Instructions:

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Consensus Guidelines for the Care of Individuals with Advanced CF Lung Disease

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Abstract:

Outcomes for individuals with cystic fibrosis (CF) have improved substantially but it remains a progressive disease. Advanced CF lung disease (ACFLD) is common, associated with reduced quality of life, and represents the most frequent cause of death in individuals with CF. Despite its importance, a relative paucity of literature is directed towards the unique needs of individuals with ACFLD.

The Cystic Fibrosis Foundation assembled a multidisciplinary expert panel to develop consensus guidelines for the care of individuals with ACFLD. Recommendations were based on a systematic literature review combined with expert opinion when appropriate. Twenty-four statements address the definition of ACFLD, pulmonary and intensive care unit management, management of selected comorbidities, symptom control, and psychosocial issues. 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.

1. Introduction

While the quality of life and survival of individuals with cystic fibrosis (CF) are improving, advanced CF lung disease (ACFLD) remains common. Approximately 18% of individuals progress to a forced expiratory volume in one second (FEV_1) of less than 40 percent predicted by age 30, and nearly 25% by age 45 (1). ACFLD remains the most common cause of death in CF and is associated with reduced quality of life, worsening clinical symptoms, increased exacerbations, and increased healthcare utilization (1, 2).

Although ACFLD-specific outcomes have improved for individuals with a $FEV_1 < 30\%$ predicted, there remains an approximately 10% per year risk of death (3). While lung transplantation may represent a key life-extending treatment, some with ACFLD may choose to forgo the option, many potential candidates are not referred (4), and even 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 relatively limited literature directed specifically at the unique medical and psychosocial challenges of individuals with ACFLD. The goal of these Consensus Guidelines is to provide guidance for providers caring for 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 efforts may be helpful.

2. Methods

The Cystic Fibrosis Foundation (CFF) assembled a multidisciplinary team including pediatric, adult, and transplant pulmonologists, a gastroenterologist, palliative care specialist, pharmacist, respiratory therapist, nurse coordinator, social worker, dietitian, methodologist, and one parent and two individuals with CF. 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 unique

aspects of care relevant to ACFLD while avoiding redundancy with previous guidelines pertaining to the overall CF population.

Workgroups performed systematic literature searches in PubMed for each PICO question between January-August 2018 (results provided in the Supplement). Members participated in monthly phone conferences and drafted recommendation statements. The committee reconvened in December 2018 to revise and vote on statements using an a priori voting threshold of 80% agreement. In May 2019 the guidelines were distributed for a two-week public comment period, after which the committee responded to feedback and revised the manuscript as appropriate.

3. Definition of Advanced CF Lung Disease

We sought to create a pragmatic definition of ACFLD encompassing individuals whose disease has progressed to a level where alterations in their care are warranted (Figure 1).

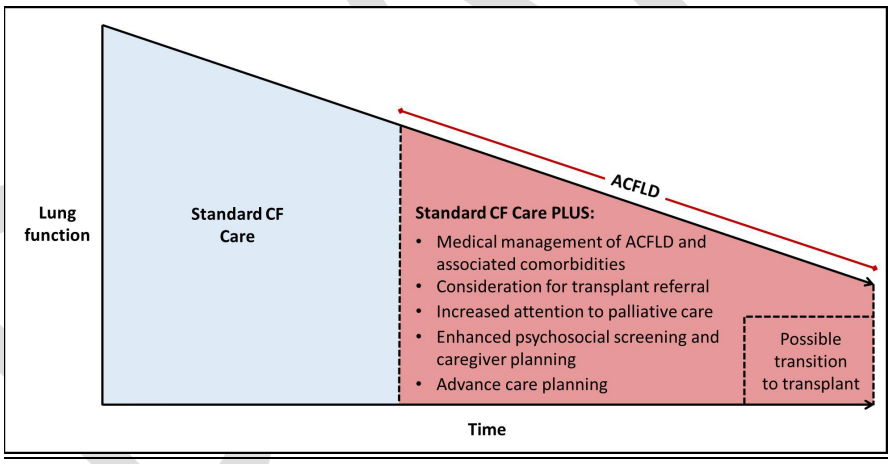

Figure 1: Alterations in care when an individual progresses to ACFLD.
CF= Cystic fibrosis; ACFLD= Advanced cystic fibrosis lung disease.

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 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 (1, 5-7). Based on this and other considerations originating from the literature search, ACFLD is defined as: FEV_1 < 40%

predicted when stable, OR referred for lung transplantation evaluation, OR one or more of the following characteristics: previous intensive care unit (ICU) admission for respiratory failure, hypercarbia, oxygen requirement at rest (at sea level), pulmonary hypertension, massive hemoptysis (>240mL) requiring ICU admission or bronchial artery embolization, severe functional impairment from respiratory disease (New York Heart Association Class IV), or 6-minute walk test (6MWT) distance < 400 meters (Table 1).

Table 1 ACFLD is defined as:

1) FEV_1 < 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 (ICU) admission for respiratory failure
- B) Hypercarbia
- C) Oxygen requirement at rest (at sea level)
- D) Pulmonary hypertension
- E) Massive hemoptysis (>240mL) requiring ICU admission or bronchial artery embolization
- F) Severe functional impairment from respiratory disease (New York Heart Association Class IV)
- G) 6-minute walk test (6MWT) distance < 400 meters

This definition yielded 100% voting consensus among members of the committee. 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 and may benefit from application of these guidelines (Table 2).

Table 2: Additional clinical manifestations associated with severe disease in cystic fibrosis
Frequent pulmonary exacerbations
Rapid rate of decline of forced expiratory volume in one second
Supplemental O_2 requirement with exercise or sleep
Worsening malnutrition despite supplementation
Pneumothorax
Infection with difficult to manage organisms
Cystic fibrosis-related diabetes

4. Discussion of consensus statements

Table 3: Recommendation statements		
Number	Recommendation	% Consensus
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.	100.0%
2	The CF Foundation recommends that individuals with advanced CF lung disease undergo screening for hypoxemia on exertion and sleep, hypercarbia, and pulmonary hypertension.	100.0%
3	The CF Foundation recommends supplemental oxygen for individuals with advanced CF lung disease and exercise induced or nocturnal hypoxemia.	100.0%
4	The CF Foundation recommends consideration of nocturnal noninvasive ventilation (NIV) for individuals with advanced CF lung disease and chronic hypercarbia.	100.0%
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.	100.0%
6	The CF Foundation recommends lung transplantation as a treatment option for individuals with advanced CF lung disease.	100.0%

7	The CF Foundation recommends that individuals with advanced CF lung disease and acute respiratory failure be considered eligible for ICU care regardless of transplant status if congruent with goals of care.	100.0%
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 NIV.	100.0%
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.	100.0%
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 (ECLS) if congruent with goals of care.	100.0%
11	For individuals with advanced CF lung disease, the CF Foundation recommends a trial of continuous inhaled antibiotics as dictated by respiratory culture results.	100.0%
12	The CF Foundation recommends that individuals with progressive advanced CF lung disease undergo screening for fungal pathogens in addition to standard microbiological screening.	90.5%
13	The CF Foundation recommends that individuals with advanced CF lung disease participate in a pulmonary rehabilitation program.	100.0%
14	The CF Foundation found insufficient evidence to make a recommendation regarding the use of systemic corticosteroids in individuals with advanced CF lung disease.	100.0%
15	The CF Foundation found insufficient evidence to recommend for or against routine screening for gastroesophageal reflux in individuals with advanced CF lung disease.	100.0%
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.	100.0%
17	The CF Advanced Lung Disease Guidelines Committee recommends the use of an in-line cartridge for individuals with advanced CF lung disease who are using enteral nutrition and lack practical options for enzyme administration during tube feedings	100.0%
18	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.	100.0%
19	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.	100.0%
20	For individuals with advanced CF lung disease with indications for opioids, the CF Foundation recommends treatment in accordance with established guidelines; this should include monitoring for adverse effects, and consultation with pain or palliative care specialists as appropriate.	100.0%

21	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.	100.0%
22	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.	100.0%
23	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.	100.0%
24	For pediatric patients with ACFLD, the CF Foundation recommends formally outlining a transition to adult care that provides flexibility in timing and coordination of transfer.	100.0%

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 (8). Early palliative care interventions in pulmonary disease are associated with more consistent ACP, reduced healthcare utilization, and improved symptoms without reducing survival (9-11). Literature supports early ACP for individuals with CF even before or while pursuing transplant (11, 12), emphasizing that ACP conversations and aggressive treatments should not be mutually exclusive (Figure 1). 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.

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

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

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 have been associated with worse prognosis (3, 13-15). Nocturnal and/or exertional supplemental oxygen in CF improves oxygenation with potential for slight worsening of hypercarbia (16). Use of oxygen in ACFLD has been shown to improve exercise capacity (17-19) and reduce absenteeism from school or work (20), although no studies demonstrate improvements in mortality or exacerbations. A Cochrane review corroborated these findings (21), with authors commenting that the risk of hypercarbia is likely clinically inconsequential.

Chronic hypercarbia has also been associated with mortality in CF, can be detected on screening, and its presence in CF is cited as an indication for lung transplant referral (14, 15, 22, 23). Management of chronic hypercarbia in CF with nocturnal NIV was evaluated in one high-quality randomized crossover trial that showed improved partial pressure of carbon dioxide, dyspnea scores, and exercise tolerance (24). Other case series have similarly demonstrated improvements in symptoms, lung function, or utility in bridging to lung transplant (25-28). A Cochrane review corroborated these findings, also suggesting NIV as a useful adjunct to airway clearance (29). Additional studies are necessary to define the optimal partial pressure of carbon dioxide thresholds and specific modalities for NIV in individuals with ACFLD and hypercarbia.

Although the exact incidence is unknown due to varying definitions, pulmonary hypertension is associated with increased mortality in ACFLD (30-32). Its detection by screening echocardiography in CF is an indication for lung transplant referral (23, 33). Despite its importance, there is limited literature on treatment of pulmonary hypertension in ACFLD. Sildenafil has been shown to be safe in CF and improves vascular endothelial function without

impairing ventilation (34, 35), 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.

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 (36-38). 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 (23, 33).

7. The CF Foundation recommends that individuals with ACFLD and acute respiratory failure be considered eligible for ICU care 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 (39), and 10-33% when transplant is not an option (39-42). Despite improvement from the 1970s, prognosis after admission to the ICU remains guarded in individuals requiring mechanical ventilation or with non-reversible conditions (43). Careful discussion between patients, families and healthcare teams is needed when ICU care is required, particularly when lung transplant is not an option.

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 high flow oxygen or NIV. Their benefit is supported by literature in other diagnoses, including high flow oxygen for hypoxemic respiratory failure (44), and NIV for hypercarbic exacerbations of chronic obstructive pulmonary disease (45). These modalities should thus 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 (46). 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, particularly those who are pursuing lung transplant.

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.

Several case series describe ECLS as a bridge to lung transplant, many of which include a large percentage of patients with CF. Outcomes with ECLS have improved with modern-era technology, and post-transplant survival after ECLS has been shown to exceed earlier reports utilizing mechanical ventilation for bridging (47-49). In view of these reports and the rationale that awake ECLS may reduce pre-transplant sedation and immobility, individuals with ACFLD and refractory respiratory failure should be considered for ECLS as a bridge to lung transplant or recovery, after discussion with the pertinent transplant team(s).

11. For individuals with ACFLD, the CF Foundation recommends a trial of continuous inhaled antibiotics as dictated by respiratory culture results.

Intermittent (28-day on/off) inhaled antibiotics are standard of care for individuals with CF and chronic airways infection (50). A continuous regimen (often alternating between two different antibiotics) may provide additional benefit to those with more severe disease and has been evaluated in patients with *Pseudomonas aeruginosa*. One randomized double-blind placebo-controlled trial 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 (51). 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 regimen (52). No adverse effects were demonstrated in either study. The CFF thus concludes that a continuous regimen should be considered in ACFLD for its potential benefit.

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.

CFF guidelines recommend microbiologic surveillance for bacteria (quarterly) and mycobacteria (yearly), and for allergic bronchopulmonary aspergillosis (ABPA) with annual laboratory evaluations (53, 54). Clinicians should screen more frequently in individuals with progressive ACFLD despite optimization of usual therapies. Although the role of fungal pathogens other than *Aspergillus fumigatus* in ABPA are currently not well-understood, organisms including *Trichosporon, Scedosporium prolificans*, and *Lomentspora* have been associated with severe CF exacerbations or worse transplant outcomes (55, 56). Therefore, evaluation with fungal cultures is advised in individuals with progressive ACFLD. 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 in CF, many having included individuals with ACFLD. Various programs at home and in healthcare settings including strength and aerobic

training were shown to improve exercise capacity and quality of life; some showed small improvements or decreased rate of decline in lung function (57-59). A pulmonary rehabilitation program may also be beneficial in preparation for lung transplantation and is required for some programs (60).

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

Previous guidelines recommend against routine, chronic oral corticosteroids for individuals with CF without asthma or ABPA (50). 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 (61). 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 (62). Cochrane reviews have corroborated these results (63), but no relevant, high quality data exists in ACFLD. Although short- or long-term systemic corticosteroids are often considered in ACFLD on a case-by-case basis, given the lack of data a recommendation cannot be made for or against routine use in this population.

15. The CF Foundation found insufficient evidence to recommend for or against routine screening for gastroesophageal reflux in individuals with ACFLD.

Gastroesophageal reflux (GER), even when “clinically silent” in patients lacking typical symptoms, has been implicated in the pathogenesis of lung diseases such as chronic cough, asthma, 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 (64-66). Some CF studies (including small numbers with ACFLD) have associated GER detected by pH testing or endoscopy with worse pulmonary outcomes (66-68). Many transplant programs routinely screen candidates for GER (33, 69), but the role of screening for asymptomatic GER in ACFLD has not been evaluated.

Surgical treatment of GER carries theoretical benefit and some pre- and post-transplant pulmonary outcomes have been shown to improve in a mixed advanced lung disease population (70). 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 (1), associated with worse pre- and post-lung transplant outcomes (71, 72), and may factor into eligibility for lung transplant. Enteral feedings lead to weight gain and potential for better maintenance of lung function in individuals with CF, including those with severe disease (73-76). Published CFF guidelines recommend against using low FEV_1 as an absolute contraindication to percutaneous or surgical enteral tube placement (77), but careful consideration should be made regarding the capacity for procedural recovery. In ACFLD, preference should be given for non-surgical placement options by either interventional radiology or upper endoscopy. Consistent with enteral tube feeding guidelines, transpyloric feeding (gastrojejunal or jejunal) should be considered in patients with gastroparesis and/or severe GER. Consultation with anesthesiology and avoidance of general anesthesia is advisable, and enteral tube placement should be avoided or delayed during acute illness (77).

17. The CF Advanced Lung Disease Guidelines Committee recommends the use of an in-line cartridge for individuals with ACFLD who are using enteral nutrition and lack practical options for enzyme administration during tube feedings.

Most relevant in ACFLD, sufficient pancreatic enzyme replacement therapy and maintenance of nutritional status is challenging during critical illness, particularly during mechanical ventilation. The systematic review did not identify literature supporting a specific enzyme replacement regimen in ACFLD. However, in-line cartridges provide a means to hydrolyze fats in enteral formulas for individuals who are unable to take pancrelipase orally.

18. 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.

With disease progression, individuals with CF generally receive higher cumulative antibiotic exposure. Both ototoxicity and nephrotoxicity related to aminoglycosides are important in ACFLD; particularly when chronic kidney disease (CKD) may impact lung transplant candidacy and outcomes. CKD may occur without increase in serum creatinine above the upper range of normal, 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 (78). 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 colistin (79). Other studies have not confirmed this relationship (78, 80), but given the antibiotic requirements and transplant implications of renal insufficiency, careful monitoring is advisable in ACFLD.

19. 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, Caesarian delivery, respiratory failure, and death, with most studies showing higher risks in those with ACFLD (81-83). On the other hand, maternal outcomes in pregnant CF women have been shown to not differ from non-pregnant women with CF and similar lung disease characteristics (84-87). Although predicting individual pregnancy outcomes based on disease severity is challenging (83), it is advisable for women with ACFLD contemplating pregnancy to carefully discuss the risks prior to conception.

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

Pain and dyspnea are common and are associated with adverse outcomes in CF (88). Concerns about respiratory depression, tolerance, addiction, and transplant eligibility may affect opioid prescribing for patients with 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 (89, 90). Studies in mixed pulmonary populations including COPD have similarly demonstrated no significant respiratory side effects of low-dose opioids (91, 92). 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 after one-month post-transplant (93). Consistent with other statements for palliative care in lung disease (94), appropriately-dosed opioids can be prescribed with proper education, safety monitoring, and proactive side effect management per general opioid prescription guidelines in those with ACFLD (95). Communication with transplant centers regarding opioid policies is advised.

21. 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 (92, 96), 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 (97). Consistent with other palliative care statements for lung disease (94), benzodiazepines should be considered standard of care for anxiety at the end of life in individuals with ACLFD.

22. 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.

Caregiver support in CF has been associated with fewer physical and emotional symptoms in adults with severe disease (98). Additionally, caregiver availability often factors into lung transplant eligibility based on pre-transplant support having been linked to adherence and post-transplant outcomes in general organ transplant populations (33, 99). Moreover, family members of individuals with CF face mental health challenges that may be amplified in ACFLD (100, 101). 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 illness progression and pursuit of transplantation.

23. In individuals with ACLFD, 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 (102, 103). 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. Public insurance, which typically covers individuals with limited income, is also associated with lower lung transplant referral and acceptance rates (4, 104), and increased wait list mortality (105). 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.

24. For pediatric patients with ACFLD, the CF Foundation recommends formally outlining a transition to adult care that provides flexibility in timing and coordination of transfer.

Transition programs comprising gradual preparation and coordination have been outlined in the CF literature and are associated with improved patient and family satisfaction, clinical stability during transfer, and reduced need for urgent transfer (106, 107). Overall concerns surrounding transition have been shown not to differ in ACFLD (108), but unique issues pertain to this population including involvement of more specialists and multiple concurrent transitions, psychosocial concerns, and end of life considerations. Opinion varies on whether transition should be delayed in ACFLD (109, 110). Proper coordination and flexibility are recommended with attention to patient factors and center-specific protocols (111, 112). Teenagers nearing end of life likely benefit from continuity with pediatric providers.

Conclusions

Outcomes for individuals with CF have improved substantially, and continued research and advances in therapeutics are predicted to bring further improvements in upcoming years. However, CF remains a progressive disease. ACFLD constitutes a significant portion of the adult population and carries many medical, transplant surgical, psychosocial, economic, and palliative care concerns. ACFLD thus represents an important “target” population for improving overall CF outcomes. These guidelines are intended 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 (as depicted in Figure 1). CF care teams should use these guidelines when partnering with their patients with ACFLD to determine the best treatment plan for each individual. As the CF community strives to improve outcomes, there is a need for more research specific to the challenges associated with ACFLD to further improve quality of life and survival for individuals with CF.

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