Title: Cystic Fibrosis Foundation Consensus Statements for the Care of Cystic Fibrosis Lung Transplant Recipients

Authors:

Abstract:

OBJECTIVE: Provide recommendations to the cystic fibrosis (CF) and lung transplant clinicians for the management of perioperative and clinical comorbidities of Cystic Fibrosis Lung Transplant Recipientsrelated to their underlying disease and impact of transplantation on these comorbidities.
METHODS: The CF Foundation organized a multidisciplinary committee to develop CF Lung Transplant Clincal Care Guidelines. Three workgroups were formed to develop focused questions. Following a literature search, consensus recommendations were developped by the committee members based on literature review, committee experience and iterative revisions, and in response to public comment.
RESULTS: The committee formulated 32 recommendation statements in the topics related to infectious disease, endocrine, gastroenterology, pharmacology, mental health and family planning. Broadly, the committee recommends close coordination of care between lung transplant team, the cystic fibrosis care center, and multidisciplinary specialists with experience in the care of CF and Lung Transplant Recipients.
CONCLUSIONS: These guidelines will help Lung Transplant providers care for CFTLR in order improve to post transplant outcomes in this population,

Introduction

Cystic fibrosis (CF) is the indication for lung transplantation in approximately 15% of adults and over 50% of children worldwide(1, 2). Furthermore, CF lung transplant recipients (CFLTRs) have the best survival among all pre transplant diagnostic groups after transplantation, with a 10-year adult survival after lung transplantation of 49%, and a 20-year survival of 29% (1). However, there is considerable variability in the proportion of patients transplanted for CF at different centers in the United States, and this appears to be independent of overall lung transplant center volume(3). This suggests that even at large-volume transplant centers, some clinicians may have limited experience in the management of CF- associated comorbidities such as malnutrition, gastrointestinal malabsorption, chronic sinus disease, osteoporosis, diabetes, and unique infectious risks that require CF-specific expertise. Notably, higher center transplant volume for individuals with CF, but not overall center transplant volume, was associated with

a significant survival advantage among CFLTRs independent of other factors(4). This suggests that CF-specific expertise, may improve long-term survival among CFLTRs . Thus, the goal of these consensus statements is to provide practical recommendations to lung transplant clinicians on topics important for the care of CFLTRs immediately prior to and after transplantation. These recommendations (summarized in Table 1) generally do not cover advanced lung disease management, transplant referral and post transplant topics that also pertain to the non CF populations. When applicable, existing CFF clinical care guidelines are referenced.

Methods:

The CF Foundation invited a multidisciplinary team (including adult and pediatric transplant pulmonologists, two infectious diseases (ID) physicians, a gastroenterologist, endocrinologist, after transplant coordinator, dietitian, pharmacist, psychologist, two adult CFLTRs, and the spouse of a CFLTR) to participate in the development of these consensus statements. The committee met for their first meeting on June 11, 2018 to determine the scope of the work and divide into three workgroups. The workgroups focused on: Infectious Disease, extra-pulmonary CF considerations, and psychologic and pharmacologic considerations. Informtion about the literature search and results can be found in Supplement X.The workgroups developed draft recommendations based on these results and established an *a priori* voting threshold of 80% agreement for approval of a recommendation. The committee reconvened on September 16, 2019 to iteratively revise and vote on the draft recommendation statements developed by the workgroups, and completed the voting on any statements that were not finalized at that meeting via video conference on September 27, 2019. Committee members who were unable to attend the conference were provided with a recording of the meeting to hear the discussion and voted by email.

The manuscript was reviewed by the whole committee and the individuals within the CF/family member focus group, before distribution for public comment on February 20, 2020. The committee reviewed and acknowledged and/or addressed each of the comments received during public comment. The literature searches for each workgroup were run again on XXX, for the workgroups to review and ensure no new key articles had been published.

1) The CF Foundation recommends that CF Lung Transplant Recipients follow up with a multidisciplinary CF care team within 6-12 months of transplant to resume extra-pulmonary CF care. Communication between the transplant and CF care teams is essential for coordination of care

Although no studies have examined the impact of resuming multidisciplinary CF care after lung transplantation, chronic extra-pulmonary manifestations of CF persist after transplant and require expertise in CF care (5-8). Ideally, individuals with CF would resume outpatient CF care at their referring CF care center. However, CF care may be provided at the transplant center or by the transplant team depending on local expertise with CF, clinical resources, and other logistical factors, particularly during the early post operative period. Close communication between the lung transplant team and the CF care team is essential to ensure appropriate communication with the patient and coordination of care (6, 8).

INFECTIOUS DISEASE

2) The CF Foundation recommends that CF and Transplant programs operationalize infection prevention and control policies across all services as indicated by the CF Foundation's Infection Prevention and Control Guidelines (9)

After transplant individuals with CF may continue to be at risk of acquiring or transmitting pathogens that are present in their upper respiratory tract. Pre-transplant person-to-person and equipment-based transmission with fatal outbreaks are well documented in individuals with CF, which led to the CF Foundation's Infection Prevention and Control (IPC) guidelines(9, 10) . Early epidemiologic studies confirmed the isolation of strains of pathogens after transplant that were isolated from the same individual before transplant, but person-to-person transmission after transplant has yet to be documented (10-14) . Nonetheless, the potential for person-to-person transmission after transplant, or between individuals with CF before and after transplant exists, especially if after those individuals are cared for in a shared clinical setting(15) .

Therefore, the CF Foundation recommends that all healthcare personnel caring for individuals with CF before or after transplant implement policies per CFF IPC guidelines(9) . This should be done in any area where individuals with CF receive care, including in-patient units, and out-patient areas such as clinics, rehabilitation units, pulmonary function laboratories, bronchoscopy units, and radiology suites. The recommendations include universal and contact precautions (gown, gloves and hand hygiene) for all staff when caring for individuals with CF, and the use of a mask for all individuals with CF while in clinical facilities. All individuals with CF, regardless of transplant status, should continue to follow the "six-foot rule" separating themselves from others with CF in all settings.

3) The CF Foundation recommends that non–invasive CF-specific bacterial, fungal, and AFB respiratory cultures be obtained by the transplant or CF center every 3 months in actively waitlisted transplant candidates and that clinicians review prior pathogen history to guide the peri-operative antibiotic regimen

4) The CF Foundation recommends an intraoperative CF bacterial, fungal and AFB culture of the native lung be obtained at the time of lung transplantation

5) **In CF Lung Transplant Recipients with multidrug resistant pathogens, susceptibility-driven antimicrobials should be administered when the recipient has a susceptible antibiotic choice with acceptable toxicity. In the absence of a susceptibility-driven perioperative choice, consider previously effective regimens**

Individuals with CF awaiting lung transplant may have chronic respiratory infection with bacteria, fungi, and mycobacteria, which are often multidrug resistant. While no randomized controlled trials exist to determine the optimal peri-operative antimicrobial management, retrospective studies suggest that treatment with susceptibility-targeted antimicrobials is ideal(16-22). Individuals with CF are often infected with organisms with changing sensitivity profiles, due to variation in the dominant strain(s) at the time of sampling and/or antimicrobial treatments. In addition, the number and range of organisms may vary due to overgrowth of a predominant organism limiting the ability of the microbiology laboratory to identify all organisms present.

Therefore, routine collection of sputum cultures every 3 months for those who are active on the transplant waitlist is recommended. In addition, sampling of the native lung for cultures at the time of transplantation is recommended, although the optimal sampling strategy is unclear. Published strategies include expectorated sputum prior to surgery, intra-operative bronchoalveolar lavage (BAL) prior to native lung explantation, or large airway swab and/or tissue culture of the native lung following explantation. There are no data to guide the timeframe of growth (e.g. 1 year, or several years prior to transplantation) to inform antimicrobial therapy at the time of transplantation. However, if an organism is repeatedly recovered from prior respiratory samples, targeted susceptibility-driven peri-operative antimicrobial therapy is appropriate, even if the isolate is not present on the most recent culture.

6) For CF Lung Transplant Recipients, the CF Foundation found insufficient evidence to recommend for or against routine intraoperative pleural and tracheal irrigation with antimicrobial agents to decrease infections after transplant

There are several reports of the use of topical disinfecting agents, such as taurolidine and povidone-iodine, at the time of surgery to irrigate the chest cavity and reduce bacterial load in conjunction with systemic antimicrobials to reduce the severity of respiratory infections after lung transplantation(18, 23-27). However, most studies employed pleural irrigation in conjunction with other antimicrobial management and did not specifically examine the effect of irrigation on after transplant outcomes. Two studies noted that taurolidine irrigation was associated with a reduction in short-term infections without affecting long-term survival; however, this agent is not available in many countries(27, 28). Higher quality studies comparing different agents and administration techniques are needed to determine optimal use. Although these agents have minimal adverse effects and little evidence of systemic absorption, there is insufficient evidence to provide a specific recommendation regarding their use.

7) The CF Foundation recommends consideration of perioperative and/or early posttransplant inhaled antibiotics for bacterial pathogens isolated prior to transplant as a complement to systemic antimicrobials in CF Lung Transplant Recipients

8) The CF Foundation found insufficient evidence to recommend for or against the use of inhaled antibiotics for prevention of recolonization or chronic lung allograft dysfunction (CLAD)

CFLTRs are at risk for re-infection with pathogens that which they were infected with before transplant. Susceptibility-driven antimicrobial therapy in the perioperative period is recommended, although antimicrobial regimens may be limited by toxicity. Randomized-controlled studies are lacking, but inhaled antimicrobials in conjunction with systemic therapy may provide additional benefit to reduce infections during the period of the most intensive immunosuppression early after transplant while reducing toxicity from systemic therapy(29, 30). Prevention of re-infection using inhaled antibiotics remains controversial, and the impact of re-infection may be related to specific organisms. Up to 87% of CFLTRs with pre-transplant infection with *Burkholderia* cepacia complex developed positive cultures after transplant despite aerosolized antimicrobial therapy (29). Recovery of gram-negative bacteria in

CFLTRs who were infected pre-transplant was not affected by administration of inhaled antipseudomonal antibiotics in at least two cohorts(30, 31) however, a subset of patients without pre-transplant infection receiving inhaled colistin did not develop any positive cultures after transplant(30) . No studies have examined the impact of inhaled antibiotics on the prevention of CLAD; however two retrospective studies showed no benefit of inhaled antibiotics in reducing CLAD progression (30, 31).

9) The CF Foundation found insufficient evidence to recommend for or against the routine collection of sputum for bacterial, fungal or AFB cultures in asymptomatic CF Lung Transplant Recipients

10) The CF Foundation found insufficient evidence to recommend for or against the use of antimicrobials for bacteria isolated from the airways in asymptomatic CF Lung Transplant Recipients

While there is consensus on the importance of prompt diagnosis and treatment of clinically symptomatic infections, the utility of routine cultures in individuals with chronic sputum production after transplant is less clear. Most transplant literature regarding the impact of infection after transplant were based on BAL samples from clinically indicated or surveillance bronchoscopy (SB) (32-34). Further, the long term benefit of antimicrobial therapy for asymptomatic bacterial isolates is not clear. Small studies implicated the persistent isolation *Pseudomonas aeruginosa* in airway samples after transplant with the development of CLAD, but these findings were not validated in larger, multivariate analyses (35, 36). Retrospective studies that examined the incidence of *Pseudomonas aeruginosa* re-isolation and CLAD progression stratified by treatment with aerosolized anti-pseudomonals did not find an association between treatment and CLAD progression among CFLTRs (30, 31). Similarly, a single-center study of antibiotic treatment of *Stenotrophomonas* in asymptomatic CFLTRs showed no impact on microbial clearance or after transplant lung function (37) .

The pathogenicity of bacteria in asymptomatic individuals after transplant is unclear, but emerging data suggest that isolation of strain-specific pathogens present prior to transplant may not confer the same risk of CLAD in CFLTRs as the isolation of new strains, even within the same species(37, 38). However, no studies specifically examined whether antimicrobial therapy in asymptomatic CFLTRs directed against de novo versus pre-transplant isolates confers protection from acute pneumonia and/or CLAD. Thus, no specific management recommendation regarding the use of antimicrobials for asymptomatic bacterial airway isolates can be made.

11) In individuals with CF and asymptomatic chronic rhinosinusitis (CRS), the CF Foundation recommends against pre-transplant prophylactic sinus surgery for the prevention of lung graft colonization

12) The CF Foundation recommends screening CF Lung Transplant Recipients for symptoms of CRS annually

13) The CF Foundation recommends that CF Lung Transplant Recipients with moderate or severe symptomatic CRS be seen in consultation with an otolaryngologist experienced in CF for consideration of optimal topical therapies and endoscopic sinus surgery

14) The CF Foundation recommends that CF Lung Transplant Recipients who have had multiple bacterial allograft infections be seen in consultation with an otolaryngologist with CF expertise regardless of their CRS symptoms

CRS is seen in the majority of CFLTRs(39). Although evidence is sparse, screening tools, such as the Sino-Nasal Outcome Test-22 (SNOT-22), discriminated symptomatic CRS from asymptomatic CRS, while radiologic imaging was less sensitive(40-42). Observational studies assessing the utility of immediate pre-transplant or after transplant sinus surgery on CFTLRs regardless of symptoms, found no substantive impact on after transplant outcomes including the risk of CLAD, graft re-infection, or survival (39, 43-48). Evidence for the impact of sinus surgery on the reduction in microbial isolates from BAL in asymptomatic CFLTRs is mixed, with some studies reporting decreases and others reporting no change,(39, 44, 46).

CFLTRs with symptomatic CRS had sinus cultures that strongly correlated with BAL cultures, particularly for *Pseudomonas aeruginosa*, MRSA, and *Burkholderia cepacia* complex(11, 39, 46, 49). One investigation observed similar gene expression profiles in *Pseudomonas aeruginosa* strains between both compartments, suggesting bidirectional movement (49). For those with symptomatic CRS, endoscopic sinus surgery after lung transplantation resulted in fewer positive bacterial isolates from the allograft, fewer infections, and less antibiotic utilization in single center observational studies(43, 45, 47, 50-55).
Small pilot randomized-controlled trials and systematic reviews have reported improved quality of life (QOL) and decreases in SNOT-22 scores in patients with CF and CRS with the use of topical nasal dornase, steroids, antimicrobials, isotonic and hypertonic saline , with no available data on these therapies in patients after lung transplant(54, 56-60). One small study examined the impact of an effective CFTR modulator, ivacaftor, on CRS and reported a clinically insignificant decrease in SNOT-22 scores and improved QOL(61). Since appropriate sinus treatment could potentially decrease allograft infection in

CFLTRs, consultation with an otolaryngologist with CF expertise to determine the most appropriate individividualized therapeutic options in CFLTRs with symptomatic CRS is recommended.

EXTRA-PULMONARY CF CONSIDERATIONS

15) For CF Lung Transplant Recipients, the CF Foundation recommends ongoing consultation with a dietitian with CF expertise, in order to receive individualized nutritional therapy to achieve an established BMI or weight-for-length goal

16) In CF Lung Transplant Recipients, the CF Foundation recommends discontinuation of "CF–specific vitamin supplementation" (combination vitamin A, D, E, K) after lung transplantation, measuring fat-soluble vitamin levels by 3 months after transplant, and individually repleting as needed

Approximately 90% of individuals with CF have pancreatic insufficiency (PI) and experience malabsorption despite pancreatic enzyme replacement therapy (PERT)(62). Immediately after lung transplant, CF-related metabolic and gastrointestinal comorbidities and complications impact nutrition in CFLTRs(63, 64). Predictive equations often underestimate energy needs in both the pre and immediate post-lung transplant periods with needs ranging from 110-200% compared to individuals without CF(65). Energy needs gradually decline after lung transplant due to decreased energy expenditure from reduced pulmonary demands and improved appetite (63, 66). Nutritional status and body weight typically improve after transplant in CFLTRs, with the most significant weight gains seen in those previously malnourished (67, 68). In CFLTRs, achieving goal body mass index (BMI) at 1 year after transplant was associated with improved survival and freedom from CLAD (69, 70). Given fluctuating energy needs, long-term individualized consultation by a CF dietitian after transplant to avoid malnutrition or obesity is recommended (65, 71-73).

Monitoring of fat-soluble vitamins should continue in CFLTRs after transplant (62, 74). In addition to well known effects on bone health, single-center investigations have demonstrated an association between vitamin D deficiency and acute cellular rejection, but the effect of vitamin D replacement in attenuating this risk is unproven (75-77).The development of hypervitaminosis in both vitamins A and E were observed in CF and non-CF lung transplant recipients, making CF-specific vitamin supplementation not empirically recommended after transplant (78-80). Instead, monitoring CFLTRs for the deficiency of fat soluble vitamins at 3 months after transplant, and at least annually in order to replete any individual observed deficiency is recommended(62).

17) The CF Foundation recommends daily symptom assessment for early signs of obstipation and obstruction that might herald emergence of distal intestinal obstruction syndrome (DIOS), particularly within the immediate post-operative period and with any narcotic medication administration

18) In CF Lung Transplant Recipients who develop DIOS, the CF Foundation recommends consideration of enteral lavage. Refractory DIOS should be managed in coordination with experts in CF gastrointestinal complications to reduce risk for prolonged obstruction and potential need for operative management

DIOS is a common complication in CFLTRs, with up to 20% higher prevalence in those with a history of meconium ileus or abdominal surgery (81-83). As DIOS occurring in the immediate post-operative period carries significant morbidity,(82, 84, 85) medical measures to reduce its incidence should be optimized and aggressively pursued when possible immediately before and after transplant.

Single-center experiences suggest that pre-operative bowel lavage with osmotic laxative may reduce the development of DIOS in the immediate post-operative period(81, 86). Immediately after transplant, proactive management including early enteral feeding, resumption of Pancreatic Enzyme Replacement Therapy, ambulation, minimization of medications that impair bowel motility, and adequate fluid and electrolyte repletion may help reduce the development of DIOS (81, 86-88). Some centers additionally employ post-operative nasogastric/gastric/enteric tube infusion of intestinal lavage solution such as polyethylene glycol (PEG) as limited data suggest a potential decrease in DIOS prevalence (81, 86).

If DIOS develops, early diagnosis and treatment is critical. History, exam, and imaging findings are important to diagnose DIOS and exclude other pathologies, such as gastrointestinal malignancies or infections (82, 87-89). There is no evidence-based optimal regimen to treat DIOS, particularly in the aftertransplant setting. Outcomes using intestinal lavage formulations such as PEG-based therapy or water-soluble iodinated radiopaque contrast (diatrizoate meglumine and diatrizoate sodium solution, *Gastrografin*) (via oral, nasogastric/enteric infusion, or enema), often in combination with adjunct therapies such as stimulant laxatives, prokinetics, enteral feeding, PERT, intestinal secretagogues, and/or oral mucolytics are largely similar (87, 88, 90-92). For refractory DIOS, surgical intervention may consist of adhesiolysis, milking of inspissated stool contents into the colon or via enterotomy, or intestinal resection with or without end-stomal diversion (82, 83).

19) For CF Lung Transplant Recipients who experience new or worsening symptoms of gastrointestinal dysmotility, the CF Foundation recommends consultation with a gastroenterologist and a dietitian with CF expertise to guide the approach to symptom control and potential interventions

Lung transplantation in CF is often associated with delayed solid and liquid phase gastric emptying by gastric emptying scintigraphy (GES), though not all patients with delayed gastric emptying (DGE) are symptomatic (93-96). In the absence of clear evidence-based practices with clinically-meaningful outcomes, GES should primarily be performed to either evaluate symptoms, or when there is concern for gastrointestinal complications of lung transplant including CLAD, symptomatic reflux, or concerns for upper intestinal dysmotility (93, 94). There are no validated strategies to guide optimal medical management, such as prokinetic medications or enteral feeding supplementation in CFLTRs; however many of the recommendations for enteral feeding in individuals with cystic fibrosis may apply after transplant (97). Use of endoscopic or surgical gastrostomy, gastrojejunostomy, or jejunostomy feeding tube placement should be individualized utilizing a multidisciplinary approach (64, 95, 97). Surgical management for severe symptomatic DGE should be reserved for highly-selected patients (94-96). It remains unclear if proactive treatment of DGE improves clinically-meaningful outcomes of GERD or CLAD, and further studies are needed.

20) The CF Foundation recommends that CF Lung Transplant Recipients have liver enzyme monitoring for CF Liver Disease (CFLD) at least annually, and when elevated, non-invasive imaging techniques for initial evaluation

The natural history of CFLD progression after transplant is not well-defined and additional research is needed(98). Ursodiol remains a mainstay of treatment for CFLD, though its efficacy and long-term impact on disease progression are unclear. Data suggest improvement in aminotransferases, bile composition and flow, and liver stiffness in CFLD that may warrant continuing use of ursodiol after transplant (99-101). Abdominal ultrasound is typically the most widely-available and affordable non-invasive imaging modality for monitoring CFLD and should be performed annually in patients with known or suspected CFLD (102, 103). Less-invasive liver metrics and liver stiffness measurement via transient elastography, may help avoid liver biopsy in CFLD, but additional investigation is needed (104-109). CFLTRs with abnormal imaging or persistent lab abnormalities, should be referred to a hepatologist for further evaluation.

21) In CF Lung Transplant Recipients who do not have Cystic Fibrosis-Related Diabetes (CFRD) and are not on insulin, the CF Foundation recommends screening with an oral glucose tolerance test (OGTT) at 3-6 months after transplant, then annually following the recommended screening guidelines for CFRD (110)

After transplant, diabetes mellitus is common, with up to 80% of cases diagnosed within 6 months post-transplant (111-116). Current guidelines for CFRD recommend that glucose should be monitored closely after surgery, and that individuals without a diagnosis of diabetes be screened annually with an OGTT (110). Glycosylated hemoglobin (A1C) is not recommended for screening individuals with CF as this may not differ significantly between those with and those without CFRD (117-121) and thus lacks sensitivity. Since the majority of CFLTRs without pre-existing CFRD develop CFRD in the first 6 months after transplant, screening at 3-6 months is recommended, once the glucocorticoid dose is stable(112, 114, 122) . CFLTRs who screen positive for CFRD by OGTT should undergo confirmatory testing, according to current clinical care guidelines(110).

22) For CF Lung Transplant Recipients who have CFRD, the CF Foundation recommends treatment with insulin, continued intensive self-blood glucose monitoring (SBGM), and individualized close clinical follow-up, in addition to lifestyle modifications. Furthermore, the CF Foundation recommends consultation with an endocrinologist with CF and transplant associated DM expertise, when possible

The prevalence of CFRD increases with age and after transplant (112, 116, 122). Some studies suggest that pre-transplant CFRD is associated with complications and increased mortality after transplant, although the data are inconsistent(113, 123-125). However, perioperative glycemic control correlates with survival, and post-operative hyperglycemia should be treated promptly (126, 127) .

After transplant, glycemic management in CFLTRs is complicated by inconsistent appetite, glucocorticoids, and fluctuating renal function(116). Those with CFRD are insulin-deficient, thus insulin is the only approved therapy for this population. Insulin use pre-transplant is associated with improved weight/BMI, lung function with decreased frequency of hospitalizations as well as mortality (110, 121, 128-130). In this population, to aid with multiple daily insulin dosing for high carbohydrate meals and snacks, insulin pump use is associated with improved glycemic control, body weight, hemoglobin A1C, lean body mass, reduced protein catabolism and hepatic glucose production(131). Data on long-term safety of noninsulin

agents in CFRD are limited and toxicity has been reported; therefore, these should not be used routinely (110, 121, 128, 132-137) .

Close SBGM is necessary post-transplant as insulin requirements will change (138). In pre-transplant individuals with CFRD, use of continuous glucose monitoring to guide insulin titration is associated with improved lung function, weight, and annual rate of pulmonary function decline, and may improve glucose monitoring after transplant (139)

23) For CF Lung Transplant Recipients, the CF Foundation recommends that bone density be assessed with dual energy X-ray absorptiometry (DEXA) at 6-12 months after transplant

Individuals with end-stage lung disease have more severe osteoporosis compared to other solid organ recipients (140-142). Osteoporosis is prevalent in individuals with CF, and bone loss can be significant in the first 6-12 months after transplant, increasing the risk of fractures, compromising lung function and QOL (74, 140, 143) . Fracture is the presenting manifestation of osteoporosis in up to 20% of CFLTRs (141, 144-147) . Factors that affect bone health in CFLTRs include vitamins D and K malabsorption, pancreatic exocrine insufficiency, CFRD, hypogonadism, failure to achieve peak bone mass, decreased mobility, low BMI, inflammation, cyclosporine use, and cumulative glucocorticoid exposure (74, 140). Screening for osteoporosis should be performed with a DEXA in the first 6-12 months post-lung transplant when bone loss can be most pronounced, and then at follow-up intervals dependent on the severity of bone disease (148).

PSYCHOLOGIC AND PHARMACOLOGIC CONSIDERATIONS

24) The CF Foundation recommends that CF Lung Transplant Recipients have mental health screening and consultation for depression, anxiety, and post-traumatic stress disorder (PTSD) within 6 months of transplant, then resume annual screening per the International Committee on Mental Health Depression and Anxiety Guidelines(149)

Lung transplant recipients are at increased risk of mental health symptoms, and those who develop depression or PTSD early after transplant are at increased risk of medical non-adherence, morbidity, rejection, and death (150-155) . Anxiety after transplant can lead to emotional distress and decreased QOL (152, 156, 157). Therefore, mental health screening for depression, anxiety, and PTSD is recommended within 6 months of transplant. Suggested screening tools are provided in Table Y. Appropriately trained healthcare providers (e.g., Transplant or CF mental health coordinators) should

perform screening, and individuals with positive screens should be referred to a mental health provider for further assessment and intervention.

Table Y. Suggested screening measures for depression, anxiety, and PTSD

Domain	Measure	# items	Age Range (years)	Positive Score
Depression	*Patient Health Questionnaire-9 or 8* (PHQ-9, or 8, for use with caregivers) or PHQ-2 (Recommended in the ICMH Depression and Anxiety Guidelines)	9, 8, or 2	12+	≥5
Anxiety	*Generalized Anxiety Disorder-7* (GAD-7) or GAD-2 (Recommended in the ICMH Depression and Anxiety Guidelines)	7 or 2	12+	≥5
PTSD	*Child and Adolescent Trauma Screen* (CATS) - caregiver report	20	3-6	≥15
	Child and Adolescent Trauma Screen (CATS) (Sachser, J Affective Disorders, 2010) available from: https://depts.washington.edu/hcsats/PDF/TF-%20CBT/pages/assessment.html	20	7-17	≥15
	Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)[a] (Prins, 2015) available from: https://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp	5	18+	≥3
	PTSD Checklist for DSM-5 Version (PCL-5)[a] (Weathers, 2013) available from: https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp	20	18+	≥31

Notes: All measures are freely available in both English and Spanish. See reference section for information on obtaining these measures. For pediatric PTSD screening, many other screeners may be available and are acceptable for use; this screener was chosen as an example as it is freely available, provides caregiver report for ages 3-6, in addition to caregiver and child self-report for age 7-17, and is available in Spanish.

[a] Based on staffing and resources, for adult lung recipients either measure (PC-PTSD-5 or PCL-5) may be used.

25) The CF Foundation recommends screening caregivers of CF Lung Transplant Recipients for depression, anxiety, and PTSD within 6 months of transplant and referral for further assessment if necessary

Primary caregivers of pediatric and adult CFLTRs are at increased risk for mental health symptoms, which can affect CFLTRs outcomes. Caregivers may experience increased stress, mental health symptoms, and PTSD after transplant (158, 159) , which may be associated with adherence concerns and a negative impact on the health for CFLTRs (159, 160)). Screening primary caregivers of pediatric and adult CFLTRs for depression, anxiety, and PTSD within 6 months of transplant is recommended. Suggested screens are presented in Table Y. ICMH guidelines for screening for depression and anxiety in caregivers of pediatric recipients should be followed. Transplant or CF providers should provide this recommendation to caregivers of adult recipients as part of social support assessment, but referral to the caregivers' primary health care team or mental health provider may be necessary to implement this screening, and any appropriate therapies. Caregivers with elevated scores should be referred for evaluation and treatment to a primary care or mental health provider.

26) The CF Foundation recommends that females with CF who are post-lung transplant and are considering pregnancy carefully assess their individual risks through shared decision making with maternal fetal medicine and transplant providers

27) The CF Foundation recommends that females with CF who are post-lung transplant avoid pregnancy for at least the first 2 years after transplantation because of the increased risk of acute rejection, accelerated chronic rejection, and death

Individuals with CF are capable of conception, carrying pregnancies to term, and giving birth, but there are increased risks associated with pregnancy, particularly after transplant (Table X). Pregnancy is contraindicated in lung transplant recipients with an unstable clinical course (161, 162). The decision to become pregnant should be made cautiously with close collaboration with a maternal fetal medicine specialist, a genetic counselor, and transplant providers. Providers should discuss the risks associated with pregnancy (Table X) with women and their partners before conception (161) and provide counseling and appropriate contraception to avoid unplanned pregnancies (162).Successful pregnancies have typically occurred late after lung transplantation (161, 163). It is recommended that CFLTRs wait at least 2 years after transplantation before attempting to become pregnant. This approach allows: (1) a careful assessment of graft function and risk of developing CLAD, (2) a lower risk of acute rejection, (3) a lower intensity of immunosuppression, and (4) optimization of comorbidities (164-166). Reporting of pregnancy outcomes to the Transplant Pregnancy Registry International (https://www.transplantpregnancyregistry.org/about-us/) is encouraged to improve research on pregnancy in individuals with CF who are post lung transplant.

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410 Table X. Risks associated with pregnancy after lung transplantation.

Domain	Specific considerations to discuss with patients
Need for contraception	High rates of unplanned pregnancies in lung/heart-lung transplant recipients (up to 41%) (161) Some medications (e.g., Mycophenolate Mofetil) are teratogenic, necessitating discontinuation prior to conception to avoid fetal exposure (162)
Genetic risk of CF	Genetic counseling to discuss risk of transmission of CF to a child
Fertility challenges	Increased likelihood of need for medically assisted treatment for conception (21% in one study)(162)
Termination of pregnancy	Increased risk for spontaneous and therapeutic abortions (25%, and 17% respectively (163, 164, 166)
Maternal morbidity	Increased risk of comorbidities: hypertension (76%), infections (33%), diabetes (33%), preeclampsia (5%), rejection (24%) , and graft loss (14%) (163)
Maternal mortality	Maternal mortality after pregnancy is up to 33% (163, 167) Female lung recipients may not live to see their children reach maturity given current survival rates (163).
Fetal risks	Live births among female lung recipients have increased risk of intrauterine growth restriction, prematurity, and low birthweight compared to other solid-organ transplant recipients (166, 167) Mean birthweight is lower for babies born to mothers with CF than other lung transplant groups (1980g and 2349g, respectively)(163) Higher incidence of preterm birth among babies born to mothers with CF (71% and 54%, respectively)(163) Other complications may be present, and there is a risk of death for neonates (163)

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412 **PHARMACOLOGY and THERAPEUTICS**

28) The CF Foundation found insufficient evidence to recommend for or against the use of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators for CF Lung Transplant Recipients

There may be unique scenarios where the use of CFTR modulators after lung transplantation is beneficial, but there have been no clinical trials examining the role of CFTR modulators in this setting. Additionally, CFTR modulators are cytochrome P450/3A4 inducers, and interact with calcineurin inhibitors thereby decreasing their blood levels. Furthermore, CFTR modulators are substrates of CYP3A, and co-administration with strong CYP3A inhibitors such as azole antifungals significantly increases CFTR modulator exposure. Nevertheless, use of CFTR modulators after other solid organ transplants (e.g., liver) for pulmonary indications has been reported and highlights the practical management of potential drug-drug interactions (168, 169) .

29) The CF Foundation found insufficient evidence to recommend for or against the use of induction immunosuppression for CF Lung Transplant Recipients

There is no evidence that induction immunosuppression is associated with a higher risk of infection or other adverse events in CFLTRs (170-172). Furthermore, retrospective analyses suggest that induction immunosuppression may be associated with a survival benefit among CFLTRs (170) (Kirby, J Cyst Fibros, 2015). Randomized controlled trials have not consistently demonstrated better outcomes with induction immunosuppression although these studies have not stratified recipients by underlying diagnosis(173).

30) The CF Foundation recommends that CF Lung Transplant Recipients have close monitoring of calcineurin inhibitor drug levels because of altered pharmacokinetics

CFLTRs have altered pharmacokinetics with several immunosuppressive medications. This is especially true with cyclosporine, where absorption may be erratic. The microemulsion cyclosporine formulation was designed to have better absorption, although relative bioavailability in individuals with CF is more than half of the relative bioavailability observed in those without CF (174-177). Similarly, tacrolimus requires higher dosing to maintain similar levels in individuals with CF compared to those without CF (178, 179). This is also true with the once a day formulation of tacrolimus(180). CFLTRs require higher doses of mycophenolate mofetil (MMF) to achieve therapeutic levels (181, 182)and have reduced absorption and clearance of mycophenolate and its metabolite, mycophenolate glucuronide (183, 184). Although data are limited, rapamycin pharmacokinetics appear to be similar in individuals with CF as those without

CF (185). CFLTRs have variable azole plasma concentrations, and azoles modify cytochrome P450s resulting in reduced clearance of calcineurin inhibitors; therefore, careful therapeutic drug monitoring is recommended to optimize efficacy and minimize toxicity (186-188).

31) Reduced renal function is common in CF Lung Transplant Recipients, and serum creatinine is often a poor surrogate for renal function. Therefore, the CF Foundation recommends medication dosing appropriate for glomerular filtration rate (GFR), and when available, the use of therapeutic drug monitoring

Many individuals with CF have chronic inflammation, a hypermetabolic state and low BMI; as such creatinine-based calculations for GFR may not be accurate and often overestimate renal function. Therefore, therapeutic drug monitoring should be performed for medications in which clearance is based on renal function such as aminoglycosides. Renal function and pharmacokinetics (PK) of aminoglycosides may vary before and after transplant, and PK parameters should be assessed during each treatment course after transplant. Two studies evaluated PK of tobramycin before and after transplant and found that they are significantly altered following transplantation although no clear trend was apparent because of inter-patient variability (189, 190). CFLTRs were found to have variable azole plasma concentrations, thus therapeutic drug monitoring should be utilized (186).

32) The CF Foundation found insufficient evidence to recommend for or against the routine use of airway clearance, dornase alfa, or hypertonic saline among CF Lung Transplant Recipients

Previous guidelines for the management of CFLTRs recommended the routine use of airway clearance (8); however, there is no evidence to support this recommendation. Randomized controlled trials demonstrated no benefit with the use of dornase alpha during lower respiratory tract infection or the routine use of airway clearance after lung transplantation(191, 192) . These studies included individuals who did not have CF, and it is possible that there may be a role for select airway clearance strategies in specific situations after lung transplantation in individuals who have CF.

No Consensus

The committee could not reach a consensus regarding the routine use of azithromycin in individuals with CF in the immediate period after lung transplantation to decrease the risk of CLAD.

In a double-blind randomized controlled trial of lung transplant recipients with bronchiolitis obliterans syndrome (BOS), treatment with azithromycin resulted in better lung function than placebo (193). In another randomized controlled trial, treatment with azithromycin early after transplantation reduced the risk of BOS (194). However, the committee had concerns about applying results from these studies to individuals with CF because they were underrepresented in these relatively small studies, and it is not clear that they would derive the same benefit.

Conclusions

Despite improvement in the overall outcomes of individuals with CF with the availability of new agents that address the cellular defect in CF, lung transplantation remains an important therapy in the spectrum of advanced CF lung disease. However, the success of transplantation is limited by chronic lung allograft dysfunction and extra pulmonary comorbidities. In particular, providers caring for CFLTRs need to not only recognize comorbidities related to transplant, but additionally recognize and manage CF-specific comorbidities and the impact of after transplant therapies on these conditions. These guidelines are intended to help lung transplant providers identify and manage important conditions frequently encountered by CFLTRs. While the evidence for some of the recommendations is limited in scope and quality, the vast majority of recommendations were made with high degree of consensus and an acknowledgement of the limitations of published literature when appropriate. At the core of these recommendations is a necessary long term partnership between multidisciplinary transplant teams, CF care teams, discipline specific specialty experts, and individuals with CF to optimize outcomes for CFLTRs. Futher, these recommendations highlight a critical need for ongoing research in lung transplantation of individuals CF to better determine optimal care of this unique population.

Table 1. Summary of Consensus Recommendations for the care of Cystic Fibrosis Lung Transplant Recipients

GENERAL CARE		% vote
1	The CF Foundation recommends that CF Lung Transplant Recipients follow up with a multidisciplinary CF care team within 6-12 months of transplant to resume extra-pulmonary CF care. Communication between the transplant and CF care teams is essential for coordination of care	100%
2	The CF Foundation recommends that CF and Transplant programs operationalize infection prevention and control policies across all services as indicated by the CF Foundation's Infection Prevention and Control Guidelines(9)	95%
INFECTIOUS DISEASE		
3	The CF Foundation recommends that non–invasive CF-specific bacterial, fungal, and AFB respiratory cultures be obtained by the transplant or CF center every 3 months actively waitlisted transplant candidates and that clinicians review prior pathogen history to guide the peri-operative antibiotic regimen	100%
4	The CF Foundation recommends an intraoperative CF bacterial, fungal and AFB culture of the native lung be obtained at the time of lung transplantation	100%
5	In CF Lung Transplant Recipients with multidrug resistant pathogens, susceptibility-driven antimicrobials should be administered when the recipient has a susceptible antibiotic choice with acceptable toxicity. In the absence of a susceptibility-driven perioperative choice, consider previously effective regimens	100%
6	For CF Lung Transplant Recipients, the CF Foundation found insufficient evidence to recommend for or against routine intraoperative pleural and tracheal irrigation with antimicrobial agents to decrease infections after transplant	100%
7	The CF Foundation recommends consideration of perioperative and/or early posttransplant inhaled antibiotics for bacterial pathogens isolated prior to transplant as a complement to systemic antimicrobials in Cystic Fibrosis Lung Transplant Recipients	100%
8	The CF Foundation found insufficient evidence to recommend for or against the use of inhaled antibiotics for prevention of recolonization or chronic lung allograft dysfunction (CLAD)	100%

9	The CF Foundation found insufficient evidence to recommend for or against the routine collection of sputum for bacterial, fungal or AFB cultures in asymptomatic CF Lung Transplant Recipients	100%
10	The CF Foundation found insufficient evidence to recommend for or against the use of antimicrobials for bacteria isolated from the airways in asymptomatic CF Lung Transplant Recipients	95%
	SINUS DISEASE	
11	In individuals with CF and asymptomatic chronic rhinosinusitis (CRS), the CF Foundation recommends against pre-transplant prophylactic sinus surgery for the prevention of lung graft colonization	100%
12	The CF Foundation recommends screening CF Lung Transplant Recipients for symptoms of chronic rhinosinusitis (CRS) annually	100%
13	The CF Foundation recommends that CF Lung Transplant Recipients with moderate or severe symptomatic CRS be seen in consultation with an otolaryngologist experienced in CF for consideration of optimal topical therapies and endoscopic sinus surgery	100%
14	The CF Foundation recommends that CF Lung Transplant Recipients who have had multiple bacterial allograft infections be seen in consultation with an otolaryngologist with CF expertise regardless of their CRS symptoms	100%
NUTRITION and GASTROINTESTINAL COMPLICATIONS		
15	For CF Lung Transplant Recipients, the CF Foundation recommends ongoing consultation with a dietitian with CF expertise, in order to receive individualized nutritional therapy to achieve an established BMI or weight-for-length goal	100%
16	For CF Lung Transplant Recipients the CF Foundation recommends discontinuation of "CF - specific vitamin supplementation" (combination vitamin A, D, E, K) after lung transplantation, measuring fat-soluble vitamin levels by 3 months after transplant, and individually repleting as needed	100%
17	The CF Foundation recommends daily symptom assessment for early signs of obstipation and obstruction that might herald emergence of distal intestinal obstruction syndrome (DIOS), particularly within the immediate post-operative period and with any narcotic medication administration	100%

18	In CF Lung Transplant Recipients who develop DIOS, the CF Foundation recommends consideration of enteral lavage. Refractory DIOS should be managed in coordination with experts in CF gastrointestinal complications to reduce risk for prolonged obstruction and potential need for operative management	100%
19	For CF Lung Transplant Recipients who experience new or worsening symptoms of gastrointestinal dysmotility, the CF Foundation recommends consultation with a gastroenterologist and a dietitian with CF expertise to guide the approach to symptom control and potential interventions	100%
20	The CF Foundation recommends that CF Lung Transplant Recipients have liver enzyme monitoring for CF Liver Disease (CFLD) at least annually, and when elevated, non-invasive imaging techniques for initial evaluation	
DIABETES and BONE HEALTH		
21	In CF Lung Transplant Recipients who do not have Cystic Fibrosis Related Diabetes (CFRD) and are not on insulin, the CF Foundation recommends screening with an oral glucose tolerance test (OGTT) at 3-6 months after transplant, then annually following the recommended screening guidelines for CFRD (110)	95%
22	For CF Lung Transplant Recipients who have CFRD, the CF Foundation recommends treatment with insulin, continued intensive self-blood glucose monitoring (SBGM), and individualized close clinical follow-up, in addition to lifestyle modifications. Furthermore, the CF Foundation recommends consultation with an endocrinologist with CF and transplant associated DM expertise, when possible	
23	For CF Lung Transplant Recipients, the CF Foundation recommends that bone density be assessed with dual energy X-ray absorptiometry (DEXA) at 6-12 months after transplant	100%
MENTAL HEALTH and FAMILY PLANNING		
24	The CF Foundation recommends that CF Lung Transplant Recipients have mental health screening and consultation for depression, anxiety, and post-traumatic stress disorder (PTSD) within 6 months of transplant, then resume annual screening per the International Committee on Mental Health Depression and Anxiety Guidelines(149)	100%

25	The CF Foundation recommends screening caregivers of CF Lung Transplant Recipients for depression, anxiety, and PTSD within 6 months of transplant and referral for further assessment if necessary	90%
26	The CF Foundation recommends that females with CF who are post-lung transplant and are considering pregnancy carefully assess their individual risks through shared decision making with maternal fetal medicine and transplant providers	100%
27	The CF Foundation recommends that females with CF who are post-lung transplant avoid pregnancy for at least the first 2 years after transplantation because of the increased risk of acute rejection, accelerated chronic rejection, and death	100%
PHARMACOLOGY and THERAPEUTICS		
28	The CF Foundation found insufficient evidence to recommend for or against the use of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators for CF Lung Transplant Recipients	100%
29	The CF Foundation found insufficient evidence to recommend for or against the use of induction immunosuppression for CF Lung Transplant Recipients	100%
30	The CF Foundation recommends that CF Lung Transplant Recipients have close monitoring of calcineurin inhibitor drug levels because of altered pharmacokinetics	100%
31	Reduced renal function is common in CF Lung Transplant Recipients, and serum creatinine is often a poor surrogate for renal function. Therefore, the CF Foundation recommends medication dosing appropriate for glomerular filtration rate (GFR), and when available, the use of therapeutic drug monitoring	100%
32	The CF Foundation found insufficient evidence to recommend for or against the routine use of airway clearance, dornase alfa, or hypertonic saline after transplantation among CF Lung Transplant Recipients	100%

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498 Topics reviewed where no consensus was reached:

PICO	Statement	voting

Should azithromycin be resumed shortly after lung transplant in patients with CF?	The Committee could not reach a consensus regarding the routine use of azithromycin in individuals with CF in the immediate period after lung transplantation to decrease the risk of CLAD.	10 – for 9 - against

Committee:

Pali Shah (Co-Chair)
Ramsey Hachem (Co-Chair)
Josh Diamond
Gary Visner
Erika Lease
Erin Lowery
Cecilia Chaparro
Fanny Vlahos
Lara Danziger Isakov
Maggie Carroll
James Abraham
Jessica Leonard
Marina Litvin
Zubin Bhakata
Lillian Christon
Chelsey Werchan
Ray Poole
Joe Pilewski
Erin Tallarico
Albert Faro
Sarah Hempstead

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