Young Cystic Fibrosis Lung Transplant Recipients: Predisposing Factors for End-stage Disease

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Abstract

Background: The largest age group among children and adolescents referred for lung transplantation for cystic fibrosis (CF) have been those who in the pubertal or post pubertal age range. However, over 100 younger patients with CF have undergone lung transplantation over the last three decades in the USA. Methods: We performed a retrospective review of our experience with 18 children with CF who underwent lung transplantation in our center before the age of 11 years. Results: Notable findings were a high prevalence of methicillin-resistant Staphylococcus aureus, a high prevalence of diabetes mellitus and an impressive prevalence of consolidated lobar or whole lung disease. Post-transplant outcomes, however, were comparable to those older than 10 years of age in our center. Conclusions: In an era of increasingly effective medications modifying the natural history of CF, identification of risk factors for early severe lung disease in CF remains relevant and potentially more important for effective intervention in order to extend life.

Youngest Cystic Fibrosis Lung Transplant Recipients: Predisposing Factors for End-stage Disease

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Abbreviations: CF = cystic fibrosis

CFTR = cystic fibrosis transmembrane receptor

MRSA = methicillin-resistant *Staphylococcus aureus* CFRD = cystic fibrosis related diabetes mellitus ECMO = extracorporeal membrane oxygenation BOS = bronchiolitis obliterans syndrome

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Conclusions : In an era of increasingly effective medications modifying the natural history of CF, identification of risk factors for early severe lung disease in CF remains relevant and potentially more important for effective intervention in order to extend life.

Advances in the care of individuals with cystic fibrosis (CF) have led to a progressive improvement in median survival around the world in developed countries.[1-3] Death due to CF advanced lung disease in childhood is becoming increasingly uncommon, especially in the earliest decades of life. The factors contributing to this phenomenon include the introduction of newborn screening for CF in many countries,[4,5] advances in nutritional support[6] and the institution of aggressive protocols to prevent and treat pulmonary infections.[7] An even greater change in the trajectory of the natural history of cystic fibrosis lung disease is expected from the most recent formulation of cystic fibrosis transmembrane receptor (CFTR) modulators.[8] Consequently, lung transplantation for children and adolescents with CF will likely become increasingly less common in the coming years with the earliest trend recently noted (Table). Nevertheless, we performed a retrospective review of our experience in a large pediatric lung transplant center with children 10 years of age or younger who underwent transplantation in our center since its inception in 2002 to discern factors that appeared to predispose to progression of lung disease to end-stage in the youngest CF patients.

[Insert Table at this point in the manuscript] MATERIALS AND METHODS: A retrospective review of all patients undergoing primary lung transplant in our center was performed identifying individuals with a primary diagnosis of cystic fibrosis from 2002 through 2020. Clinical data was collected and certain comparisons were made between the younger cohort (10 years of age and younger) and the older cohort ([?]11 years). Follow-up information on outcome after lung transplantation was also obtained from the medical record and the cohorts were compared for survival. For the comparison of survival after lung transplantation between age cohorts, we used the Wilcoxon log-rank method of comparison of survival times (SAS v9.4) in Figure 2. RESULTS: Since 2002, over 220 infants, children, adolescents and young adults have undergone lung transplantation in our center through December 2020. Of the total, 122 patients (55%) had underlying CF; 18 of these (14%) were 10 years of age or younger at transplant. Among the older cohort, five individuals underwent liver-lung and one each heart-lung and one heart-liver-lung transplant; none in the younger cohort had multiple organ transplants. We did not exclude these individuals from our comparative analysis. Eighteen children with CF aged 4.2 to 10.9 (median = 8.1) years of age underwent primary bilateral lung transplantation in our center. Eight were female and ten were male. Eleven were residents of Texas at the time of referral, five were from other states and two were from outside the United States, one from the United Arab Emirates and the other from Pakistan. Seven had Hispanic ethnicity in at least one parent, one was African American, nine were Caucasian, one Middle Eastern and one South Asian in background. Of US citizens, all but four had public insurance as primary healthcare insurance. Six of the children lived in single parent households. Two others were in the primary care of their grandparents due to cessation of parental involvement. Ten lived in two parent households. Four of the US children had CF care in a satellite CF Center where continuity of care was not clearly consistent. The two children from outside the USA did not receive regular hospitalizations for advanced lung disease.

Clinical characteristics reveal a morbid patient population. Four of the patients were hospitalized for chronic respiratory failure at the time of transplantation, all on non-invasive ventilation. Three others were using non-invasive ventilation via bi-level positive pressure devices at home at night only prior to transplantation. Four others were out-patients on oxygen supplementation at the time of transplantation. Microbiology

among these patients included 10 (55%) of 18 with methicillin-resistant *Staphylococcus aureus* (MRSA), six with*Pseudomonas aeruginosa* , three with *Stenotrophomonas maltophilia* , two with *Achromobacter xylosoxidans* , two with non-tuberculous mycobacteria (*Mycobacterium avium-intracellure*and *Mycobacterium abscessus*), two with significant fungal burdens (one with Trichosporon species and the other with *Geotrichum capitatum)* and one each with *Escherichia coli* and*Burkholderia multivorans.* Eight patients (44%) had a diagnosis of CF-related diabetes mellitus (CFRD) prior to transplant. Nine patients (50%) had lobar or whole lung consolidation prior to transplantation and one of those had undergone lobectomy prior to listing (Figures 1-3).

[insert Figures 1, 2 and 3 within or adjacent to the text] The median BMI Z score at evaluation was 0 with a range of +2.05 to -3.96. Four patients were well below the 1%ile for height suggesting a history of chronic malnutrition in earlier childhood. All patients had gastrostomy tubes at the time of referral except the two international patients who underwent surgical gastrostomy placement early after referral due to severe malnutrition. All patients underwent bilateral lung transplant and survived transplant hospitalization. Three died within three years of the transplant surgery, one from acute graft failure of unknown etiology one year after transplant complicated by a cerebral vascular accident while on extracorporeal membrane oxygenation (ECMO), two others had early onset chronic lung allograft dysfunction which fit the criteria of bronchiolitis obliterans syndrome (BOS). Each of these two children had proven or suspected non-adherence. Five other patients died at 3.4, 4.5, 5.4, 8.9 and 14.4 years after transplant with non-adherence noted in three of the five and all met criteria for BOS. One of the patients with BOS developed post-transplant lymphoproliferative disease that contributed to her death. Survival of the cohort compared favorably to the older CF cohort (Figure 2).

DISCUSSION Lung transplantation for pediatric patients with cystic fibrosis has been a major focus of pediatric lung transplant programs with >50% of the total transplant population often representing CF.[9] Although the numbers of such patients are likely to decrease in the years to come (table 2), the CF community should be informed of those clinical complications or factors that may lead to more rapid progression of CF-associated lung disease. In this paper, we present a retrospective cohort of pediatric patients referred, evaluated and transplanted over the last 18 years. We have noted common themes derived from this experience that we believe should be noted in order to prevent progression or lead to early education and later referral of these patients to transplant centers. We embrace the concept of modifiable barriers to lung transplantation as recently published.[10]

Because respiratory failure associated with chronic infection is the most common life-threatening complication of CF and a clear indication for lung transplantation, the microbiology of CF lung disease is a primary consideration for CF caregivers in terms of indication for therapeutic intervention. With the exception of a high incidence of MRSA, the bacteriology of this cohort of patients did not generally set them apart from other patients within their own CF centers with a few exceptions. One patient had *Burkholderia multivorans* and two had fungal pneumonias, both of which were challenging to treat. Interestingly, the *Pseudomonas aeruginosa* isolates in this cohort were not multi-drug resistant despite the prevalence of such organisms in our center.[11] Of note, six of eight individuals with major lung consolidation, which we will subsequently address, were chronically infected with MRSA. Two patients had serious fungal infections which have been described but are unusual in CF patients[12] – one with transient *Geotrichum capitatum* infection and the other with chronic Trichosporon infection. However, we conclude that there does not appear to be a clear or obvious microbiologic signature that signals a poor prognosis for young CF patients. It may be important to distinguish MRSA with small colony variants as a more virulent and less treatable subset of MRSA and may require a different antimicrobial strategy. An unexpected finding in our cohort was the high prevalence of chronic lobar or lung consolidation associated with volume loss. Lobar collapse has been described in the CF literature for decades but has not been interpreted as a prelude to advanced lung disease.[13,14] Whole lung consolidation has led in the past to pneumonectomy and single lung transplantation.[15] Our surgeons were able to perform bilateral pneumonectomy with full size bilateral lung transplants in all of our recipients. As noted above, six of the eight children with lobar or lung collapse were chronically infected with MRSA. Staphylococcal empyema was not seen in this subset of patients as a complication of transplant surgery.

CFRD is unusual in pediatric CF patients prior to puberty. Prevalence in children has been estimated at 2% in the prepubertal age group and a recent Canadian study suggested that there has been no increase in incidence over time.[16] Almost 50% of our cohort had CFRD requiring daily insulin therapy prior to transplant. It has been known for years that CFRD is a risk factor for more rapid progression of lung disease.[17] Thus, early detection and treatment for diabetes in the sickest of prepubertal CF patients may be indicated and important in preventing relentless progression of advanced lung disease. Frank nutritional deficiency with the exception of our international patients was not common in our patients at the time of referral with only two patients with BMI Z scores more than two standard deviations below normal at initial evaluation. The median BMI Z score at evaluation was, in fact, zero. Almost all patients were below the 50%ile for height and four were well below the 1%ile for height which we interpreted as consistent with chronic undernourishment earlier in life. Poor nutritional status affects overall exercise capacity and immunity and has been clearly associated with worsened lung function in CF patients.[6,18]

Other investigators have delineated risk factors in children with CF for severe lung disease. We will review our findings in this cohort in light of selected previous publications. Recent experience suggests that MRSA may be a greater risk for severe early lung disease.[19]McColley utilizing a large patient database in a proximate era identified female gender, public health insurance, minority ethnicity, chronic Pseudomonas infection, and low weight for height status as risk factors for early mortality.[20] Aurora and colleagues in the UK suggested that resting tachycardia, hypoalbuminemia and anemia in addition to low lung function and hypoxemia at rest were predictive of CF mortality in childhood.[21] In a meta-analysis in 2016 by VanDeventer, meconium ileus, early lung disease, radiographic evidence of "irreversible lung disease" early in life and decreased access to routine CF Center care were identified as factors predisposing to early progression of lung disease.[22]In consideration of these findings from investigators who evaluated large populations of CF children, we find notable consistencies and inconsistencies. In terms of modifying clinical factors associated with progression in childhood lung disease in CF, we believe that careful testing for respiratory microbiology is prudent and aggressive treatment of early chronic infection with particular attention to MRSA may be merited. Nutritional intervention with oral nutritional supplements with early consideration of gastrostomy tube has become the standard of care in many CF Centers in the USA. All but one of our transplant recipients had a gastrostomy tube which was used for supplemental nutrition. CFRD was surprisingly common in our cohort but was only listed as a risk factor in one of the studies referenced above. Although screening for CFRD is not recommended until age 10 years at this time in the CF Foundation clinical guidelines,[23] we believe that patients with early nutritional deficits and/or signs of early lung disease should be screened for glucose intolerance and treated aggressively if CFRD is detected. The advent of continuous glucose monitors and continuous insulin pumps may be difficult to use in young children but our experience suggests its consideration.

Early signs of focal lobar or unilateral pulmonary disease may or may not be amenable to therapy. The largely anecdotal published literature provides no definitive guidance. Aggressive antibiotic therapy and mucus clearance therapies make logical sense. We are not inclined to recommend early resection of lobes although we believe that there is anecdotal evidence that such surgery may be beneficial in selected patients. Nonetheless, we believe that our cohort suggests to the CF community for the first time that this development should label such patients as high risk for progression of disease to transplantation or mortality. Publications on predictors of mortality in CF date back to the earliest period of lung transplantation. Kerem and colleagues emphasized the importance of lung function as a primary indicator of mortality in 1992.[33] However, other than gender and age, Kerem did not specify clinical characteristics of individuals with low lung function.

Lastly, the evidence of the association of lower socioeconomic status (SES) and early progression of lung disease has become convincing. CF cuts across all classes of people. In a series of publications dating back over 20 years, Schecter has documented this association.[24-26] Our cohort certainly provides corroboration of this association. Virtually every CF center in the USA accepts patients with public insurance so "limited access to care" is not a cogent explanation. There are host of environmental and behavioral factors that are more common in the homes of children with lower SES including parental mental health disorders (treated and untreated), less hygienic home environments including exposure to tobacco smoke, difficulties in arranging

transportation to access CF care and to community pharmacies, less access to healthful foods, and limited understanding of the importance of adherence to an often complex and onerous home treatment program. It is imperative that CF caregiving teams reach out to these families and discern – without judgment – how barriers to effective CF care and treatment can be modified or eliminated.

We would like to highlight one other particular finding in our study. In terms of post-transplant survival, despite identified risk factors prior to transplant which might predispose to lower survival, this cohort of children has actually fared favorably compared to our older patients, many of whom are transplanted in the throes of adolescence (Figure 2). There is a well-documented literature in liver, kidney, and heart transplantation of a notable decline in survival after transplant in the adolescent age group.[27,28] Non-adherence remains a huge challenge for clinicians managing adolescents. With respect to lung transplantation where allograft rejection is more common and more severe than in other transplanted organs, the risk of death from sustained non-adherence to immunosuppression is high. Perhaps, if CF patients undergo lung transplantation in the preadolescent age period, they may be more easily educated and trained, prior to puberty, to keep the responsibilities of transplant care in perspective, especially during the critical first two years after surgery when acute allograft rejection is most common. CONCLUSIONS: We join the broad CF community in hoping that advances in therapy and knowledge will continue to lead to a progressive decline in the early onset of severe lung disease in children with CF. We have presented our own experience in a limited cohort of prepubertal CF patients over the last two decades and have identified the factors that were associated with life-threatening disease progression with the hope that in future patients, they might be detected early as an opportunity for modification.

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