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 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