Published in final edited form as:

Pediatr Transplant. 2016 March ; 20(2): 307–315. doi:10.1111/petr.12648.

Perceived barriers to medication adherence in pediatric and adolescent solid organ transplantation

Lara Danziger-Isakov¹, Thomas W. Frazier², Sarah Worley², Nikki Williams³, Diana Shellmer⁴, Vikas R. Dharnidharka⁵, Nitika A. Gupta⁶, David Ikle⁷, and Stuart C. Sweet⁵ on behalf of CTOTC-05 Consortium

¹Cincinnati Children's Hospital Medical Center, Cincinnati, OH

²Cleveland Clinic Children's, Cleveland, OH

³National Institute for Allergy and Infectious Diseases, Bethesda, MD

⁴University of Pittsburgh, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

⁵Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO

⁶Emory University School of Medicine, Atlanta, GA

⁷Rho, Chapel Hill, NC

Abstract

Comparisons of perceived barriers to adherence in pediatric and adolescent solid organ transplantation (SOT) have not been systematically conducted despite association between medication non-adherence and poor outcome.

Fifteen centers in Clinical Trials in Organ Transplantation in Children enrolled patients in a cross-sectional study. Subjects' guardians completed the Parent Medication Barriers Scale (PMBS) and subjects over 8 completed the Adolescent Scale (AMBS). Association of three identified PMBS factors and subject age was assessed. Secondary analyses assessed associations between PMBS, AMBS, and patient demographics.

Three hundred sixty-eight subjects or their guardians completed PMBS or AMBS. 107 subjects were 6–11 years; 261 were 12. Unadjusted and propensity-adjusted analyses indicated higher perceived barriers in guardians of adolescents as compared to guardians of pre-adolescents medication scheduling and frustration domains regardless of organ ($p < 0.05$). PMBS and AMBS comparisons revealed that guardians reported fewer ingestion issues than patients ($p = 0.018$), and differences appeared more pronounced within younger responders for scheduling ($p = 0.025$) and frustration ($p = 0.019$).

Screening revealed guardians of older patients report increased perceived barriers to adherence independent of socioeconomic status. Guardians of adolescents reported fewer perceived barriers to ingestion/side effects than patients themselves, particularly in pre-adolescents (8–11 years). Brief screening measures to assess perceived barriers should be further studied in adherence improvement programs.

Keywords

Adherence; Pediatric; Solid organ transplant

Introduction

Medication non-adherence has been associated with poor outcomes after pediatric and adult solid organ transplantation (SOT). Investigators have reported overall non-adherence to post-SOT treatment regimens ranging from 5–70% in pediatric patients, indicating the difficulty of generalization associated with single-center studies using variable markers for non-adherence [1–4]. Simons et al. have reported non-adherence to be approximately ~ 50–55% in pediatric patients compared to ~65% in adolescent recipients, and other studies have confirmed increased non-adherence in adolescent populations [2, 5]. However, differences in perceived barriers to adherence between pediatric and adolescent patients have not been evaluated in large-scale studies involving multiple solid organ transplant groups.

Medication non-adherence results from various barriers that are often difficult to discern, especially in complex patients with chronic medical illness. The barriers to medication adherence have included demographic, disease factors, child/family variables and healthcare system factors. In SOT recipients, neurodevelopmental and psychosocial factors are important constructs related to the ability to adhere to their recommended treatment regimens [6–8]. Studies report that psychosocial factors exhibit the strongest relationship with non-adherence compared to other factors recorded [3, 9, 10].

Studies of medication non-adherence in pediatric transplant recipients suffer from several limitations. Early studies demonstrated that self-reporting from physician, caregivers and patients were poor correlates of adherence [11]. Additionally, limited sample sizes and variability in treatment regimens hinder the generalizability of the results to larger pediatric transplant population. In the past several years questionnaires that measure perceived barriers to adherence have been developed as a surrogate measure of adherence. These instruments can be administered quickly and efficiently in the outpatient setting and have been validated by comparing them to objective measures of adherence including pill counts, medication event monitoring systems (MEMS®) and serum drug levels [2, 12, 13]. We employed these surrogate adherence measures to evaluate perceived barriers to adherence in a large cross-sectional sample of pediatric and adolescent SOT recipients postulating that guardians of older recipients would report more perceived barriers than guardians of younger recipients. In addition to comparing responses between guardians of younger and older SOT recipients, we hypothesized that older recipients would report similar perceived barriers to their guardians.

Methods

After institutional review board approval at each site, 15 centers in the United States participating in the Clinical Trials in Organ Transplantation in Children (CTOT-C) serially enrolled 502 first-time SOT recipients during outpatient clinic visits after hospital discharge in a cross-sectional study; however only subjects over 5 years of age are included in this

analysis (Figure 1). Recipients less than one month post-transplant or who did not take an immunosuppressive drug were also excluded. Parent Medication Barriers Scale (PMBS) and Adolescent Medication Barriers Scale (AMBS) were developed and evaluated in the context of adherence in pediatric solid organ transplantation with the AMBS being developed in 11–21 years old [2, 13]. The PMBS consists of a 16-item questionnaire which is parallel to the structure of the 17-item AMBS. Each item reports the response on a Likert scale (1=strongly disagree to 5=strongly agree), with high ratings indicating greater perceived barriers. The PMBS was completed by a guardian along with demographic and socioeconomic information including a Hollingshead SES scale[14]. In addition, the Brief Medication Questionnaire (BMQ), which consists of four binary subscores that are summed to create total number of barriers, was completed[15]. Higher BMQ scores reflect more potential adherence barriers. The AMBS was completed by children 8 years of age and older without significant developmental delay who were capable of independently completing the tool. AMBS and PMBS were completed independently in the outpatient clinic area without intervention from the research coordinator, while the BMQ was administered by the research coordinator. Comparisons between pre-adolescent (ages 8–11) and adolescent (ages 12–21) patients were chosen based on the development of the AMBS tool [2] as well as data regarding age-associated graft failure rates in adolescents[16]. A single result of an immunosuppressive blood level was collected around the time of the questionnaire for comparison to perceived barriers reported. This was not intended to directly measure adherence.

Observed age differences on any measure can result from two possibilities. The first is that real age differences exist and the second is that the measure is not evaluating the same construct in each age group. To exclude the latter, we conducted measurement equivalence analyses (Supplemental Methods). The analyses revealed a three-factor structure for the measures that was used throughout our analysis, and a parallel AMBS factor structure was created from the overlapping items. As each PMBS and AMBS factor had different number of items, the factors were analyzed as item means.

The primary analyses compared younger and older patients on each PMBS factor using linear regression models with multiple imputation: unadjusted models included only age group as the dependent variable, and propensity-score adjusted analyses included age group and a propensity score for age group as dependent variables [18, 19, 20]. The differences between older recipients and guardian perceptions of barriers to adherence were assessed by performing paired t-tests on the participants' PMBS and AMBS factor scores, calculated on shared items only; consistency between the matched PMBS and AMBS factor scores was assessed using intraclass correlation coefficients (random rater model [2,1])[17, 18]. Secondary analyses assessed the interaction between age group and transplant type, and between age group and insurance type, on PMBS and AMBS factors using linear regression models. Other univariable analyses were performed using correlations, ANOVA, two-sample t-tests, Wilcoxon rank sum tests, Chi-square tests, and Fisher's exact tests as appropriate.

Statistical analyses were performed using SPSS 20 (Chicago, IL), MPlus 5.2 (Los Angeles, CA), SAS 9.4 (Cary, NC), and R 3.0.0 (Vienna, Austria). All tests were two-tailed and

performed at a significance level of 0.05. Additional details of the statistical analyses are provided in the Supplemental Methods

Results

Demographics

Three hundred sixty-eight subjects or their guardians completed the PMBS or AMBS or both, and demographic information. Of these, 107 subjects were 6–11 years while 261 were 12 years or older (Table 1, Figure 1). The younger group had significantly lower mean age at transplant, higher mean Hollingshead SES score, higher primary guardian education level, and were more likely to be of non-Hispanic white ethnicity and race. In addition, the older subjects had more kidney recipients (61%) but fewer liver (11%) and heart (17%) recipients compared to the younger group (40% kidney and 22% liver, and 27% heart). Similar proportions in each group had received a lung transplant (10% each group). No statistically significant differences between the groups were appreciated for gender or insurance status.

Guardians of older subjects report increased perceived barriers

Of the 368 subjects whose guardians completed the PMBS, 107 subjects were 6–11 years old while 213 were 12 years or older. With exploratory factor analysis, PMBS questions mapped to three primary factors (medication scheduling, ingestion problems/ side effects, and medication or disease frustration) which were similar to those identified previously[2] (Supplemental Table 1). Guardians of older recipients reported significantly greater perceived barriers to adherence than did guardians of younger subjects (Figure 2). Both unadjusted and propensity-adjusted analyses indicated more substantial differences in the medication scheduling and medication/diseases frustration domains of approximately one-third to one-half point on a five-point scale ($p < 0.05$, Table 2). Additional propensity-adjusted analyses revealed no significant interactions between organ type and age group for PMBS barrier factors; however, guardians of older patients with Medicaid reported increased perceived barriers to medication scheduling and ingestion problems/side effect compared to guardians of younger Medicaid patients; this was not true of patients with non-Medicaid insurance. Older age at transplant was associated with guardian-reported increased perceived barriers to adherence for ingestion problems and medication/disease frustration by the PMBS with correlation coefficients ranging from 0.14 to 0.20 ($p \leq 0.01$ for each, Supplemental Table 2).

AMBS reporting in pre-adolescents and adolescents

The AMBS was completed independently by 287 subjects including 33 pre-adolescents (8–11 years) and 254 adolescents (12 years and older). Among patients who completed the AMBS, kidney recipients ($N=171$, 60%) dominated the older cohort with heart ($N=49$, 17%), liver ($N=38$, 13%), lung ($N=28$, 10%), and heart-lung ($N=1$) making up the remainder. Pre-adolescent and adolescent scores were not statistically different for any of three factors, and there were no significant interactions between age group and organ or insurance for any AMBS factor ($p > 0.05$ for main and interaction effects; linear regression models).

Guardians report fewer ingestion issues/side effects compared to pre-adolescents and adolescents

A comparison between PMBS and the AMBS was performed to assess comparability of the organ recipients and guardians perceptions of barriers to adherence. Thirty-three subjects 8 to 11 years old (mean 10.9) and 206 subjects 12 to 21 years old (mean 15.9, Table 3), had paired PMBS/AMBS available. The consistency between the matching PMBS and AMBS factors was only moderate, with intraclass correlation coefficients ranging from 0.40 to 0.47. Guardians reported significantly fewer ingestion issues/side effects compared to AMBS scores obtained from the pre-adolescent/adolescent subjects ($p=0.018$); paired t-test. These differences were primarily driven by the response to two questions that reflected difficulty swallowing the medication and medication taste. Pre-adolescent responders reported increased perceived barrier for the number of pills ingested, but not medication taste, compared to their guardians' reports (Table 4). However, the scores for medication scheduling and medication/disease frustrations showed similar levels of perceived barriers reported on the PMBS by guardians and AMBS by subjects ($p=0.87$ and 0.45 , respectively; paired t-test). Interestingly, within age groups, responders aged 8–11 and their guardians differed significantly on medication scheduling ($p=0.025$; paired t-test) and medication/disease frustrations ($p=0.019$; paired t-test), while there were no significant differences between responders aged 12 and over and their guardians ($p>0.05$ for each; paired t-test).

Association between perceived barriers and tacrolimus levels

Fluctuations in the standard deviation of tacrolimus levels over time have been associated with non-adherence in liver, kidney and heart recipients [11, 19, 20]. However, only one tacrolimus level was available in this cross-sectional survey to assess for associations with perceived barriers to adherence. Using the single result recorded around the time of study participation, tacrolimus levels that were more than 50% below the lower threshold targeted by the primary center for that individual were not associated with perceived barriers as reported by either guardians (PMBS) or subjects (AMBS) (data not shown).

BMQ only weakly correlated to PMBS/AMBS

BMQ responses were not clearly correlated to the perceived barriers identified in the PMBS and AMBS responses. The composite BMQ scale had only a weak correlation (Spearman rank correlation coefficients 0.09–0.24) to perceived barriers reported in the PMBS and AMBS with age group-specific Spearman rank correlations ranging from 0.08–0.33.

Further, subset evaluation of the 4 BMQ reporting components (adherence, belief, access, and recall) compared to the factors identified in the PMBS and AMBS were investigated (data not shown). In both the AMBS and PMBS, the BMQ adherence sub-scale was not associated with an increase in perceived barriers in medication ingestion present on the AMBS/PMBS, while the BMQ belief sub-scale did not register medication scheduling barriers on the AMBS. The BMQ recall sub-scale was not associated with any PMBS and AMBS factors. Only the BMQ access screen was significantly associated with all three AMBS factors and two of the three PMBS factors (with a marginally significant association with the third PMBS factor, medication and disease frustration).

Prediction of perceived barriers based on Hollingshead SES

Finally, correlations were assessed between perceived barriers as reported in the PMBS and AMBS and socioeconomic status as reported in the Hollingshead SES score. Pearson correlation coefficients were very weak, ranging from -0.04 to 0.08 , and not statistically significant between the Hollingshead SES score and either the PMBS or AMBS factors, indicating that socioeconomic status as assessed in this study did not reliably predict the perceived barriers reported.

DISCUSSION

Progress continues to be made in the ability of transplant teams to assess for medication non-adherence in pediatric transplant recipients. Advances in the identification of non-adherence through objective measures including standard deviation of immunosuppressive levels are more frequently and consistently employed providing medical providers with an opportunity to intervene [12, 15, 16]. However, investigation into perceived barriers to adherence has been limited and a thorough understanding of these factors is lacking. The use of simple questionnaires to assess these barriers could provide novel targets for exploration and a route to treat (perhaps even prevent) non-adherence if active monitoring is employed.

In this study, we sought to examine perceived barriers to adherence from both guardian and patient perspectives bringing into the forefront the factors that are of particular importance among pediatric transplant recipients. Previous research in this area has been primarily carried out within one organ group, most commonly kidney transplant patients, in single centers and with small samples [2, 12]. In this study we sought to obtain a broader sample of solid organ transplant patients from multiple centers using an easy to administer set of questionnaires. Our intent was to explore potential differences by age and organ type, and allow for broader generalizability and potential incorporation into clinical practice in the future.

We found that perceived barriers were more frequently reported by guardians of older recipients compared to guardians of younger transplant recipients, predominantly in the areas of medication scheduling and medication/disease frustration. Medication scheduling and medication/disease frustration have been similarly endorsed as significant perceived barriers by guardians [21]. Interestingly, guardians appeared to report fewer perceived barriers to ingestion/side effects compared to the patients themselves. This difference was even more striking in the pre-adolescent participants aged 8–11 who completed the AMBS perhaps indicating limited understanding in this age group. Notably, there were fewer pre-adolescent than adolescent participants. However, this difference could alternatively point toward a disconnect between the child's experience and the guardian's assessment of perceived barriers. Potential reasons for these differences may indicate increased communication challenges within the 8–11 year age group such that younger children find it difficult to discuss their experience effectively with their guardians and/or are unaware that guardians would be interested in these concerns. Family functioning including poor family cohesion and lack of supervision has been associated with nonadherence[22] [3]. Among other factors, developmental level of the child, family environment, communication patterns within the family, psychosocial functioning of the child and guardian, and open discussion

regarding medical management and day-to-day medical care could potentially impact the ability of patients to communicate with their guardians about medication specific issues.

Previously identified demographic factors that have been associated with adherence itself such as gender were not significantly associated with perceived barriers to adherence in this cohort[1]. Hollingshead SES scores specifically were not associated with reports of perceived barriers. It suggests that financial status does not easily map to perceived barriers of adherence and that perceived barriers can be very similar regardless of availability of financial resources. Given that most of the reported barriers were associated with scheduling and medication ingestion it seems appropriate that SES would not be differentially associated with these issues.

The lack of association between perceived barriers to adherence reported in the AMBS/PMBS and a single blood level of the primary immunosuppressant likely demonstrates the limitation of the adherence measure that was captured as a snapshot in this cross-sectional study design; additionally, missing data on this metric limits its usefulness. In this cohort, we could not assess for fluctuations in the standard deviation of immunosuppressive levels that have been previously associated with non-adherence in pediatric kidney, liver and heart transplant recipients. We did, however, adjust for differing target levels by organ and time since transplant by collecting the targeted range for each individual level collected and using this to benchmark the single immunosuppressive level. Although this is a clear limitation of the study, it provides an opportunity to explore the evolution of perceived barriers from being identified to their direct effect on medication management.

Additional limitations of this study include its cross-sectional single snapshot design, which may be influenced by acute or recent events that could under or overestimate barrier reporting. A longitudinal evaluation of perceived barriers in a subset of these patients is in process to address this issue. A recent study reported that specific barriers in adolescents and young adults remained fairly stable over the 18 months between assessments[21]. Since the subjects included were at a broad range of different time points post-transplant in cross-section, the degree of acuity versus chronicity of disease may have been different for each subject and was difficult to assess. Chronicity of disease and type of transplanted organ may also impact medication regimen complexity; the lack of information available in this regard could be considered as an additional limitation. Liver transplant recipients dominated in the younger age subgroup and the study group had relatively few lung transplant recipients overall. We did not collect demographic information on those who declined to participate. The study results may therefore not be completely generalizable, but it does reflect the largest cohort of pediatric solid organ transplant recipients evaluated to date. In addition, the subjects were enrolled at 15 different CTOT-C centers representing a broad range of social experiences; however all testing was completed in the outpatient area with the AMBS/PMBS being completed independently from a medical care provider for consistency. While the study may not be generalizable to cohorts outside of the United States, the increase in perceived barriers for guardians of older subjects was maintained across organ types indicating similarities that are unrelated to organ type or underlying etiology for transplantation.

Overall, our findings provide a window into the patient and caregivers' perceived barriers to medication management in the post-transplant period. Our study suggests that perceived barriers to adherence can be readily and effectively assessed through relatively simple and direct means in the outpatient setting with minimal additional time required from the patients and their families. A thorough understanding of perceived barriers to adherence can provide an avenue for intervention and improvement of the pediatric patient experience. Based on our findings, the perspective of both patients and their guardians is necessary as perspectives differ and caregivers may not always have a clear sense of the experience of the adolescent or pre-adolescent. As adolescents prepare for transition, unspoken or unknown barriers to adherence pose a significant threat to effective medication management. Barriers increase the challenges that guardians and medical providers experience in helping pediatric patients manage medical care and may undermine efforts to transition patients from pediatric to adult care if not effectively identified. In addition, perceived barriers could potentially escalate over time if not readily identified by the medical team. This could lead to increased frustration in patients and guardians as they try to navigate the "familial transition" of care from the parent to the child. Insight into the challenges faced by patients and caregivers can help focus efforts to ease the burden of medical management on families. For example, providers could address scheduling challenges by discussing alternatives with families, discussing single dosing (if feasible), and/or providing suggestions that would ease the burden. Providers could also point families toward appropriate support services such as adherence experts or mental health professionals who could work with families on swallowing medication or anticipatory anxiety before taking multiple medications.

Based on our findings we suggest that easily administered, brief screening measures can be utilized to assess perceived barriers among patients and guardians. Early identification of issues and provision of support/intervention could improve adherence, ease medication management, and potentially improve quality of life among pediatric and adolescent transplant patients and families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was performed as a project of the Clinical Trials in Organ Transplantation in Children, a collaborative clinical research project headquartered at the National Institute of Allergy and Infectious Diseases. The study was supported by a supplement to National Institutes of Health U01 grant (U01 AI077810) awarded to S. Sweet. We acknowledge feedback from Nancy Bridges at NIAID on the study design and interpretation of results.

The CTOT-05 consortium members thank the following personnel for the support of the work: Boston Children's Hospital, Boston MA: William Harmon, Leslie Spaneas, Erin Leone Thakkallapalli, Kate Garrigan, Molly O'Brien, Beatrice Dubert, Stephanie Valcourt-Dexter; Children's Hospital of New York, New York, NY: Linda Addonizio, Warren Zuckerman, Rose Rodriguez; Children's Hospital of Philadelphia: Samuel Goldfarb, Rosa Kim, Sara Nguyen; Children's Hospital of Pittsburgh: Steven Webber, Brian Feingold, Shawn West, Jane Luce; Children's Hospital Seattle: Ruth McDonald, Jodi Smith, Robert Johnson; Cleveland Clinic, Cleveland, OH: Johanna Goldfarb, Donna Lach; Emory University: Sandra Amaral, Verena Weissenborn, Rachel Dodd, Gail Schwartz, Monica Haughton, Lu Arechiga; Lucille Packard Children's Hospital at Stanford, Palo Alto, CA: Carol Conrad, Emily Orbe, Nirvi Mistry, Elisabeth Merkel, Suvarna Bhamre; Mattel Children's Hospital at UCLA, Los Angeles, CA: Eileen Tsai, Maggie Holloway, Claire White; Nationwide Children's Hospital, Columbus, OH: Don Hayes, Stephen Kirkby, Ashley Nance, Kerri Nicholson, Susan Meyer; Shands Children's Hospital, Gainesville, FL: Tracie

Kurtz; St. Louis Children's Hospital, St. Louis, MO: Colleen Eisenbarger; Texas Children's Hospital, Houston, TX: George Mallory, Marc Schecter, Tina Melicoff, Janet Bujan, Charles Sellers, Nicoline Schaap, Mea Ebenbichler; University of Alabama, Birmingham, AL: David Askenazi, Dan Feig, Amy Logue, Stephanie Clevenger, Rajesh Koralkar, Susan Keeling; University of California, San Francisco, CA: Marsha Lee, Stephanie Lemp, Jenny Chu, Vino Lakshamanan.

REFERENCES

1. Rianthavorn P, et al., Noncompliance with immunosuppressive medications in pediatric and adolescent patients receiving solid-organ transplants. *Transplantation*, 2004 77(5): p. 778–82. [PubMed: 15021848]
2. Simons LE and Blount RL, Identifying barriers to medication adherence in adolescent transplant recipients. *J Pediatr Psychol*, 2007 32(7): p. 831–44. [PubMed: 17522111]
3. Dew MA, et al., Meta-analysis of medical regimen adherence outcomes in pediatric solid organ transplantation. *Transplantation*, 2009 88(5): p. 736–46. [PubMed: 19741474]
4. Dobbels F, et al., Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. *Pediatr Transplant*, 2010 14(5): p. 603–13. [PubMed: 20214741]
5. Fredericks EM, et al., Assessment of transition readiness skills and adherence in pediatric liver transplant recipients. *Pediatr Transplant*, 2010 14(8): p. 944–53. [PubMed: 20598086]
6. Hsu DT, Biological and psychological differences in the child and adolescent transplant recipient. *Pediatr Transplant*, 2005 9(3): p. 416–21. [PubMed: 15910401]
7. Lawrence K, et al., Further exploration: maturity and adherence in adolescent and young adult heart transplant recipients. *Prog Transplant*, 2008 18(1): p. 50–4. [PubMed: 18429582]
8. Fredericks EM, et al., Psychological functioning, nonadherence and health outcomes after pediatric liver transplantation. *Am J Transplant*, 2007 7(8): p. 1974–83. [PubMed: 17617862]
9. Kahana S, Drotar D, and Frazier T, Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. *J Pediatr Psychol*, 2008 33(6): p. 590–611. [PubMed: 18192300]
10. Kahana SY, Frazier TW, and Drotar D, Preliminary quantitative investigation of predictors of treatment non-adherence in pediatric transplantation: a brief report. *Pediatr Transplant*, 2008 12(6): p. 656–60. [PubMed: 18798360]
11. Shemesh E, et al., Medication adherence in pediatric and adolescent liver transplant recipients. *Pediatrics*, 2004 113(4): p. 825–32. [PubMed: 15060234]
12. Simons LE, et al., Medication barriers predict adolescent transplant recipients' adherence and clinical outcomes at 18-month follow-up. *J Pediatr Psychol*, 2010 35(9): p. 1038–48. [PubMed: 20410021]
13. Guilfoyle SM, Goebel JW, and Pai AL, Efficacy and flexibility impact perceived adherence barriers in pediatric kidney post-transplantation. *Fam Syst Health*, 2011 29(1): p. 44–54. [PubMed: 21417523]
14. Hollingshead A, Four factor index of social status., 1975, Yale University, NewHaven, CT.
15. Svarstad BL, et al., The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. *Patient Educ Couns*, 1999 13: p. 113–124.
16. Foster BJ, et al., Association between age and graft failure rates in young kidney transplant recipients. *Transplantation*, 2011 92(11): p. 1237–43. [PubMed: 22124283]
17. Shrout P and Fleiss J, Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin*, 1979 86: p. 420–428. [PubMed: 18839484]
18. Winer B, Statistical Principles in Experimental Design 1971, New York: McGraw Hill.
19. Venkat VL, et al., An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. *Pediatr Transplant*, 2008 12(1): p. 67–72. [PubMed: 18186891]
20. Pai AL, et al., System for integrated adherence monitoring: real-time non-adherence risk assessment in pediatric kidney transplantation. *Pediatr Transplant*, 2012 16(4): p. 329–34. [PubMed: 22353189]

21. Lee JL, et al., Longitudinal stability of specific barriers to medication adherence. *J Pediatr Psychol*, 2014 39(7): p. 667–76. [PubMed: 24824613]
22. Delucchi A, et al., Factors that influence nonadherence in immunosuppressant treatment in pediatric transplant recipients: a proposal for an educational strategy. *Transplant Proc*, 2008 40(9): p. 3241–3. [PubMed: 19010243]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.
CTOTC-05 Cross-sectional Study Participant Flow

Figure 2.

Each PMBS item is rated on a 5-point scale from 1 (strongly disagree, low barrier) to 5 (strongly agree, high barrier). Factor scores are presented as the mean of the factor item ratings. Boxplots represent the inner quartile range of the data, with the median indicated by the center line, whiskers extending up to 1.5 times the length of the box, and outliers represented by an open circle. The mean for each age-organ group is represented by a solid colored circle, with colored lines connecting the means of the two age groups for the same organ.

Table 1

Demographics of study cohort by age group (N=368)

Factor	6–11 years (N=107)	12–21 years (N=261)	p-value
Male, No. (%)	63(59)	143(55)	0.47 ^c
Ethnicity and predominant race, No. (%)			0.073 ^c
. Non-Hispanic White	66(62)	128(49)	
. Non-Hispanic Black	15(14)	42(16)	
. Hispanic	14(13)	63(24)	
. Other/unknown	12(11)	28(11)	
Type of transplant, No. (%)			0.002 ^c
. Heart	29(27)	45(17)	
. Kidney	43(40)	159(61)	
. Liver	24(22)	29(11)	
. Lung	11(10)	27(10)	
. Heart/Lung	0(0)	1(0.4)	
Age at Transplant (yrs), Mean ± SD	5.6±3.6	12.4±5.0	<0.001 ^a
Months Transplant To study visit, Median (Min, Max)	24.0(1.2,131.1)	24.4(1.2,239.8)	0.87 ^b
Parent 1: male *, No. (%)	31(29)	85(34)	0.33 ^c
Education Score for Parent 1 *, Mean ± SD	5.1±1.2	4.8±1.6	0.018 ^a
Occupation score for Parent 1 *, Mean ± SD	6.5±1.8	5.8±2.3	0.012 ^a
Overall Hollingshead SES score *, Mean ± SD	47.8±12.0	42.2±15.1	<0.001 ^a
Parents married *, No. (%)	77(72)	166(67)	0.32 ^c
Medicaid, No. (%)	44(41)	119(46)	0.43 ^c
Difficulty paying for medication *, No. (%)	12(11)	24(9)	0.54 ^c
Receive multiple dose regimen *, No. (%)	102(96)	241(93)	0.25 ^c
Primary Immunosuppressive: Tacrolimus, No. (%)	90(84)	228(87)	0.41 ^c
Immunosuppressive levels under target *, No. (%)	35(37)	53(22)	0.006 ^c

* Data not available for all subjects. Missing values: Parent 1 male = 13, Education Score for Parent 1 = 12, Occupation score for Parent 1=108, Overall Hollingshead SES score = 55, Parents married = 12

Difficulty paying for medication =5, Receive multiple dose regimen = 3, Immunospressive levels under target=37

p-values

^aUnequal variance t-test

^bWilcoxon rank sum test

^cPearson's chi-square test.

Table 2.

Unadjusted and propensity-adjusted relationships between age at study visit and PMBS factors.

PMBS Factor	Age 6–11 (N=107) Mean (95% CI)	Age 12–21 (N=213) Mean (95% CI)	Mean difference (95% CI)	p-value
Medication Scheduling				
Unadjusted	1.75 (1.58, 1.91)	2.09 (1.98, 2.21)	0.35 (0.15, 0.55)	<0.001
PS adjusted	1.75 (1.58, 1.91)	2.09 (1.93, 2.26)	0.35 (0.12, 0.57)	0.002
Ingestion and Side Effects				
Unadjusted	1.90 (1.76, 2.03)	1.98 (1.89, 2.08)	0.09 (−0.08, 0.25)	0.30
PS adjusted	1.89 (1.76, 2.03)	1.95 (1.82, 2.09)	0.06 (−0.12, 0.24)	0.51
Medication and Disease Frustration				
Unadjusted	2.20 (2.00, 2.40)	2.60 (2.46, 2.75)	0.40 (0.16, 0.65)	0.001
PS adjusted	2.19 (1.99, 2.40)	2.57 (2.37, 2.78)	0.38 (0.11, 0.65)	0.006

Each PMBS item is rated on a 5-point scale from 1 (strongly disagree, low barrier) to 5 (strongly agree, high barrier). Factor scores are presented as the mean of the factor item ratings. Propensity-score adjusted group means are estimated at a propensity score of 0.50. All analyses performed with multiple imputation to account for missing data. Similar results were obtained when analysis was repeated on subjects after selecting on propensity range with greatest overlap (middle 80%).

Table 3.

Differences in PMBS and AMBS barriers overall (N=239) and by age at study visit. PMBS-AMBS < 0 indicates higher barriers on AMBS.

PMBS-AMBS Difference	Total (N=239)		Ages 8–11 (N=33)		Ages 12–21 years (N=206)	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Medication scheduling *	0.01±0.99	0.87	−0.35±0.87	0.025	0.07±1	0.32
Ingestion problems and side effects	−0.12±0.77	0.018	−0.28±0.66	0.019	−0.09±0.79	0.092
Medication and Disease frustration *	0.06±1.2	0.45	−0.45±1.37	0.066	0.14±1.17	0.081

Each PMBS and AMBS item is rated on a 5-point scale from 1 (strongly disagree, low barrier) to 5 (strongly agree, high barrier). Factor scores are presented as the mean of the factor item ratings.

* Data not available for all subjects. Missing values: Medication scheduling =2, Medication and disease frustration=1.

p-values are from paired t-tests of the hypotheses that there is no difference between PMBS and AMBS factor scores within each patient.

Table 4.

Differences in PMBS and AMBS items on the Ingestion Problems and Side Effects factor overall (N=239) and by age at study visit. PMBS-AMBS < 0 indicates higher barriers on AMBS.

Ingestion Problems and Side Effects Factor Item: PMBS-AMBS Difference	Total (N=239)		Ages 8–11 (N=33)		Ages 12–21 years (N=206)	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Medicine is hard to swallow	−0.23±1.07	0.001	−0.48±1.06	0.013	−0.19±1.06	0.011
Has too many side effects *	−0.12±1.2	0.11	−0.30±0.95	0.077	−0.09±1.2	0.28
Don't like what it does to my appearance *	−0.06±1.3	0.49	−0.30±1.3	0.19	−0.02±1.3	0.83
Medicine tastes bad *	−0.31±1.4	<0.001	0.06±1.4	0.81	−0.38±1.3	<0.001
Too many pills to take *	−0.06±1.4	0.47	−0.52±1.3	0.024	0.01±1.4	0.92
Don't want others to notice *	0.09±1.6	0.36	−0.15±1.3	0.52	0.14±1.6	0.24

Each PMBS and AMBS item is rated on a 5-point scale from 1 (strongly disagree, low barrier) to 5 (strongly agree, high barrier). Factor scores are presented as the mean of the factor item ratings.

* Data not available for all subjects. Missing values: Has too many side effects=2, Don't like what it does to my appearance=1, Medicine tastes bad=4, Too many pills to take=2, Don't want others to notice=5.

p-values are from paired t-tests of the hypotheses that there is no difference between PMBS and AMBS item scores within each patient.