

PEDIATRIC HEART TRANSPLANTS AND COMPLIANCE

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ABSTRACT

This study aimed to establish a better candidacy protocol for pediatric heart transplant patients at the University of Arizona Medical Center through a retrospective chart review of pediatric heart transplants held there between the years of 2004 -2009. Sequential patterns related to noncompliance investigated included patient and guardian demographics and past medical, familial, social and psychiatric history. Trends between gender and noncompliance were found as 5/5 noncompliant rejectors were male. Four out of the 5 were between the ages of 16.5 and 21 years old. Seventy percent of medication changes due to medication intolerance were associated with noncompliance. Patients with family members currently or previously suffering from life-threatening illnesses (7/16) had a greater likelihood of having subtherapeutic immunosuppressive trough levels. Of noncompliant rejectors, 4/5 (80%) had a duration of illness prior to transplant > than 6 months. Also, 4/4 patients with pre-transplant depression experienced rejection and 2/4 were noncompliant rejectors.

INTRODUCTION

Organ transplantation takes a tremendous amount of dedication but can add decades to patient's lives. In patients with end-organ failure, this is the gold standard of practice. Though transplantation comes with a notable cost, it can often eliminate dollars spent on chronic morbidity and loss of productivity which, in the long term can prove to be more costly. In order for this paradigm to work, an immense amount of support and dedication is required of not only the patient, but his family and friends as an entire lifestyle change must occur. The success of the transplant relies upon patients following through on stringent medical regimens as well as the attending of follow-up appointments. If a patient falls short of these post-operative expectations, this major healthcare expenditure not only fails to benefit the patient, it also fails to benefit the transplant program. At this point, healthcare costs are further increased to enable the treatment of organ rejection as well as a potential retransplantation. A number of immunosuppressants are not well tolerated due to systemic symptoms or nephrotoxicity and leucopenia. They can also be extremely expensive for patients. Because of these obstacles, there are extensive, well-established screening protocols involving psychosocial and medical assessments to aid in the ranking of adult patients' candidacy for transplantation. An assessment of the support and capability of the patient to comply with such an intense medical regimen is done.

Despite these efforts, 5-50% of solid organ transplant patients are considered to be noncompliant during the post-operative therapy period[1,2]. Typical reasons for the lack of compliance include but are not limited to the medication cost, medication side effects, lack

of emotional support, lack of comprehension, absentmindedness, bad taste, difficulty swallowing, denial of need and depression [1-4].

A population that takes on even more complexity is the pediatric heart transplant patient population. According to the registry of International Society for Heart and Lung Transplantation, about 350-400 pediatric heart transplants are performed per year which comprises nearly 10% of the total number of heart transplants performed worldwide [6]. One of the primary indications for infant heart transplantation is congenital malformations that have an occurrence of 1 in 10,000 live births and cardiomyopathies such as dilated, hypertrophic or restrictive cardiomyopathy in older children[6]. Survival for infants and children undergoing heart transplantation is around 70 percent to 5 years post-transplant[6]. Alternatives for transplantation include ventricular assist devices, total artificial hearts, open heart procedures and pharmacotherapy. If a patient does not fit the criteria for mechanical assist devices or their conditions are not amenable to surgical correction, transplantation is considered.

What is important to note about pediatric heart patients is that their compliance is almost entirely dependent on the compliance of their guardians. This distinctive characteristic should be noted when assessing the candidacy of the pediatric transplant patient. Though this is true, no studies have been done that lay out a specific candidacy profile for pediatric heart transplant patients. This lack of an overall picture of candidates impedes efforts to decrease the noncompliance rate in pediatric transplantation. In terms of all solid organ transplants, long-term allograft survival is least successful in adolescent recipients and the major cause of late graft failure in adolescents can be attributed in large

measure to medication noncompliance which leads to immune rejection [7]. In fact, medication noncompliance in teenagers has been shown to be more than 4 times greater in adolescents than in adults [9]. Furthermore, pediatric transplant clinicians report elevated rates of noncompliance with medications, appointment keeping, and laboratory tests as well as elevated rates of high-risk behaviors among older children and young adult recipients. The caregivers also report symptoms of identity confusion, social immaturity, and failure to appreciate consequences of risky behavior among recipients [14]. Many theories have been proposed to explain this disparity, yet it is primarily attributed to the limited cognitive skills and intellectual maturation of adolescents. Adolescents with chronic illnesses have difficulty with abstract thinking, specifically the conceptualization of future consequences of present actions. This leads to characteristic risk-taking behaviors, involving noncompliance with medical regimens [9]. Perhaps taking note of this lack of a definite candidacy profile has contributed to the high numbers of allograft failures in adolescents and doing so can aid in the improvement of pediatric heart transplant recipient survival.

A number of studies have been done to characterize some common trends in pediatric heart transplant noncompliance. A study done by Stilley et al assessed adherence, high-risk behaviors, and maturity in 27 heart transplant patients aged 15–31 who underwent heart transplantation in childhood or adolescence at Children's Hospital of Pittsburgh. Participants in the study completed a projective ego development measure and questionnaire about adherence to the post-transplant regimen [8]. From this group, 9 patients who matched in age, were intentionally chosen for good or poor compliance

according to the standards determined by the transplantation team. These patients were used in qualitative interviews as well as mood assessments. What was found was that 63% of the phase 1 sample missed medications and 67% missed appointments [8]. These numbers are notable as they are signs of noncompliance to the medical regimen established by all transplant teams. As allograft survival relies upon the taking of medications, it is important that patients not only take their immunosuppressive drugs but also attend follow-up appointments for immunosuppressive trough level assessments. Patients must attend biopsy appointments that test for rejection and since 67% had missed appointments, 67% were putting themselves at risk for rejection and were proving to be noncompliant. Also, it was found that , 11% smoked, 37% had difficulty with diet, 89% exercised infrequently, 33% had tattoos, 26% had more than 2 body piercings, and 11% used street drugs. These are all signs of noncompliance as post-transplant regimens require that a patient maintain a healthy weight by exercising frequently along with maintaining a good diet and limiting the amount of potential infections (as one would find with intravenous street drugs, tattoos, and piercings). From this information, it was found that poor adherers were less mature on every theme and habitually scored at a less mature level on the projective measure of ego development. Chronological age was found to be unrelated to the level of maturity in qualitative or projective data but it was concluded that non-adherence and high risk behaviors were prevalent in young adult and adolescent heart recipients and that the level of maturity was associated with the patients' capability to comply with the post-transplant regimen and avoid high-risk behaviors [8].

Another study conducted to find trends in noncompliance in pediatric heart transplants looked at 53 children and adolescents with a mean age of 10.3 years [10]. Patients were followed up for 12 months after heart or heart- lung transplantation. At every follow up appointment, trough levels of cyclosporine were measured and medical diaries were checked. Satisfactory adherence to medication and satisfactory completion of the diaries were found in 37 children (70%). Adequate adherence to medication but unsatisfactory completion of diaries was found in 11 children (21%). Poor adherence to medication in 5 children (9%) was found irrespective of whether the diary was completed. Single parent or blended families were associated with poor adherence.

A study done to measure the associations between post-transplant outcome and guardian psychosocial evaluation was also done by Stone et al. In the study, researchers evaluated relative risk of rejection and hospitalizations (days of all-cause hospitalization) following initial post-transplant discharge in patients in risk and control groups that were defined by their pretransplant parental psychosocial evaluation [11]. Immunosuppressive trough levels were monitored and the ratio of levels that fell below 50% of the recommended level was recorded. There were 7 patients in the risk group with a median age of 0.25 years and total follow up was 20.5 patient-years. There were 21 patients in the control groups with a median age of 2.1 years and total follow up of 71.3 patient-years. During the first 6 months post-transplant, there was no difference in rejection risk nor days of all-cause hospitalization; however, in the following 6 months, there were 11 rejection episodes in the risk group over 17.4 patient-years and 4 rejection episodes in the control group over 61.8 patient-years of follow up. Patients in the risk group were 2.9 times more

likely to have immunosuppressive trough levels below 50% of the target level during both early and late periods after adjustment for patient age and race. It was concluded that pre-transplant parental psychosocial risk assessment was related to post-transplant morbidity in pediatric cardiac transplant patients [11].

The present study aimed to use these studies to help achieve our long range goal of establishing a better protocol to assess the candidacy for pediatric heart transplant patients so that the noncompliance rate may decrease. The present study is an IRB approved, retrospective chart review of all consecutive pediatric heart transplants patients between the years of 2004 and 2009 at the University of Arizona Medical Center. We aimed to investigate any sequential patterns related to noncompliance, detect reasons for noncompliance within this population and include any medical, social, or socioeconomic factors not already incorporated into the University of Arizona Medical Center screening protocol. Though our study only included patients that were ages 0-17 years of age during transplantation, it investigates a diverse population in terms of not only socioeconomic class, but also race, education level, primary diagnosis, and comorbidities. Our central hypothesis was that a variety of factors contribute to non-compliance and that most can be attributed to the lack of compliance of the caregiver. Based on the study by Serrano-Ikkos et al, we hypothesized that non-compliance would be associated with single parent households or blended families. We also hypothesized that psychiatric disease would play a role in noncompliance as well. The rationale for our study was that once factors that influence compliance were found, we would be able to better identify more suitable pediatric heart transplant candidates and decrease the high non-compliance rate. Our

research team was particularly well suited to undertake this challenge as we combined the skill sets of recognized experts in pediatric heart surgery, general surgery, as well as anesthesia and medical pharmacology. A state of the art clinical research facility along with access to medical records aided in making this study possible. The outcome of this study was intended to not only help redesign the University of Arizona Medical Center's pediatric heart transplant candidacy protocol but also to aid in the metamorphosis of other institutions' protocols as well.

METHODS

Patients between the ages of 0 and 17 years of age who received a heart transplant between the years of 2004 to 2009 were investigated. Seventeen patients met initial criteria. One of the patients was eliminated from the study due to perioperative mortality and therefore, an inability to display signs of noncompliance. Immunosuppressive trough levels, missed laboratory appointments as well as missed biopsy appointments were used as our primary outcomes of noncompliance. Secondary outcomes included rejection and survival.

In terms of immunosuppressive trough levels, it was established that an incidence of noncompliance with medications would be a trough level that was less than the recommended level established by the transplant team. A grace period where subtherapeutic levels were not recorded was established in the three month period following initial transplantation as well as three months subsequent to any changes in immunosuppressive therapy. A patient was considered to be a “noncompliant patient” with immunosuppressive therapy if he had subtherapeutic trough levels more than 3 times in one year.

Regarding missed appointments, a patient was considered to be noncompliant if they missed more than three biopsies, three laboratory appointments or three general follow-up appointments in a one year time period. The standard follow up for patients transplanted at the University of Arizona Medical Center is weekly laboratory appointments for 8 weeks then monthly given that there are no issues with finding

therapeutic levels of immunosuppressive therapy. Patients have a monthly echocardiogram for the first year. Annual right and left heart catheterizations with intravascular ultrasound, endocardial biopsy, and echocardiograms are carried out for the rest of the patient's life. Patients will be asked to be seen more frequently if basic laboratories or immunosuppressant trough levels are abnormal or a patient experiences rejection. It is important to keep in mind that infants are not biopsied. In addition, patients are asked to reside in Tucson for at least 3 months post-transplant. This is important considering many heart transplant patients are referred from outside of the Tucson Metropolis.

Data was collected using a variety of patient charts. Electronic charting systems, Chartaxx and Sunrise Clinical Manager, were used to collect patient data. Since these charting systems include only dictated documents, paper charts were utilized. In addition, contact with transplant coordinators was also made and patient charts from the University of Arizona Medical Center Transplant Program were also investigated. Pre and post-transplant data was collected on patient and guardian demographics, past medical history, family medical history, psychiatric history as well as social history. Some specific areas that were investigated in terms of demographics were age of the patient at time of transplant, gender, ethnicity, primary language spoke at home, parent highest level of education and parent marital status as well as number of siblings. In regard to past medical history, prior transfusions, use of mechanical circulatory support including intra-aortic balloon pumps, Extracorporeal Membrane Oxygenation, ventricular assist devices and total artificial hearts within 30 days of transplantation, medications prior to transplant

and previous and primary diagnoses were recorded. In terms of psychiatric history, both the guardians and children were investigated and any history of psychiatric disorders including anxiety, depression, substance abuse, and history of suicidal attempt was noted. In regard to social history, the patient's primary caregiver, parent employment status, insurance status and pre-operative noncompliance with medications or follow-up were recorded. All of these criteria were investigated pre-transplant as well as post transplant. In addition, immunosuppressive drug trough levels, incidences of rejection as well as complications post-transplant and overall survival were recorded.

RESULTS

As mentioned, 17 patients were included in this study and one was eliminated due to perioperative mortality. The total mean of follow up years was 5 years with all patients being followed up between 2 and 7 years. The median age was 12 years with a mean of 10 years of age. Patients ranged from 0.5 to 17 years old. Ten males and 6 females were included in the study and the ethnicity breakdown was as follows: Hispanic: 7, White: 3, Black: 3, Native American: 2 and Asian: 1.

Primary diagnosis and medical history prior to transplant were investigated for each patient. Eight patients had a primary diagnosis of dilated cardiomyopathy, 5 had restrictive cardiomyopathy, and 3 had congenital cardiomyopathy. Five patients had prior cardiac surgery and 4 out of the 16 were on mechanical support immediately prior to transplantation. Six patients had an AICD and 11 were on inotropic therapy 30 days or less prior to transplant. Six patients were on multiple inotropes.

Substance abuse, history of depression, and psychiatric illness was also recorded. Not all 16 patients included in the study had substance abuse that was mentioned in their charts. Five out of 11 patients (45%) had guardians who smoked tobacco and 1 out of 11 (9%) abused alcohol. Two out of 10 patients (20%) had guardians with a history of illicit drug use. Two out of 10 guardians (20%) had a history of depression and psychiatric illness. In terms of the patients, no patients were found to abuse alcohol or tobacco and 1 out of 15 (7%) had a history of illicit drug use. Four out of 15 patients (27%), had a history of psychiatric illness.

Of the 15 patients who had primary caregiver documented at discharge, 10 were discharged to the care of a parent, 4 were discharged to a facility, and 1 was discharged to a family member other than his biologic parent. Marital status of caregivers both during the preoperative period and the postoperative period were 8 out of 13 married and 5 out of 13 single. The mean number of siblings was 2.4 and ranged between 1 and 5 siblings. English was the primary language spoken in the home for 14 out of 16 patients (87%). Two out of 16 patients (13%) spoke Spanish as a primary language.

In regard to primary outcomes, not enough data was found in patient charts to be able to assess noncompliance due to missed appointments and missed laboratories; however, subtherapeutic trough levels were found and recorded. By this study's standards, 16 out of 16 patients were found to be noncompliant. Six out of 15 patients were considered to be noncompliant over three years. This is discounting one patient due to the fact that his transplant was too recent to follow-up three years. Interestingly, only one out of these 6 patients had an incidence of rejection.

Rejection episodes and survival statuses were recorded. Seven out of 16 patients were found to have incidences of rejection. Five out of 7 had incidences that were clearly associated with noncompliance with medications. It was found that incidences of rejection occurred after extremely low trough levels or at subtherapeutic trough levels for a period of time that extended beyond 3 months. It is important to note that not all incidences of rejection were found to be due to noncompliance by this study's standards. Fifteen out of the 16 of the patients included in this study are surviving today. The demographics investigated such as ethnicity, primary language spoke at home, parent highest level of

education, parent marital status as well as number of siblings were found to lack any correlation with noncompliance. Prior transfusions, prior mechanical circulatory support, medications prior to transplant and previous and primary diagnoses, were also found to be poor indicators of noncompliance. Also, there was no association found between incidences of noncompliance and the psychiatric history of guardians. In regard to social history, the patient's primary caregiver, parent employment status and insurance status were not found to have any relationship with incidences of noncompliance.

Gender and age were included in this study. Five out of 5 patients who suffered from incidences of rejection and had troughs below therapeutic values more than 3 times in one year (and thus considered to be noncompliant) were male. Also, more males had incidences of rejection (6 out of 7 patients). Four out of the 5 patients were between the ages of 16.5-21 years of age at time of rejection.

Medication intolerance was recorded. Though a change in medication regimen was not associated with noncompliance in this study, a change in medication regimen due to medication intolerance appeared to be associated with noncompliance in 7 out of 10 patients. This did not, however, correspond to incidences of rejection.

Family medical history appeared to be associated with noncompliance. Seven out of 16 patients had a family member who was currently or recently suffering from a life-threatening illness. These patients had an increased frequency of low troughs yet these trough levels were not found to be correlated with rejection.

Duration of illness prior to transplant was assessed. The median time frame was 6.5 months and the range was 1-172 months. Of the noncompliant rejectors, 4 out of 5 (80%) had duration of illness prior to transplant that was greater than 6 months.

In terms of psychiatric history of the patient, some trends were found. Four out of 4 patients with pre-transplant depression experienced rejection. Two out of 4 were considered to be noncompliant transplant rejectors.

DISCUSSION

Heart transplantation has become an accepted standard of practice for children with end-stage cardiomyopathies. Though transplantation can serve as a tremendous benefit, it presents an immensely stressful transition for patients and their families [12]. If strict medical regimens are not followed, rejection becomes an issue and a further healthcare expenditure is made to help treat patients with chronic rejection. Pediatric heart transplant patients are a unique population as there are often different challenges that are faced when compared to adults including the role of family and changes of adolescence [12].

In this study, we aimed to identify predictors of noncompliance among pediatric heart transplant patients who were transplanted between the years of 2004 and 2009 at the University of Arizona Medical Center. We intended to this by recording missed follow-up, laboratory, and biopsy appointments. Three or more missed appointments in one year would define a patient as noncompliant. Unfortunately, information from all patient charts was not complete and the study was unable to make any conclusions in terms of this type of noncompliance.

However, immunosuppressant trough levels were recorded for all patients included in the study. Because of the low N value (small number of patients in the study), our study was underpowered, making meaningful statistical analysis impracticable. By this study's definition of noncompliance with medications, which was greater than 3 subtherapeutic levels in 1 year, all 16 patients were considered to be noncompliant. Though it is true that

immunosuppressive regimens ought to be altered with maturation of the immune system [19] and that some low trough levels could be attributed to a biological change in the child, even when the correct therapy was found for these patients, they still had incidences of low trough levels that fell far below the target trough.

Males were found to be the most likely of patients found to be noncompliant with immunosuppressive therapy and suffered from rejection (5/5). An explanation for this could be that a greater number of male subjects were included in the study and more males had incidences of rejection (6 out of 7 patients). However, 4 out of the 5 patients were between the ages of 16.5-21 years of age at time of rejection. This may serve as support for previous studies that state that as a child enters adolescence, they become less compliant with the medication regimens that come with transplantation [8]. Other studies have attempted to provide a more in depth explanation for this and have said that as patients are entering adulthood and are more responsible for taking immunosuppressive medications, they could intentionally refrain from doing so due to the immunosuppressant's negative effects. A study by Lawrence et al suggests that as patients enter adolescence, caregivers report symptoms of identity confusion, immaturity in social settings, and failure to understand or acknowledge consequences of dangerous behavior and may put themselves at risk in terms of noncompliance [14].

In another study, researchers sought to point out specific life events that could occur during young adulthood that may be leading to noncompliance. These events may provide explanations as to why this study had a higher incidence of noncompliance that lead to rejection between the ages of 16.5 and 21 years of age. In the study, it was stated that

young adulthood brought along many stresses including but not limited to graduating from high school, moving out of the guardian's home, starting new educational directions, and making decisions in terms of relationships, marriage, childbearing, careers, and lifestyle [15]. Additional stressors included peer pressure to abuse alcohol, tobacco, illicit drugs and to have sex. Though this is true for all young adults, it is most difficult for patients battling a chronic illness and dealing with the strict medical regimen that comes along with transplantation. It is also important to note that from this study, we learned about an additional stressor for young adult heart transplant patients: the transition from the pediatric care team to the adult team. It was stated that this transition often leaves patients insecure and untrusting as they have become so accustomed to the pediatric team that was there for the entire procedure [15]. This lack of "closeness" could lead to incidences of noncompliance with medications, missed appointments, and a lack of communication between the young adult and new healthcare team.

Another trend found in this study was the correlation between noncompliance and intolerance to medications. Though an alteration in medication regimen was not linked to noncompliance in this study, a change in medication regimen due to medication intolerance appeared to be associated with noncompliance in 7 out of 10 patients. This corroborates previous studies that have stated that a strong deterrent to compliance with post-transplant medical regimen is the side-effects of immunosuppressive therapy [18]. These medications can contribute or lead to opportunistic infections, short stature, obesity, hirsutism, depression as well as anxiety. Korch et al states that the yearning to belong makes the negative effects of immunosuppressants more aversive in the pediatric patient.

The effects that immunosuppressive drugs have on the patients' physical appearance as well as on their health could lead to noncompliance [18]. Though this correlation was found in this study, it did not correspond to incidences of rejection.

This study also found that patients with ill family members have greater frequency of lower trough levels. Seven out of 16 patients in this study had a family member who was currently or previously suffering from a life-threatening illness. Though they had a greater incidence of lower trough levels, this was not found to be associated with rejection. This find is novel and should be further explored in later studies.

In addition, it was found that if a patient had a duration of illness greater than 6 months prior to transplant, they had more of a likelihood to be classified as noncompliant. In fact, of the noncompliant transplant rejectors, 4 out of 5 (80%) had duration of illness prior to transplant that was greater than 6 months. Studies have found that the waiting period of the preoperative stage has been described as the most nerve-racking for transplant candidates and their families [12]. Perhaps this prolonged period of illness prior to transplant leads to additional psychosocial issues that may contribute to noncompliance.

Also, pre-transplant depression was found to be associated with rejection. Four out of 4 patients with pre-transplant depression experienced rejection. Two out of those 4 were considered to be noncompliant transplant rejectors. A study by Wray et al states that medically noncompliant patients show co-morbid psychological symptoms [17]. In one study, 80 pediatric renal transplant recipients were investigated. It stated that these

patients displayed less self-esteem and a larger occurrence of social adjustment problems than did healthy control patients. In addition, it was found that 14 patients stopped their immunosuppressive therapy at one point during the 10-yr study phase [18].

In another study that aimed to assess the occurrence and some potential correlates of noncompliance to medications in adolescent and young adult transplant patients, fifty patients who had undergone heart or heart-lung transplantation between the ages of 1.4–14.9 years old were investigated. Standardized questionnaires regarding illness perception and demographics were utilized and medical notes were investigated to find incidences of rejection, previous psychiatric referral, complications and documented concerns about compliance [16]. Noncompliance determined from the questionnaires was correlated with forgetting to take medication and was categorized as unintentional noncompliance. Unintentional noncompliance was reported by 11 (28%) patients. Seven patients (18%) displayed evidence of deliberate noncompliance, which was categorized as intentional. Intentional noncompliance was associated with depression and transplant-related lymphoma. [16] Their finding is supported by this study as patients who suffered from depression were more likely to suffer from rejection. Though only 2 out of 4 patients were considered to be noncompliant transplant rejectors, more studies must be done to prove this to be an irrelevant finding as the n value is too small to say.

There were a number of weaknesses in this study. As mentioned previously, this study had a low N value. In addition, researchers had difficulty defining noncompliance as there is no formal way of doing it. As evidenced by our 100% rate of noncompliance with medications, we have not yet established a definition of noncompliance that is truly able to

differentiate those who are compliant and those who are not. Since this was a retrospective study, we relied upon charting and reporting systems, some of which were dependent on someone hand-entering data. Future studies should be carried out through the amendment of the IRB approval. The main goal would be an increase in the number of years of pediatric heart transplants included in the study. This would allow the N value to be increased. In addition, with an increase in N, perhaps a greater variety of primary diagnosis can be found and investigators can see how primary diagnosis may affect compliance. In a study by Collier, Nathanson, and Anderson, it was stated that different personality features were found when patients were transplanted because of congenital disease as opposed to those who had acquired cardiac diseases [13]. Amendment of the current study to include contacting patients to complete surveys regarding compliance may also be warranted.

Though these weaknesses existed, this study had many interesting findings that may help to contribute to a more thorough pediatric heart transplant candidacy profile at the University of Arizona and other pediatric heart transplant centers. There have been many conflicting findings in regard to the likelihood of a pediatric patient being classified as noncompliant. However, one issue that is not debated is that better predictors can be useful and can not only benefit patients but also pediatric heart transplant programs. The role of the family is essential to the success of the transplant [20]. Medication adherence perhaps can be aided by the parent when a child reaches young adulthood and is more likely to be noncompliant.

In addition, the transplant program must make strides to ensure that the patient has access to all of the tools necessary to keep him on his medical track. The association with noncompliance and intolerance to medications can be aided through a swift alteration in medications by the transplant team and the limiting of negative symptoms as soon as possible. The fact that patients with ill family members were more likely to have lower trough levels could be an indicator that additional help in a nursing or psychological form is necessary for patients of this kind. Access to this type of aid is not only the responsibility of the guardian but also the responsibility of the transplant program. Also, because patients who had a duration of illness that were greater than six months prior to transplant proved to be more noncompliant, efforts should be made by the transplant program to swiftly decide whether the patient is a transplant candidate and facilitate listing. Though this does not ensure that an organ will be available, it may help with psychosocial outcomes that effect noncompliance. Lastly, because pre-transplant depression was associated with rejection, the transplant program as well as the guardian must make strides to provide psychological support for the child. This must be done to ensure that the child is equipped with the necessary psychological support that he needs to endure this traumatic and life-altering experience.

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