more likely to have received a continuous alternating regimen [64]. No adverse effects were demonstrated in either study. A continuous alternating inhaled regimen should therefore be considered in ACFLD for its potential benefit. It should also be recognized that some centers consider prolonged, even continuous intravenous antibiotics in select individuals with ACFLD approaching lung transplantation, but the risks and benefits of this approach require further study.

12. The CF Foundation recommends that individuals with CF and progressive advanced lung disease undergo screening for fungal pathogens in addition to standard microbiological screening.

CF Foundation guidelines recommend microbiologic surveillance for bacteria (quarterly) and mycobacteria (yearly), and for allergic bronchopulmonary aspergillosis (ABPA) with annual laboratory evaluations [65,66]. The role of fungal pathogens other than *Aspergillus fumigatus* in ABPA are currently not well-understood, but organisms including *Trichosporon, Scedosporium*, and *Lomentspora* are associated with severe CF exacerbations and potentially worse transplant outcomes [67,68]. ECFS guidelines note the potential pathogenicity of *A. Fumigatus* in some patients and advise that fungal cultures be available [20], though no specific recommendations are made for individuals with ACFLD. Based on these points, annual culture of sputum specifically for fungus is advised in individuals with progressive ACFLD and continued deterioration despite optimization of usual therapies. Further study is needed to better understand the implications of fungal pathogens in CF.

13. The CF Foundation recommends that individuals with ACFLD participate in a pulmonary rehabilitation program.

Multiple studies have evaluated exercise programs at home and in healthcare settings in individuals with CF including ACFLD. Both strength and aerobic training improve exercise capacity and quality of life, and some studies demonstrate small improvements or slowing in the rate of decline in lung function [69-71]. Although data on pulmonary rehabilitation programs specifically in CF are limited, enrollment may also be beneficial in preparation for lung transplantation and is required by some transplant programs [72]. Pulmonary rehabilitation should therefore be considered for patients with ACFLD.

14. The CF Foundation found insufficient evidence to make a recommendation regarding the use of systemic corticosteroids in individuals with ACFLD.

Previous general CF guidelines recommend against routine, chronic oral corticosteroids for individuals with CF without asthma or ABPA [20,62]. One long-term randomized trial of high-dose every other day oral corticosteroids in mild-to-moderate CF lung disease showed slightly better preservation of lung function compared to placebo, but growth retardation and abnormalities of glucose metabolism were seen in steroid-treated patients [73]. One short-term trial involving 20 adults with stable ACFLD showed no benefit from steroids, and deterioration in lung function was seen after steroids were withdrawn [74]. Cochrane reviews corroborate these results [75], but no relevant, high quality data exists in ACFLD. One additional consideration in ACFLD, as discussed in ECFS guidelines [20], is that due to concerns regarding wound healing many transplant programs require that pre-transplant chronic corticosteroid doses be limited to <15–20 mg (prednisolone equivalent) per day. Although a trial of systemic corticosteroids is often considered in ACFLD on a case-by-case basis, given the lack of data a recommendation cannot be made for or against this practice in the ACFLD population.

15. The CF Foundation found insufficient evidence to make a recommendation regarding routine screening for gastroesophageal reflux in individuals with ACFLD.

Gastroesophageal reflux (GER), even when "clinically silent" in patients lacking typical symptoms is implicated in the pathogenesis of some lung diseases including idiopathic pulmonary fibrosis and bronchiolitis obliterans syndrome after lung transplantation. Existing literature reports a high prevalence of GER in ACFLD with features including proximal acid and bile reflux, pulmonary micro-aspiration, lower esophageal sphincter weakness, and prolonged clearance of refluxate [76-78]. Some CF studies (including small numbers with ACFLD) associate GER detected by pH testing or endoscopy with worse pulmonary outcomes [78-80]. Many transplant programs routinely screen candidates for GER [42,81], but evidence to support screening for asymptomatic GER in ACFLD is lacking. Some pre- and post-transplant pulmonary outcomes improve with surgical treatment of GER in a mixed advanced lung disease population [82]. However, without further data, no specific approach can be recommended in individuals with ACFLD.

16. The CF Foundation recommends the use of enteral tube feeds for individuals with ACFLD and malnutrition after consideration of procedural risks vs benefits.

Malnutrition is common in individuals with ACFLD [2], is associated with worse pre- and post-lung transplant outcomes [83,84], and may factor into eligibility for lung transplant. Enteral feeding leads to weight gain and potential for better maintenance of lung function in CF including individuals with severe disease [85-88]. Published CF Foundation guidelines recommend nasoenteral tube feeding in individuals with CF who require short-term (< 3 months) nutritional repletion [89]. ECFS general guidelines add that nutritional rehabilitation can take at least 3–6 months [20], a fact that may be especially relevant in ACFLD when caloric requirements increase and oral intake may become more difficult. For long-term supplementation, guidelines recommend percutaneous or surgical tube placement with the statement that low FEV_1 is not an absolute contraindication [89], but careful consideration should be made regarding the capacity for procedural recovery. Particular attention to post-procedure analgesia is important to allow effective airway clearance therapy while avoiding opioid-induced respiratory suppression and bowel obstruction. In ACFLD, preference should be given for non-surgical placement options by either interventional radiology or upper endoscopy. Consultation with anesthesiology is advisable, and tube placement should be avoided or delayed during acute illness. Transpyloric feeding (gastrojejunal or jejunal) should be considered in individuals with gastroparesis, severe GER, and/or poor tolerance of gastric feeds [89]. There are limited data to guide the use of short or long term total parenteral nutrition in ACFLD. In addition, sufficient pancreatic enzyme replacement therapy and maintenance of nutritional status is challenging during critical illness, but the systematic review did not identify literature supporting a specific enzyme replacement regimen in ACFLD.

17. For individuals with advanced CF lung disease with frequent prior and continuing exposure to nephrotoxic and ototoxic

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agents, the CF Foundation recommends increased monitoring for accumulating toxicity.

With disease progression, individuals with CF often acquire resistant organisms and receive more frequent courses of antibiotics with higher cumulative exposure. Both ototoxicity and nephrotoxicity related to aminoglycosides and other antibiotics are important in ACFLD, particularly when chronic kidney disease (CKD) may impact lung transplant candidacy and outcomes. CKD may occur without a serum creatinine above the normal range, particularly in the setting of reduced muscle mass. One large registry study demonstrated an annual prevalence of CKD of 2.3% in individuals with CF; this rate doubled with every 10-year increase in age [90]. In another study of 80 adolescents and adults with CF, between 31–42% had impaired renal function that was strongly correlated with aminoglycoside exposure and potentiated by use of intravenous colistin [91]. Due to risks as well as clinical efficacy, tobramycin is the preferred aminoglycoside for exacerbations in individuals with *Pseudomonas*. Although some studies do not confirm a relationship between antibiotic exposure and renal insufficiency [90,92], given the antibiotic requirements and transplant implications careful monitoring is advisable in ACFLD, particularly during administration of intravenous ototoxic or nephrotoxic drugs.

18. The CF Foundation recommends that women with ACFLD contemplating pregnancy first carefully consider the risks in consultation with high-risk obstetrics and CF providers.

Compared to the general non-CF population, pregnancy in CF is associated with an increased risk of perinatal complications including maternal deterioration, preterm labor, low birth weight, Caesarian delivery, respiratory failure, and death, with most studies showing higher risks in those with ACFLD [93-95]. The associated maternal complications may be a function of the lung disease itself, as outcomes in pregnant women with CF do not appear to differ from outcomes in non-pregnant women with CF who have similar lung disease characteristics [96-99]. International guidelines regarding pregnancy in CF note that pregnancy can occur regardless of severity of pulmonary disease, with outcomes (for mother and infant) being closely linked to lung function and stability. Pulmonary status needs to be optimized in planned fashion in all women prior to pregnancy [100]. Although predicting individual pregnancy outcomes based on disease severity is challenging [94], it is advisable for women with ACFLD contemplating pregnancy to carefully discuss the risks prior to conception.

19. For individuals with ACFLD with indications for opioids, the CF Foundation recommends treatment in accordance with established Center for Disease Control guidelines, including monitoring for adverse effects and consultation with pain and/or palliative care specialists as appropriate.

Pain and dyspnea are common and associated with adverse outcomes in CF [101]. Concerns about respiratory depression, tolerance, addiction, and transplant eligibility may affect opioid prescribing for patients with specific indications including moderate-severe acute or chronic pain, painful therapies, dyspnea in ACFLD, or end of life symptoms. In two CF studies (one in the ACFLD population), no patients experienced severe opioid-induced respiratory side effects, and subsequent misuse behaviors were extremely rare [102,103]. Studies in mixed pulmonary populations including COPD similarly demonstrated no significant respiratory side effects of low-dose opioids [104,105]. Another study of 59 lung transplant candidates co-managed in palliative care programs also found no important opioid side effects, and only 23% continued opioids one-month post-transplant [106]. Consistent with other statements for palliative care in lung disease [107], appropriately-dosed opioids can be prescribed for individuals with ACFLD when coupled with proper education, safety monitoring, and proactive side effect management including monitoring of bowel function and prevention of constipation. Communication with transplant centers regarding opioid policies is advised. Specific strategies regarding opioid initiation, dosage, duration, and risks are reviewed in Center for Disease Control Guidelines [108].

20. For individuals with ACFLD and anxiety, the CF Foundation recommends management in accordance with the International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety, reserving benzodiazepines for refractory symptoms or end of life symptom palliation.

Anxiety is common and warrants increased attention in ACFLD. Benzodiazepine use has been associated with exacerbations, respiratory failure, and mortality in COPD [105,109], but CF-specific data are lacking. The International Committee on Mental Health in CF's consensus statements recommend a stepped-care model, using psychological interventions as first-line anxiety treatment and reserving short-term benzodiazepines for refractory symptoms with close monitoring [110]. Consistent with other palliative care statements for lung disease [107], benzodiazepines should be considered standard of care for anxiety at the end of life in individuals with ACLFD.

21. When individuals with CF meet criteria for advanced lung disease and with subsequent changes in clinical or social status, the CF Foundation recommends a formal care conference involving caregiver(s) and selected team members to develop a plan for ongoing psychosocial support.

In adults with CF and severe disease, caregiver support is associated with fewer physical and emotional symptoms [111]. Additionally, caregiver availability often factors into lung transplant eligibility based on pre-transplant support being linked to adherence and post-transplant outcomes in general organ transplant populations [42,112]. Moreover, family members of individuals with CF face mental health challenges that may be amplified in ACFLD [113,114]. Proactive communication allows better preparedness while approaching complex health issues and decisions. Care teams should thus formally identify support systems for those with ACFLD, while normalizing the need for support and offering education on caregiver roles during disease progression and pursuit of transplantation.

22. In individuals with ACFLD, the CF Foundation recommends assessing the adequacy of financial resources at least biannually and with changes in clinical or social status.

Low socioeconomic status is associated with worse adherence, nutrition, lung function, mental health, and survival in CF [115,116]. Although the specific impact in ACFLD is unknown, experience suggests greater financial challenges including treatment burden and associated costs, change in work status, disability, and caregiver economic strain [117]. Public insurance, which typically covers individuals with limited income, is also associated with lower lung transplant referral and acceptance rates [4,118], as well as increased wait list mortality [119]. The American College of Physicians, in a recent position paper, recommended increased screening and collection of social determinants of health data for all patients [120]. Therefore, more frequent assessment is indicated for individuals with ACFLD and their caregivers to identify cost barriers, provide resources, educate regarding health care coverage and transplant fundraising if applicable, and reduce stigma associated with needing assistance.

23. For pediatric patients with ACFLD nearing the age of transition to an adult CF care program, the CF Foundation recommends

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formally outlining a transition plan that provides flexibility in timing and coordination of transfer.

Structured programs for transition to adult care are outlined in the CF literature and are associated with improved patient and family satisfaction, clinical stability during transfer, and reduced need for urgent transfer [121,122]. Programs for adolescents and young adults with ACFLD approaching transition should thus include gradual preparation and proper coordination of transfer as described in the general CF population [123].

Overall concerns surrounding transition do not differ in ACFLD [124], but many unique issues are pertinent including involvement of more specialists and multiple concurrent transitions, psychosocial and adherence concerns, and end of life considerations. Caregiver and psychosocial assessment should proceed as described in Recommendation Statements 21 and 22. Opinions vary on whether transition should be delayed in ACFLD [125,126], and there are no data to guide optimal timing. Adolescents and young adults nearing end of life may benefit from continuity with pediatric providers. In all others with ACFLD, proper coordination and flexibility are recommended with attention to patient factors and center-specific protocols [123,127].

5. International considerations

ACFLD is also common and the most frequent cause of death in individuals with CF beyond the U.S. In Europe, by the FEV_1 threshold used in these guidelines, 2017 ECFS data indicate the presence of ACFLD in nearly 15% of adults with CF aged 18 to 29 years, and 20% of those 30 years and older, with this latter prevalence exceeding 30% in several Eastern European countries [1]. ACFLD is similarly common in adults with CF in Australia and Canada, with these nations' registries reporting a prevalence of 14% and 16%, respectively [11,12]. In children with CF across the world, the reported prevalence of ACFLD is much lower at approximately 1% in Australia and Canada, 2% in Europe as a whole, and 4% in 18-year-olds in the U.S [2], but does vary by region even exceeding 10% in some Eastern European countries [1]. Moreover, although the prevalence and impact of ACFLD are difficult to estimate in less developed regions and/or those lacking robust registry data, many additional barriers to care may exist in these settings and contribute to more rapid disease progression [128]. Thus, ACFLD threatens the life and well-being of many people with CF globally, and improving care in this population should be an important priority for the international CF community.

There is limited literature to guide whether management of ACFLD should be adapted to different regions of the world. Nevertheless, several pertinent disparities should be appreciated in developing and low-/middle-income countries including late diagnosis, misdiagnosis, socioeconomic status, and access to medical therapies or lung transplantation [128]. For instance, the advent of highly effective CFTR modulator therapy represents a monumental breakthrough for CF care, but accessing these expensive treatments globally will be extremely dependent on reimbursement policies and availability within individual healthcare systems. Even more specific to ACFLD, while the current guidelines endorse lung transplant consideration for those with advanced disease consistent with the European perspective [129,130], it is important to note that the availability of transplant varies significantly around the world for individuals with CF and other diagnoses. In fact, of 47,591 total lung transplants recorded in the ISHLT Thoracic Transplant Registry between 2005 and 2018, approximately 56% took place in North America, 36% in Europe, but only 8% elsewhere [48]. Even within Europe, the percentage of individuals with CF who receive lung transplant varies significantly, particularly when comparing European Union to non-European Union countries [1]. These differences certainly have the potential to influence the development, progression, and available treatment options for ACFLD, and thus, the current guidelines need to be applied in the context of an individual patient and healthcare provider's global setting.

Even in developed countries where access to therapies is similar, it is necessary to interpret these guidelines within their international context, whereby comparisons with international transplant referral guidelines [7,42] and recently revised ECFS Best Practice Guidelines [20] are useful. The recently published CF transplant referral guidelines emphasize a pre-emptive approach to screening for markers of disease severity, transplant consideration, and intervening on modifiable barriers to transplant [7]. The issue of late or non-referral exists globally even among developed countries, with one study from France demonstrating that at least 40% of individuals with ACFLD who died were referred for transplant late or not at all [5]. The current guidelines were therefore designed to provide consistency with these previously published documents, recommending identical screening for markers of disease severity, while also elaborating on management of hypoxemia and hypercarbia. Similarly, although the ECFS Guidelines [20] do not offer specific focus on ACFLD, general recommendations on several pertinent topics including nutritional rehabilitation, antibiotic therapy and complications, and oxygen screening and therapy are all consistent with the current manuscript. Notably, when managing acute respiratory failure, the European document advises caution against invasive mechanical ventilation in individuals without a clearly reversible precipitant, especially those who have not previously completed transplant evaluation. Recommendations 7–10 in the current guidelines pertaining to ICU management should thus be interpreted in the framework of the available means of support in a given care setting. Finally, our emphasis on preemptive and routine ACP in individuals with ACFLD are similar to the European perspective, although clinical experience suggests that end-of-life and palliative care concerns are not frequently enough emphasised around the world, and thus represent an area of need for the global CF community.

6. Conclusions

Outcomes for individuals with CF are improving, and continued research and therapeutic advances are predicted to bring further improvements in upcoming years. However, CF by nature remains a progressive disease; even with the landmark development of new CFTR modulator therapy, some individuals will not be eligible, long-term efficacy remains unknown and responses may be heterogeneous, and many with CF today already have established advanced lung disease. ACFLD will therefore continue to be an important issue and carries many pulmonary, general medical, transplant surgical, psychosocial, economic, and palliative care concerns. These guidelines intend to provide direction to CF care teams on the unique management concepts, which should be considered and paired with standard care when individuals reach a state of advanced disease (Fig. 1). Moreover, as the CF community strives to improve outcomes, more research specific to the manifestations of ACFLD is needed, particularly as the CF population ages and extra-pulmonary considerations become more important. For now, providers should use these guidelines when partnering with their patients with ACFLD to determine the best treatment plan for each individual, with an ultimate goal to further improve quality of life and survival for individuals with CF.

Declaration of Competing Interest

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CRediT authorship contribution statement

Siddhartha G. Kapnadak: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **Emily Dimango:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Denis Hadjiliadis:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Sarah E. Hempstead:** Conceptualization, Methodology, Investigation, Resources, Visualization, Supervision, Project administration. **Erin Tallarico:** Conceptualization, Methodology, Resources, Supervision, Project administration. **Joseph M. Pilewski:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **Albert Faro:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **James Albright:** Writing - original draft, Visualization. **Christian Benden:** Investigation, Writing - original draft, Visualization. **Shaina Blair:** Investigation, Writing - original draft, Visualization. **Elisabeth P. Dellon:** Investigation, Writing - original draft, Visualization. **Daniel Gochenour:** Investigation, Writing - original draft, Visualization. **Peter Michelson:** Investigation, Writing - original draft, Visualization. **Baharak Moshiree:** Investigation, Writing - original draft, Visualization. **Isabel Neuringer:** Investigation, Writing - original draft, Visualization. **Carl Riedy:** Investigation, Writing - original draft, Visualization. **Teresa Schindler:** Investigation, Writing - original draft, Visualization. **Lianne G. Singer:** Investigation, Writing - original draft, Visualization. **Dave Young:** Investigation, Writing - original draft, Visualization. **Lauren Vignola:** Investigation, Writing - original draft, Visualization. **Joan Zukosky:** Investigation, Writing - original draft, Visualization. **Richard H. Simon:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2020.02.015.

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