Published in final edited form as:

Pediatr Transplant. 2019 May ; 23(3): e13361. doi:10.1111/petr.13361.

Perceived barriers to medication adherence remain stable following solid organ transplantation

DR. Lara Danziger-Isakov¹, Thomas W. Frazier², Sarah Worley², Nikki Williams³, Diana Shellmer⁴, DR. Vikas R. Dharnidharka⁵, Nitika A. Gupta⁶, David Ikle⁷, DR. Eyal Shemesh⁸, Stuart C. Sweet⁵ on behalf of the 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

⁸Icahn School of Medicine at Mount Sinai, New York City, NY

Abstract

Perceived barriers to adherence have previously been investigated in solid organ transplantation (SOT) to identify plausible intervention targets to improve adherence and transplant outcomes. . Fifteen centers in Clinical Trials in Organ Transplantation in Children enrolled patients longitudinally. Patients >8 years completed Adolescent Scale (AMBS) at two visits at least 6 months apart in the first 17 months post-transplant while their guardians completed Parent Medication Barriers Scale (PMBS). Differences over time for pre-identified AMBS/PMBS factors were analyzed. Perceived barrier reporting impact on subsequent tacrolimus (TAC) levels was assessed.

123 patients or their guardians completed PMBS or AMBS. 26 were 6–11 years; 97 were ≥ 12 . The final cohort consisted of kidney (66%), lung (19%), liver (8%), and heart (7%) recipients. Unadjusted analysis showed no statistically significant change in reported barriers from visit 1 (median 2.6 months, range 1.2–3.7 post-transplant) to visit 2 (median 12, range 8.9–16.5). Of 102 patients with TAC levels, 74 had a single level reported at both visits. The factor of 'Disease frustration' was identified through the PMBS/AMBS questions about fatigue around medication and disease. Each point increase in 'disease frustration' at visit 1 on the AMBS/PMBS doubled the odds of a lower-than-threshold tacrolimus level at visit 2.

Corresponding Author: Lara Danziger-Isakov, MD, MPH, 3333 Burnet Avenue, MLC 7017, Cincinnati, OH 45229, Office: 513-636-9101, Lara.Danziger-Isakov@cchmc.org.

Authorship Statement: Lara Danziger-Isakov, Thomas W. Frazier, Sarah Worley, Nikki Williams, David Ikle, Stuart C. Sweet: Designed the study, analyzed the data, and wrote the manuscript; Eyal Shemesh, Diana Shellmer, Vikas R. Dharnidharka, Nitika A. Gupta: Critically reviewed the manuscript and contributed to writing the paper.

No clear change in overall level of perceived barriers to medication adherence in the first-year post-transplant were seen in pediatric SOT. However, disease frustration early post-transplant was associated with a single subtherapeutic TAC levels at 12 months. A brief screening measure may allow for early self-identification of risk.

Keywords

Adherence; Pediatric; Solid organ transplant

Background

Medication non-adherence has been associated with poor outcomes after pediatric and adult solid organ transplantation (SOT). Investigators have reported a broad range (5–70%) of non-adherence to post-SOT treatment regimens [1–4], with increased non-adherence in adolescent populations (30–55%) [2, 5]. However, medication adherence is dynamic and barriers related to patient and family beliefs or experiences, social and economic factors, or health-system structure can potentially fluctuate in these complex patients with chronic medical illness.

Instruments that can be administered quickly and efficiently in the outpatient setting evaluating perceived barriers to adherence have been validated by correlating them to objective measures of adherence including pill counts, medication event monitoring systems (MEMS®) and serum drug levels [2, 6]. We previously evaluated perceived barriers to medication adherence with these questionnaires in a cross-section of pediatric and adolescent solid organ transplant recipients. Screening revealed guardians of older patients reported increased perceived barriers to adherence independent of socioeconomic status [7]. While no differences were seen in the reporting of perceived barriers based on the time from transplant in this cross-sectional cohort, changes over time in perceived barriers were not evaluated. If changes in perceived barriers can be predicted and/or the change can be identified as signaling risk, then it may allow for additional intervention and resource allocation for adherence improvement to significantly at-risk patients. Previously, studies have evaluated the changes in perceived barriers in pediatric organ transplant recipients over an 18 month period starting at least 4 months post-transplant finding that perceived barriers did not significantly change the study period. However, the post-transplant window for entry into the study was not standardized.

Therefore, we performed a longitudinal assessment of very recent transplant recipients over the first year post-transplant to evaluate the hypothesis that perceived barriers to adherence reported by pediatric and adolescent patients and their guardians would increase in severity as time from transplant increased.

Methods

After institutional review board approval at each site and registration at Clinicaltrials.gov (NCT01370746), 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[7]; however only outpatients over 5 years of age who were enrolled within 3 months of transplant were included in this analysis due to the validation of the measures (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), developed and evaluated in context of adherence in pediatric solid organ transplantation and previously described [2, 7, 8], were administered at 1–3 months post-transplant and 6–14 months after visit 1. Both the PMBS and ABMS were originally developed and validated with adolescent patients and their caregivers, but we have conducted further research to establish these measures are valid in their younger cohort[7]. 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 if present at the visit, and the AMBS was completed by children 8 years of age and older without significant developmental delay who were capable of independently completing the tool as assessed by the enrolling center staff. AMBS and PMBS were completed independently in the outpatient clinic area without intervention from the research coordinator. The PMBS and AMBS questions were each mapped to three factors (medication scheduling, ingestion problems/side effects, and medication or disease frustration) identified in our previous research including equivalence analyses of the measures [8]; factors were analyzed as item means. A single result of an immunosuppressive blood level was collected around the time of each visit for comparison to perceived barriers reported. This was not intended to directly measure adherence; however, targeted range for each level collected for that specific subject was collected and used to determine if the level was outside of the targeted immunosuppressive level range.

Data were described using medians and ranges or means and standard deviations for continuous variables and counts and percentages for categorical variables. Each of the 3 PMBS and 3 AMBS factors were analyzed separately. For analysis, race and ethnicity were collected and comparisons were made between non-Hispanic White and all other groups, and medical insurance was categorized as government-only and all others.

Several analyses were used to assess changes in perceived barriers over time. First, unadjusted analyses for change from visit 1 to visit 2 were performed using paired t-tests on data from patients with barrier score available at both visits; Cohen's *d* statistics were computed as a measure of effect size. Next, longitudinal mixed effects regression models were used to evaluate the relationship between PMBS and AMBS barriers and months from transplant to visit (treated as a continuous variable to take into account the range of time in which follow-up visits were scheduled); these models allow the inclusion of data from all available study visits for patients with incomplete data and the inclusion of a random intercept effect for study site Demographic and clinical characteristics (age at visit, transplant type, gender, race/ethnicity, insurance type, and parent marital status) and interactions between demographics/clinical variables and time since transplant were included as covariates when preliminary analyses indicated significant differences between groups. PMBS/AMBS measurements were treated as repeated measures effects within patients with unstructured correlation and transplant site was included as a random intercept

effect. Finally, for patients with barrier score available at both visits, mixed effects linear regression models for change in PMBS and AMBS factors from visit 1 to visit 2 assessed for associations between changes in self-reported perceived barriers and the baseline value of the barrier. We adjusted for time variables (time from transplant to first visit and time between visits) and demographic and clinical characteristics (see above), and interactions between demographics/clinical variables and barrier at visit 1 where significant, with a random intercept effect for transplant site. For all mixed effects regression models, effect sizes were calculated using Cohen's f^2 (local effect version)[9].

Tacrolimus levels were compared to target ranges and classified as below, or not below, target ranges. Target ranges were defined by the individual center for each patients based on time from transplant and clinical status. . The associations between perceived barriers at visit 1 and below-threshold Tacrolimus levels at visit 2 were assessed using logistic regression models, and odds ratios with their 95% confidence intervals were estimated.

Statistical analyses were performed using SAS 9.4 (Cary, NC). Longitudinal mixed effects regression models included all eligible patient visits with complete data on outcome and predictor variables. Analyses for change from visit 1 to visit 2, both unadjusted paired t-test and adjusted linear regression models for change, included only patients with complete data on outcome and predictor variables at both visits. All tests were two- tailed and performed at a significance level of 0.05.

Results

Patient Demographics

One-hundred twenty-three patients were enrolled and followed for the study (Figure 1). After excluding ineligible visits, there were 223 patient-visits available for analysis. Patients were a median of 15 years old at enrollment (range 6 to 20) with 79% between 12 and 21 years of age, and 56% were male (Table 1). Kidney transplant recipients were most common (66%) followed by lung (19%), liver (8%) and heart (7%) transplant recipients. Visit 1 occurred at a median of 2.6 months (range: 1.2–3.7 months) post-transplant, while Visit 2 occurred at a median of 12 months (8.9–16.5 months) post-transplant. The majority were receiving tacrolimus at both the first (93%) and second (82%) with 16% having a change in primary immunosuppressive medication between visits. Additionally, the percentage of patients on single drug immunosuppressive regimens increased from 1% at visit one to 6% at visit 2.

No clinically significant changes in perceived barriers over time

The internal consistency of the PMBS and AMBS barriers was assessed at both visits using Cronbach's alpha. Values for the medication scheduling, ingestion problems/side effects, and medication/disease frustration barriers for each questionnaire and visit were: PMBS at visit 1: 0.81, 0.72, and 0.72; PMBS at visit 2: 0.84, 0.77, and 0.67; AMBS at visit 1: 0.81, 0.72, and 0.72; and AMBS at visit 2: 0.70, 0.73, and 0.72). Only PMBS disease frustration at visit 2 was less than the acceptable threshold of 0.7. Unadjusted analysis showed no statistically significant change in reported perceived barriers from visit 1 to visit 2 for all six

of factors within the PMBS and AMBS (paired t-tests, $p \geq 0.10$, Table 2). In the longitudinal mixed effects regression models which treated time since transplant as a continuous variable, only ingestion problems on the PMBS were associated with time since transplant with a small but significant decrease in perceived barriers over time; however the mean decrease 0.02 per month (0.12 over a 6 month period) on the 5 point barrier scale between the two visits is unlikely to be clinically significant. In addition, a great deal of patient-to-patient variability was observed in the plots (Figures S1 and S2; 2b, ingestion problems). Some responses to perceived barriers were steady, others increased or decreased. No consistent directionality to the changes in perceived barrier reporting was evident for any of the six factors.

In the mixed effects regression models for change in PMBS and AMBS factors from visit 1 to visit 2 (Table 3), the models for all 6 factors show a significant association between barrier at visit 1 and change in barrier. Higher perceived barriers at visit 1 were negatively associated with changes in perceived barriers for all six factors in the PMBS and AMBS. This may reflect a limitation of the 5-point scale with higher perceived barrier reporting at visit 1 precluding substantial increases on the scale or a regression to the mean.

In addition, both the linear regression model and the longitudinal mixed model revealed a statistically significant association between non-Hispanic whites and disease frustration on the AMBS but not the PMBS; other interactions were not statistically significant.

Correlation between barriers and tacrolimus levels

One-hundred two patients had tacrolimus levels reported at the time of the first questionnaire and 85 at the time of the second questionnaire, with 74 having levels at both visits. Deviations outside of reported thresholds for each individual subject were reported, with about 30% below and 20% above the intended threshold identified for each patient by the enrolling center at both visits 1 and 2. Extreme deviations more than 25% above or below the intended threshold occurred in only 15% of patients at each visit. Visit 1 report of disease frustration on the AMBS and PMBS was associated with a two-fold increased risk of lower than threshold tacrolimus level at visit 2 (Table 4). The numbers of patients taking other immunosuppressive regimes were too small for analysis.

Discussion

We performed serial assessment of recent transplant recipients over the first year post-transplant to evaluate the hypothesis that perceived barriers to adherence reported by pediatric and adolescent patients and their guardians would increase as time from transplant increased. At the group level, the analyses did not identify clear and consistent increase or decrease in perceived barriers over time from transplant that were clinically significant, but there was substantial variability at the individual level. This finding is consistent with studies of smaller populations of pediatric solid organ transplant recipients conducted during similar time periods [6, 10]. The lack of clinically significant changes and stability of the measures in the group indicate that substantive change is unlikely without specific intervention although difference may be seen at the individual level.

Increasing literature indicates that more specific measures of non-adherence like Medication Level Variability Index (MLVI), which requires serial measurements of immunosuppressive levels acquired over time and beginning at least 3 months post-transplant, can evaluate adherence over time. Further, the Medication Adherence in Children who had a Liver Transplant (MALT) study identified that adherence can develop over time but non-adherence was unlikely to resolve in the absence of intervention [11]. In our study a potential early indicator, disease frustration within 1 to 3 months post-transplant which is prior to MLVI availability, on an easily administered questionnaire identified the risk for a sub-therapeutic tacrolimus level within the first post-transplant year, although we acknowledge a single tacrolimus level is not an ideal correlate for non-adherence. It could be hypothesized that frustration with medications and underlying disease state including additional transplant-specific complications and interventions could lead to avoidance of care. Additional factors that were not primarily assessed including complications or significant life events unrelated to transplantation could also contribute frustration with transplant outcomes. A very recent report by Eaton et al. suggests that self-reported measures of non-adherence underestimate non-adherence by the objective MLVI[12]. With the understanding that non-adherence is unlikely to abate without intervention based on the MALT study, it could be suggested that early identification of a barrier, within 3 months of transplantation prior to the availability of objective measures like MLVI, could prompt more intensive monitoring to detect non-adherence and intervene more efficiently. However, these hypotheses would require additional investigation.

As with our previous cross-sectional study in this population, there were some inherent limitations. First, when performing evaluations related to adherence, selection bias can occur as non-adherent patients may be less likely to present for therapy. However, in this cohort being assessed in the early post-transplant period (with enrollment from 1–3 months post-transplant), this bias is likely to be less evident as visits are more routinized although Visit 2 did occur between 6 and 14 months after visit 1. While some enrolled patients were participating in other CTOTC studies with multiple visits and serial monitoring, enrollment in this study was extended to any recent transplant recipient at a participating center and was not contingent on participation in a more intensive study protocol. Selection bias might be present, but it is less likely than most other adherence studies with the high-rate of completion of both study visits (92/123 enrollees, 75%) and the minimization of participant burden consistent with recommendations for avoiding selection bias in the transplant populations [13, 14]. Further, we acknowledge the distribution of transplant type in this study which includes a substantial proportion of lung transplant recipients, is different than the general population of pediatric organ transplant recipients which is largely renal. The study results may therefore not be completely generalizable, but it does reflect enrollment at 15 different CTOT-C centers representing a broad range of social experiences and all testing was completed in the outpatient area with the AMBS/PMBS being completed independently from a medical care provider for consistency. Additionally, our study only measured perceived barriers based on patient perception. Emerging evidence has ascertained that multi-level influences exist including barriers at the provider, organizational and policy level [15]. These were not addressed in the current study. The inclusion of two tacrolimus levels addresses some of the concerns raised with the prior cross-sectional study [14].

In conclusion, the evaluation of perceived barriers over time did not reveal substantial changes in the window of time (the first year post-transplant) that we observed indicating that patient-reported perceived barriers are stable over time. However, early report of disease frustration on the AMBS and PMBS was associated with a two-fold increased risk of lower than threshold tacrolimus level at the second visit. Early measurement with this basic tool may potentially provide early identification of individuals at risk who could benefit from closer objective monitoring of adherence measures, like MLVI which is determined in a later period post-transplant. Further evaluation of the predictive capacity of early screening in conjunction with other measures of non-adherence is warranted.

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; Lucile 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.

ABBREVIATIONS:

AMBS	Adolescent Medication Barriers Scale
CTOT-C	Clinical Trials in Organ Transplantation in Children
MALT	Medication Adherence in Children who had a Liver Transplant Study
MEMS®	medication event monitoring systems
MVLI	Medication Level Variability Index
PMBS	Parent Medication Barriers Scale
SOT	solid organ transplant
TAC	tacrolimus

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FIGURE 1:

CTOT-05 Longitudinal Study Participant Flow. a Includes one patient enrolled in cross-sectional study with two visits. b Four patients also completed one AMBS. c Four patients also completed one PMBS.

Table 1.

Descriptive statistics of study cohort (N=123)

Factor	n missing	Summary statistics
Age at visit ^a , Median (Min, Max)	0	15(6,20)
Sex, No. (%)	0	
. Female		54(44)
. Male		69(56)
Ethnicity and predominant race, No. (%)	0	
. Non-Hispanic White		51(41)
. Non-Hispanic Black		28(23)
. Hispanic		31(25)
. Other/unknown		13(11)
Type of transplant, No. (%)	0	
. Heart		9(7)
. Kidney		81(66)
. Liver		10(8)
. Lung		23(19)
Insurance: Government only, No. (%)	0	56(46)
Primary Immunosuppressive Medication at visit 1, No. (%)	0	
. Tacrolimus		115(93)
. Cyclosporine		5(4)
. Sirolimus		3(2)
Tacrolimus level below intended trough at visit 1, No./Total (%) ^b	21	31/102(30)
Receive multiple dose regimen at visit 1, No. (%)	15	107(99)
Primary Immunosuppressive Medication at visit 2, No. (%)	9	
. Tacrolimus		93(82)
. Cyclosporine		3(3)
. Sirolimus		18(16)
Tacrolimus level below intended trough at visit 2, No./Total (%) ^b	38	24/85(28)
Receive multiple dose regimen at visit 2, No. (%)	18	99(94)
Months Transplant To Visit at visit 1, Median (Min, Max)	13	3(1,4)
Months Transplant To Visit at visit 2, Median (Min, Max)	10	12(9,17)
Months from visit 1 to visit 2, Median (Min, Max)	23	9(6,14)

^a Age calculated at first visit. For 13 patients with excluded first visit, age was calculated at second visit.^b Total=number of patients with tacrolimus level recorded at that visit.

PMBS and AMBS factors at visit 1 and visit 2, differences, effect sizes, and unadjusted and adjusted changes (N=123). All factors were analyzed on a 5-point item mean scale with 1 indicating low barriers and 5 indicating high barriers.

Table 2.

Unadjusted analysis										Adjusted longitudinal analysis			
Visit 1		Visit 2		Change from visit 1 to visit 2			Change in factor per month, Time from transplant to visit						
N ^a	Mean ± SD	Mean ± SD	Mean (95% CI)	Effect size ^b	t statistic	p-value ^c	N visits/ N patients ^d	Estimate (95% CI)	Effect size ^e	t statistic	p-value ^f		
PMBS factors													
Medication scheduling	90	1.74±0.77	1.83±0.81	0.09 (−0.06, 0.24)	0.12	1.18	0.24	203/113	0.01 (−0.01, 0.02)	0.00	0.90	0.37	
Ingestion problems	88	2.05±0.68	1.93±0.68	−0.12 (−0.26, 0.02)	−0.18	−1.64	0.10	199/111	−0.02 (−0.03, 0.00)	0.02	−2.20	0.030	
Disease frustration	89	2.49±0.96	2.49±0.97	0.01 (−0.18, 0.19)	0.01	0.06	0.95	202/113	0.00 (−0.02, −0.02)	0.00	0.09	0.93	
AMBS factors													
Medication scheduling	81	1.58±0.57	1.71±0.68	0.13 (−0.04, 0.29)	0.17	1.56	0.12	179/101	0.01 (0.00,0.03)	0.01	1.55	0.12	
Ingestion problems	81	2.29±0.72	2.20±0.72	−0.10 (−0.25, 0.06)	−0.14	−1.22	0.23	179/101	−0.01 (−0.03,0.00)	0.01	−1.48	0.14	
Disease frustration	81	2.38±1.07	2.41±1.05	0.03 (−0.16, 0.22)	0.04	0.33	0.75	179/101	0.00 (−0.02, 0.02)	0.00	0.15	0.88	

CI=confidence interval

^aPatients with barrier factor calculated at both visits.

^bCohen's *d* statistic.

^cPaired t-test for change from visit 1 to visit 2.

^dPatients with barrier factor at 1 or 2 visits and complete data on all other factors.

^eCohen's *f*² statistic (local effect version) for time from transplant to visit.

^fLongitudinal mixed effects regression models treated months from transplant as a continuous variable, with adjustment for age at visit, transplant type, gender, race/ethnicity, insurance type, and parent marital status, and a random intercept effect for study site

Table 3.

Mixed effects linear regression models for change in PMBS/AMBS factors from visit 1 to visit 2^a

PMBS Factor:	Medication Scheduling			Ingestion Problems			Med/Disease Frustration		
Number of patients analyzed ^b :	90			88			89		
	Mean Change (95% CI)	Effect size ^c	P-value	Mean Change (95% CI)	Effect size ^c	P-value	Mean Change (95% CI)	Effect size ^c	P-value
Age at visit 1, per year higher	-0.00 (-0.05, 0.04)	0.00	0.88	0.00 (-0.04, 0.04)	0.00	0.93	-0.02 (-0.07, 0.03)	0.00	0.52
Liver vs kidney	0.04 (-0.50, 0.58)	0.00	0.88	-0.22 (-0.71, 0.26)	0.00	0.36	-0.08 (-0.68, 0.53)	0.00	0.80
Lung vs kidney	-0.22 (-0.66, 0.22)	0.00	0.32	-0.05 (-0.49, 0.40)	0.00	0.84	-0.38 (-0.88, 0.12)	0.02	0.14
Heart vs kidney	-0.22 (-0.99, 0.56)	0.00	0.58	-0.21 (-0.91, 0.49)	0.00	0.55	-0.25 (-1.11, 0.60)	0.00	0.56
Male vs female	0.02 (-0.29, 0.33)	0.00	0.88	-0.19 (-0.46, 0.09)	0.01	0.18	-0.21 (-0.55, 0.14)	0.00	0.23
Non-Hispanic White vs other	0.12 (-0.22, 0.46)	0.00	0.48	0.03 (-0.26, 0.33)	0.00	0.82	0.10 (-0.29, 0.49)	0.00	0.60
Insurance: Government Only	0.22 (-0.16, 0.59)	0.01	0.26	0.09 (-0.25, 0.43)	0.00	0.62	0.11 (-0.31, 0.52)	0.00	0.61
Parents Married	-0.03 (-0.39, 0.33)	0.00	0.86	-0.00 (-0.31, 0.30)	0.00	0.98	-0.01 (-0.40, 0.38)	0.00	0.95
Time from visit 1 to visit 2, per month	0.01 (-0.11, 0.12)	0.00	0.92	0.07 (-0.04, 0.17)	0.01	0.22	0.12 (-0.01, 0.25)	0.04	0.063
Time from transplant to visit 1, per month	-0.03 (-0.29, 0.23)	0.00	0.81	-0.09 (-0.32, 0.15)	0.00	0.45	-0.22 (-0.51, 0.07)	0.01	0.14
PMBS Factor at visit 1, per unit increase in score	-0.36 (-0.55, -0.16)	0.16	<0.001	-0.54 (-0.74, -0.34)	0.39	<0.001	-0.42 (-0.60, -0.23)	0.25	<0.001
AMBS Factor:	Medication Scheduling			Ingestion Problems			Med/Disease Frustration		
Number of patients analyzed ^b :	78			78			78		
	Mean Change (95% CI)	Effect size ^c	P-value	Mean Change (95% CI)	Effect size ^c	P-value	Mean Change (95% CI)	Effect size ^c	P-value
Age at visit 1, per year higher	-0.04 (-0.10, 0.03)	0.00	0.26	0.00 (-0.05, 0.06)	0.00	0.90	-0.01 (-0.08, 0.06)	0.00	0.82
Liver vs kidney	0.18 (-0.41, 0.76)	0.00	0.55	-0.05 (-0.59, 0.50)	0.00	0.86	0.22 (-0.47, 0.91)	0.00	0.53
Lung vs kidney	-0.05 (-0.54, 0.45)	0.00	0.85	0.32 (-0.12, 0.76)	0.02	0.15	0.26 (-0.30, 0.83)	0.00	0.36
Heart vs kidney	-0.35 (-1.09, 0.39)	0.00	0.35	0.22 (-0.46, 0.90)	0.00	0.53	0.45 (-0.43, 1.32)	0.00	0.31
Male vs female	-0.01 (-0.34, 0.32)	0.00	0.95	-0.00 (-0.31, 0.31)	0.00	0.99	0.11 (-0.28, 0.49)	0.00	0.57
Non-Hispanic White vs other	0.17 (-0.21, 0.55)	0.00	0.37	0.27 (-0.09, 0.62)	0.02	0.14	0.69 (0.22, 1.15)	0.12	0.004
Insurance: Government Only	-0.04 (-0.43, 0.35)	0.00	0.84	0.11 (-0.26, 0.48)	0.00	0.55	0.19 (-0.28, 0.66)	0.00	0.42
Parents Married	-0.42 (-0.79, -0.06)	0.06	0.025	-0.04 (-0.38, 0.30)	0.00	0.80	0.06 (-0.37, 0.49)	0.00	0.78
Time from visit 1 to visit 2, per month	-0.05 (-0.18, 0.08)	0.00	0.43	-0.01 (-0.13, 0.12)	0.00	0.93	-0.03 (-0.18, 0.13)	0.00	0.73
Time from transplant to visit 1, per month	-0.15 (-0.41, 0.10)	0.01	0.24	-0.24 (-0.48, 0.01)	0.04	0.056	-0.07 (-0.37, 0.23)	0.00	0.64

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AMBS factor at visit 1, per unit increase	-0.60 (-0.88, -0.33)	0.27	<0.001	-0.55 (-0.76, -0.33)	0.38	<0.001	-0.44 (-0.62, -0.26)	0.34	<0.001
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^aModels include all variables in the table as fixed effects and a random intercept effect for transplant site. PBMS/AMBS factors are analyzed as continuous variables.

^bPatients with the barrier factor available at both visits and with complete data for the specified variables.

^cCohen's χ^2 statistic (local effect version) for each factor.

Table 4.

Barriers predicting Tacrolimus level below intended trough at visit 2. Odds ratios are for 1 point increase in barrier on item mean scale as estimated in a logistic regression model treated barrier item mean as a continuous variable.

Barrier at visit 1	N below target /total ^a	Odds ratio (95% Confidence interval)	P-value
PMBS Medication scheduling	22/74	1.6 (0.85, 3.1)	0.137
PMBS Ingestion problems and side effects	21/72	1.7 (0.74, 3.9)	0.21
PMBS Medication and Disease frustration	22/74	1.9 (1.0, 3.6)	0.040
AMBS Medication scheduling	17/65	2.0 (0.77, 5.0)	0.16
AMBS Ingestion problems and side effects	17/65	2.2 (0.92, 5.3)	0.077
AMBS Medication and Disease frustration	17/65	2.1 (1.2, 3.9)	0.013

^aPatients with two visits and with tacrolimus target and level at visit 2.