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Implementing a Process to Systematically Identify and Address Poor Medication Adherence in Pediatric Liver Transplant Recipients

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Abstract

Objectives: Poor adherence to medication following pediatric liver transplantation remains a major challenge, with some estimates suggesting that 50% of adolescent liver transplant recipients exhibit reduced medication adherence. To date, no gold standard has emerged to address this challenge; however, system interventions are most likely to be successful. We sought to implement a system to identify and address adherence barriers in a liver transplant clinic. **Methods:** Using structured quality improvement methods, including multiple plan-do-study-act cycles, we developed a system to screen for patients at risk of poor adherence, identify patient- and/or parent-reported barriers to adherence, and partner with patients to overcome identified barriers. We developed a process to track key outcomes, including the variability in tacrolimus trough levels and episodes of late acute cellular rejection. **Results:** The practice saw a total of 85 patients over 6 months, and about half were females. Over this period, the improvement team implemented this system-level process with high reliability (>90% of patients received the bundle of interventions). The most commonly identified adherence barrier by patients and caregivers was "forgetting." The second most commonly identified adherence barrier by patients was that the medication "gets in the way of their activities," whereas by caregivers, it was "difficulty swallowing pills." **Discussion:** We identified challenges and opportunities to screen for poor adherence and identify patient- and/or caregiver-reported barriers to immunosuppression adherence. Identifying such barriers and partnering with patients to overcome those barriers using patient-centered, barrier-specific interventions could improve long-term graft survival through improved medication adherence. *(Pediatr Qual Saf 2020;3:e296; doi: 10.1097/pq9.0000000000000296; Published online May 5, 2020.)*

BACKGROUND

Effective self-management is necessary to achieve ideal outcomes[1] following pediatric liver transplantation. Poor adherence to immunosuppression affects more than 50%[2,3] of solid organ transplant recipients, especially adolescents, and accounts for 90% of episodes of late T-cell–mediated rejection (TCMR).[4–6] Recurrent TCMR episodes and persistent poor adherence jeopardize the organ transplant.[2]

There is no gold standard for addressing poor medication adherence in pediatric liver transplant recipients,[7] yet patient-reported barriers for taking medication may predict adverse outcomes such as rejection, hospitalization, and death following transplantation.[8] A system-based program to screen for patients at risk for poor adherence[6,9] and to identify barriers to taking medication[10] could allow for targeted medication adherence interventions. Systems-based approaches have been developed and implemented for children with chronic diseases,[11] including those with a kidney transplant.[10] In the latter group, implementation of a system to screen for poor adherence, identify patient- and/or parent-reported barriers to adherence, and deliver patient-centered barrier-specific interventions was associated with a decrease in late acute rejection.[12] This system was developed using the model for improvement to address poor adherence after pediatric kidney transplantation.[9,10,12]

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The goal of this project was to adapt and implement a similar approach[9,10] in a population of liver transplant recipients. This objective was an institutional priority because of the high prevalence of poor adherence after liver transplantation and the recent successes in kidney transplant recipients. Importantly, this program focused on adherence to tacrolimus immunosuppression because: (1) this is the most common immunosuppressive agent used after solid organ transplant; (2) providers routinely measure drug levels; and (3) increased drug level variability is a surrogate for poor adherence and predicts adverse outcome.[6,13] The SMART aim was to implement, within 6 months, the intervention bundle in >90% of eligible patients presenting for their annual liver transplant appointment. We report our experience using the SQUIRE 2.0 guidelines.[14]

METHODS

Context
The Liver Transplant Center includes 9 pediatric transplant hepatologists, 13 clinical fellows, 5 nurse coordinators, 1 pharmacist, a nursing manager, and a program manager. The institution performs approximately 20 transplants annually and follows about 300 liver transplant recipients. After the first year, patients have outpatient laboratory monitoring quarterly and clinic appointments annually. When a patient arrives, a medical assistant (MA) obtains vital signs, and then a transplant nurse coordinator and a hepatologist both evaluate the patient. A clinical fellow may also evaluate the patient. The hepatologist assesses for medical complications, whereas the transplant nurse coordinator ensures that the patient/caregivers understand changes to the management plan. The transplant nurse coordinator discharges the patient. The care team can engage the pharmacist if needed. Before beginning this work, there was no formal process of assessing adherence to immunosuppression or identifying patient- or parent-reported barriers to medication adherence. Patients were eligible for inclusion if they were presenting for their annual appointment, received an isolated liver transplant, taking tacrolimus, and receiving posttransplant care at our institution. This process was implemented between October 2018 and April 2019. Data collected included: tacrolimus trough levels, history of TCMR episodes, and patient- and/or caregiver-reported barriers to medication adherence. This project was a quality improvement initiative and not human subject research. Therefore, review and approval by the institutional review board were not required.

Interventions
Key Drivers
We assembled a multidisciplinary team consisting of a gastroenterology fellow, quality improvement consultant, administrative intern, clinical nurse manager, pharmacist, nurse transplant coordinator, a hepatologist, and data analyst to adapt, test, and implement MAPS.[12] The team met for 60 minutes weekly to develop the process. Early in the process, a "key driver" diagram (Fig. 1) was adapted to represent the theoretical model of system change necessary to identify and address adherence barriers in our population. The overarching goal was to implement a set of complementary processes to (1) screen for risk of poor adherence using an objective risk score; (2) assess patient- and/or caregiver-reported barriers to medication adherence using a barriers assessment tool (BAT); and (3) provide a targeted intervention directed at patient- and/or caregiver-reported barriers to medication adherence. We followed the model for improvement,[15] using iterative plan-do-study-act (PDSA) cycles to implement bundle components reliably.

Adherence Risk Score
We adapted a risk score[9] to screen patients for poor adherence before their annual appointment. We designed this score to augment clinical reasoning using data available from the electronic health record (EHR) rather than as a diagnostic tool. The score included: (1) Medication Level Variability Index (MLVI) >2.0 (a known predictor of late TCMR[6] defined as the SD of tacrolimus troughs collected over the past year); (2) missed laboratory appointments (<4 tacrolimus trough levels in the preceding year); and (3) previous late TCMR (defined as TCMR older than 1 y after transplant).[6,13,16,17] A positive flag for MLVI was 2 points, and positive flags for missed laboratory appointments or history of late TCMR are 1 point. Patient charts were identified as green (0 points), yellow (1 point), or red (≥2 points). Providers identified patients with persistently low or undetectable levels at the time drug levels were drawn. We assumed that providers knew when a patient was undergoing intentional drug minimization.

Barriers Assessment Tool
To identify patient- and parent-reported barriers to medication adherence, we administered the BAT during the annual visit.[10] This instrument was developed for use in kidney transplant recipients[18] and is available in English, Spanish, and Arabic. It asks "what gets in the way of taking your immunosuppressive medication" and includes 14 barriers spanning multiple dimensions. Patients and/or caregivers can identify multiple barriers. Caregivers completed the BAT for patients younger than 10 years of age, and both patients and caregivers, if present, completed the screen in patients 10 years and older of age.

Patient-centered, Barrier-specific Interventions
The transplant nurse coordinators and attending hepatologists were each responsible for addressing a subset of the barriers, if identified, and for partnering with patients to identify the most acceptable approach to overcome the identified barrier. Shared decision-making tools had been previously developed by clinical psychologists and members of the kidney transplant team to address the most common barriers (forgetting, dislike the taste, hard to swallow pills, do not like the side effects, do not want others to

know I take medicine). For example, if a patient identified "forgetting" as a barrier, the transplant nurse coordinator could utilize the "Forgetting Action Plan" tool to develop strategies to overcome this barrier collaboratively. Other barriers might prompt the provider to refer the patient to a social worker (eg, socioeconomic barriers identified), psychology referral (eg, mental health concerns or intentional nonadherence), or a more in-depth discussion with the provider (eg, the patient perceives too many medications). The provider team had discretion on how to address identified barriers and how to prioritize them when patients and/or caregivers identified multiple barriers.

Culture of Nonjudgment
Once the process began, we realized that additional training on medication adherence counseling was necessary. We partnered with 2 clinical psychologists with expertise in medication adherence to provide training for all transplant coordinators and attending physicians on evidence-based adherence counseling. The goal of the training sessions was to provide instruction on normalizing discussions around medication adherence and create a safe environment for patients to discuss barriers that they encounter.

Measures
Process Measure
The primary process measure was the percentage of eligible patients that received the entire "bundle" at the time of their annual visit. The bundle consisted of (1) point-of-care delivery of the adherence risk score; (2) correct completion of the BAT; and (3) an intervention is undertaken when the patient/caregiver identified a barrier to adherence. We defined the presence of an intervention if the transplant nurse coordinator and/or hepatologist discussed medication adherence when a barrier was identified. The denominator was each consecutive group of 5 eligible patients seen in the clinic, and the numerator was the number of those patients who properly received the "bundle." We aimed for 90% reliability of bundle implementation. We defined failure as missing any of the 3 components. The nurse transplant coordinator on the implementation team tracked bundle success weekly for patients seen the preceding week in a spreadsheet outside of the EHR. Following implementation, we monitored bundle delivery to ensure continued reliability.

Outcome Measures
Outcome measures included the percentage of the target population with MLVI > 2.0 and patient-days between episodes of TCMR in the population (G-chart).[19] We calculated the percentage of patients with an MLVI > 2.0 monthly. We calculated the number of patients followed in the practice who met inclusion criteria on the first of each month. We calculated the patient-days between each episode by multiplying the number of days between each rejection episode by the average number of eligible

patients followed in the practice during that period. We chose patient-days between each episode of rejection because, in time-series analysis, patient-days between episodes is a sensitive measure to detect improvement for rare events[19] and late TCMR is a rare event. Although we did not anticipate these measures to improve throughout the implementation phase of this project, we aimed to create a tracking system to monitor outcomes over the long term. Therefore, these charts included all patients in the practice as the goal of this project is to ultimately improve outcomes for the entire cohort of pediatric liver transplant recipients at this single center.

Statistical Analyses
We performed time-series analyses on process and outcome measures. Process and outcome measures were plotted on run charts or statistical process control charts, as described earlier. For a run chart, a shift was made in the centerline according to published run chart rules.[15] We considered 8 consecutive points above the median line as evidence of improvement. We plotted the percentage of the population with MLVI > 2.0 on a p-chart. We plotted patient-days between TCMR episodes on a G-chart.[19] We developed these outcome measures primarily to establish baseline rates for future studies on the effectiveness of this system-level intervention. Therefore, we did not adjust centerline or control limits for this study.

RESULTS
Table 1 depicts the demographic characteristics of the patients seen for annual appointments during the

Table 1. Patient Characteristics (N = 85)

Variable	Mean ± SD or N (%)
Age	13.6 ± 5.9
Female	44 (51.8)
Race	
White	71 (83.5)
Black	6 (7.0)
Asian	2 (2.4)
Hispanic	5 (5.9)
Other	1 (1.2)
Underlying liver disease*	
Biliary atresia	47 (55.3)
Other cholestatic	11 (12.9)
Acute liver failure	5 (5.9)
Metabolic	7 (8.2)
Tumor	12 (14.1)
Autoimmune hepatitis	3 (3.5)
Other	2 (2.4)
Adherence risk score†	
0	26 (30.6)
1	9 (10.6)
≥2	34 (40)
No. barriers identified	
0	62 (72.9)
1	11 (12.9)
≥2	12 (14.1)

*Two patients had a liver tumor secondary to underlying cholestatic liver disease.
†When this initiative first began, the adherence risk score was not yet calculated. Therefore, not all patients have a risk score available during the study period.

implementation phase of the project. Approximately, 40% of our patients flagged as high risk for poor adherence, and 27% of patients identified at least one barrier to medication adherence. Figure 2 depicts the run chart for the adherence bundle. It took approximately 6 months to implement the bundle. Over this time, we tested multiple PDSAs (annotated in Fig. 2). Figure 3 displays the outcome data on statistical process control charts. Descriptions of the PDSAs are below:

Adherence Risk Score

The team adapted a risk score from a renal transplant program.[9] For the first trial, we incorporated the risk score into weekly emails distributed to the clinical team. We found that providers were unaware of the score at the time of the clinic visit. For the second trial, providers discussed the risk score at a weekly previsit planning meeting. Again, we found that providers were unaware of the patient's risk at the clinical encounter. For the third trial, we tested point-of-care delivery. A list of scores was sent to the lead clinic MA weekly. The MA placed a small green, yellow, or red card indicating the risk level in the patient's examination room at the time of the appointment. The MA placed the score underneath the completed barriers screen to present it discretely to the hepatologist and transplant nurse coordinator and not the patient/family. Based on positive feedback from the providers, we increased the reliability of this process. For the fourth

trial, we collaborated with the lead MA to train the alternate MAs in the clinic. Furthermore, we included the MAs in the weekly distribution of the risk score. Informally, the MA reported no difficulty in incorporating this process into their workflow.

Barriers Assessment Tool

The MA provided the BAT on paper to patients and/or caregivers when rooming the patient. For the first trial, the MA set the completed BAT on the physician's desk; however, the physicians were overlooking the BAT. Furthermore, transplant nurse coordinators reported being unaware of any identified barriers. For the second trial, we adapted the process to keep the completed BAT in the room. We found that all providers preferred this strategy. The MA reported no detriment to clinic efficiency. Figure 4 displays a Pareto chart of the barriers identified by the patient/caregiver. The most common barrier identified for both caregivers and patients was "forgetting." Patients identified "getting in the way of their other activities" as the second most common barrier, whereas caregivers described "difficulty swallowing pills." The third most common barrier identified by both caregivers and patients was "side effects."

Patient-centered, Barrier-specific Interventions

For the first trial, we displayed a care algorithm in the clinic for providers to determine the correct intervention.
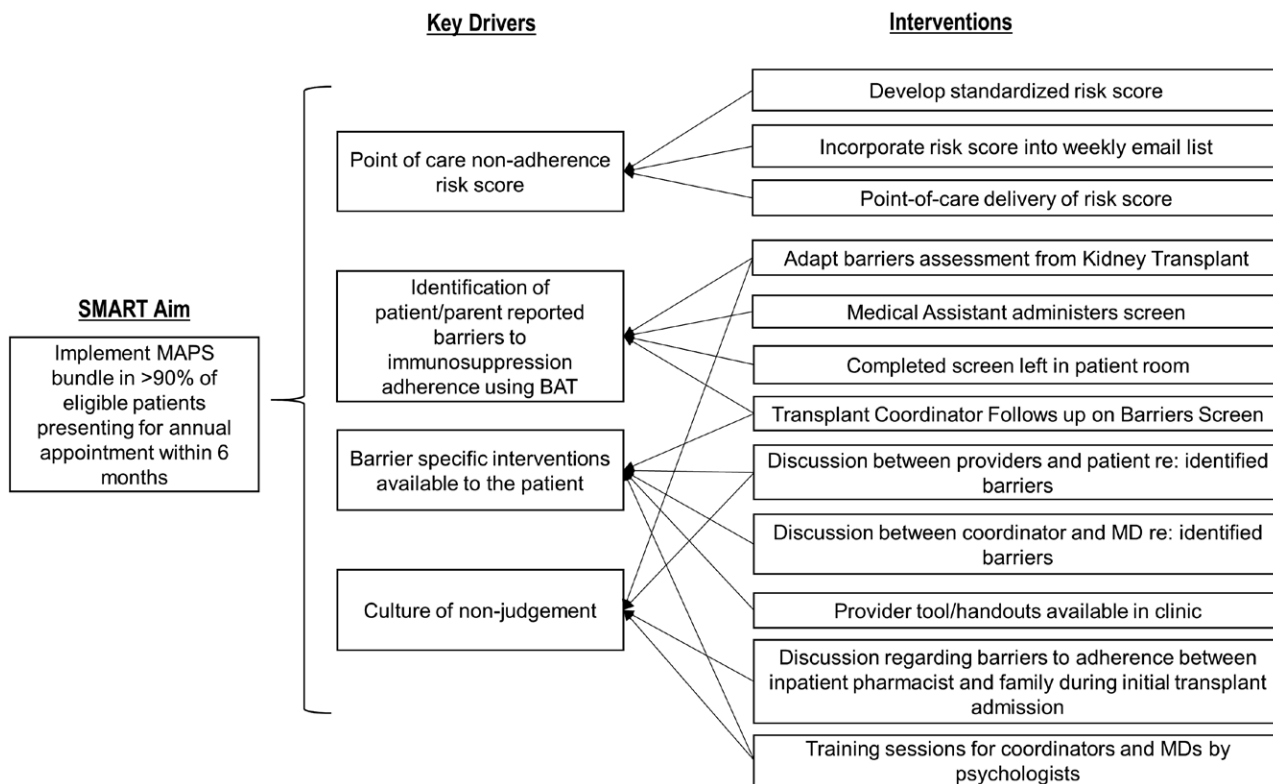

Fig. 1. Key driver diagram. The key driver diagram is the theory of change for the improvement initiative and informs plan-do-study-act cycles. MD, medical doctor; POC, point of care; PVP, previsit planning; Re, regarding; SMART, specific, measurable, achievable, relevant, time-bound.
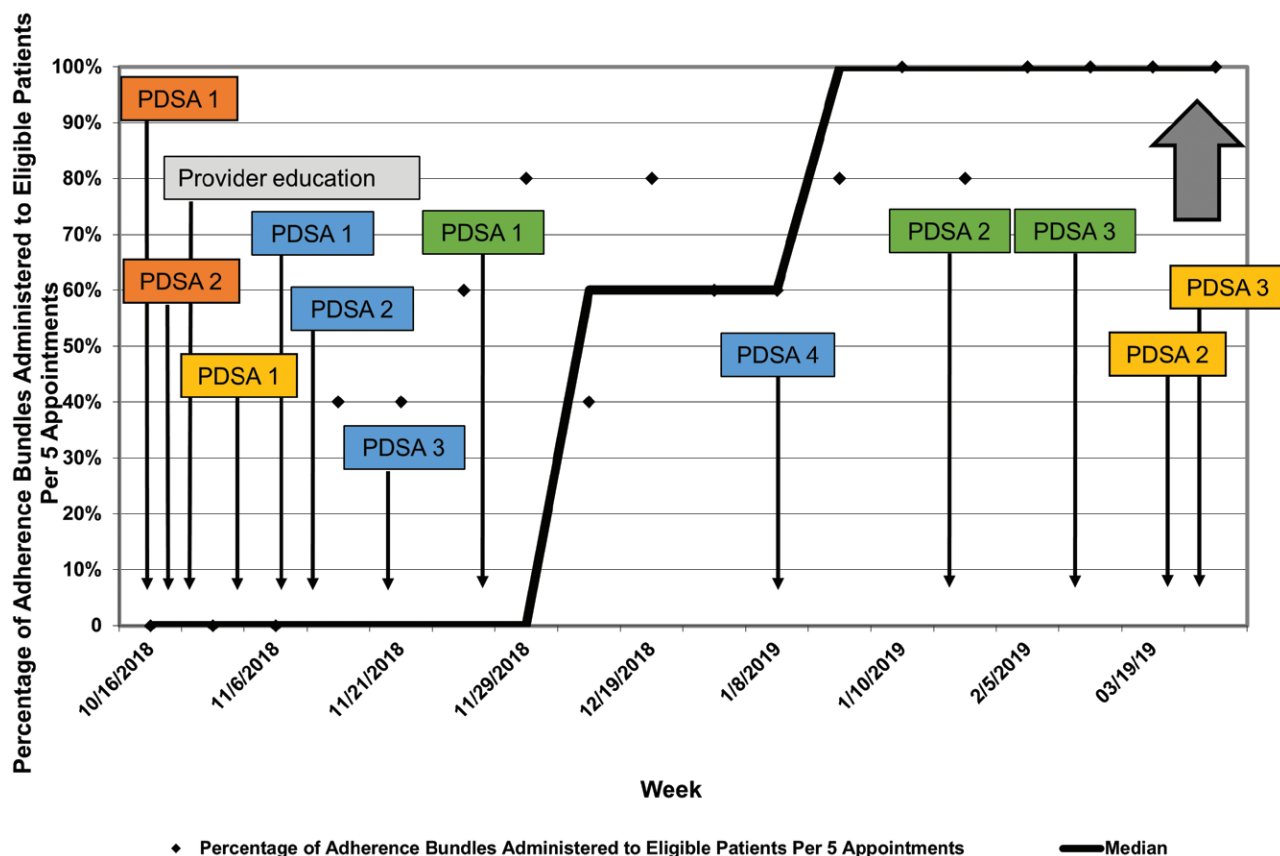
Fig. 2. Run chart for implementation of the adherence bundle. This is a run chart that displays the implementation of the adherence bundle over time. Each point represents the percentage of patients (per 5 patients seen) who correctly received the bundle. A shift in the median line can only occur when there are 8 consecutive points above the line. The arrow indicates the desired direction of the median line. The authors annotated the chart by PDSA cycles color-coded by the component of the bundle that they were designed to address. Risk score (blue boxes): PDSA 1—emailing risk score weekly; PDSA 2—discussing risk score at weekly previsit planning meeting; PDSA 3—point of care risk score delivery; PDSA 4—teaching all medical assistants how to deliver risk score. Barriers Assessment (orange boxes): PDSA 1—paper assessment brought out to physician after being completed; PDSA 2—paper assessment left in the examination room for physician and coordinator after being completed. Intervention (green boxes): PDSA 1—shared decision-making tools and intervention map available in clinic workroom; PDSA 2—shared decision-making tools and intervention map in each examination room; PDSA 3—started implementing follow-up phone calls. Culture of nonjudgment (yellow boxes): PDSA 1—training session for transplant nurse coordinators; PDSA 2—training session for select hepatologists; PDSA 3—in-patient adherence counseling by a pharmacist. PDSA, plan-do-study-act cycle.

Barrier-specific shared decision-making tools were available in the clinic workroom. The providers reported difficulty leaving the examination room to obtain a shared decision-making tool. For the second trial, we installed a folder containing the laminated care algorithm and shared decision-making tools within each room. The providers reported improved efficiency during the encounter, and the MA reported that restocking the rooms did not impact workload. For the third trial, we tested a follow-up phone call. If the patient identified a barrier, the transplant coordinator scheduled a phone call 4–6 weeks after the appointment to discuss progress on addressing the barrier. Further follow-up calls were at the discretion of the provider.

Culture of Nonjudgment
For the first trial, the transplant coordinators received a 1-hour interactive training session on nonjudgmental

adherence counseling. They reported a positive experience. For the second trial, a group of 3 attending hepatologists received a 30-minute interactive training session. They reported it useful to hear techniques in shared decision making. They advocated for the other attending physicians and trainees to undergo similar training, which has thus far not occurred. Finally, for the third trial, to further normalize medication adherence discussions, we implemented adherence counseling by the inpatient pharmacist at the time of discharge from the transplant admission. The pharmacist would also attempt to identify barriers before any discharges for late TCMR admissions.

DISCUSSION
We used the model for improvement and iterative testing to implement a systems-based approach to identify and address patient-reported barriers to medication
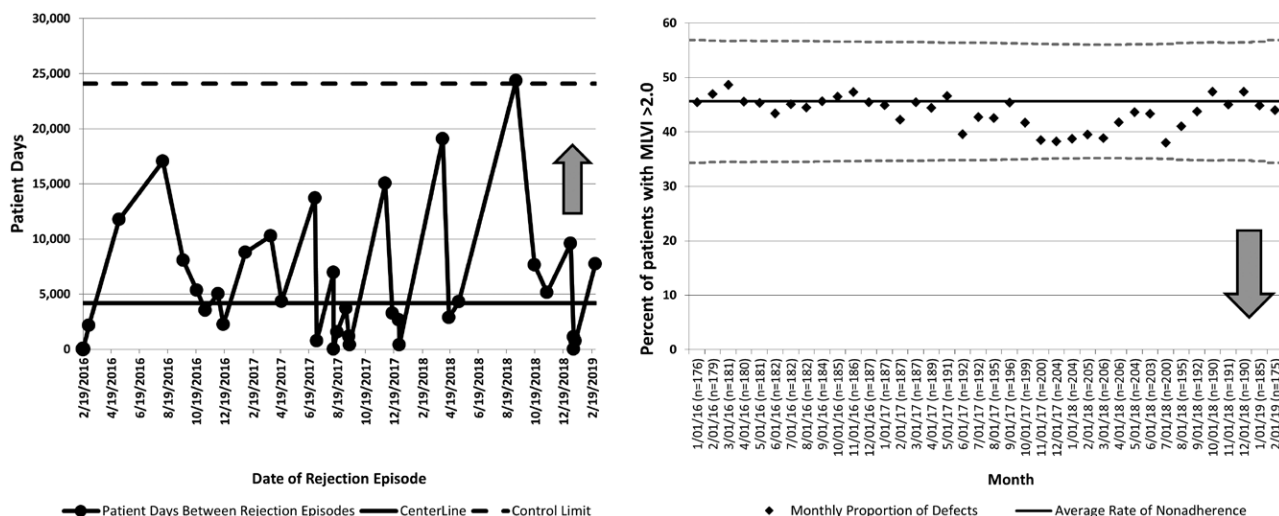
Fig. 3. Control charts for outcome measures. A, Patient*days between biopsy-proven TCMR events. B, Percent of patients with MLVI > 2.0 by month. Arrows indicate the desired direction for the data. A, A G-chart is used for attribute data when the events are rare. Because late TCMR is a relatively rare occurrence, a G-chart is a useful tool for measuring changes in the incidence of late TCMR. This chart measures patient-days between episodes of rejection. A point depicts each episode of rejection on the graph. We depict the total number of patients in practice multiplied by the number of days since the previous episode of rejection on the *y* axis and the date of the rejection episode on the *x* axis. The goal is for the patient-days to increase between rejection episodes.

adherence. Through training by clinical psychologists and shared decision-making tools, we sought to create a culture of nonjudgment. The providers reported that this process helped frame the discussion on medication adherence. Although other liver transplant centers looking to adapt this work may have different team structures, we believe implementing the core elements of this process (risk stratification, patient- and/or caregiver-reported barriers assessment, targeted interventions, and a nonjudgmental culture) might lead to improved outcomes for pediatric liver transplant recipients.

Interestingly, "forgetting" was the most common barrier identified by both caregivers and patients in our population, which is similar to the most commonly identified barrier as reported by Varnell et al.[10] However, the second most commonly identified barrier by patients in our cohort was that it "gets in the way" of their other activities. For caregivers in our cohort, the most common barrier identified was that their child had "difficulty swallowing pills." This finding differed from Varnell et al.[10] where patients and caregivers reported "side effects" as the second most common barrier. The reasons for these differences across organs are unclear but may reflect the age at transplant, different posttransplant medication regimens, or different practice patterns. We suspect that barriers to medication adherence may vary by population and age—underscoring the importance of system-level interventions capable of addressing a variety of adherence barriers at the point of care. The most challenging and subjective aspect of this initiative was fostering a culture of nonjudgment. There is evidence that collaborative problem-solving between providers and patients leads to greater self-management.[3,20] The BAT, along with the training sessions with clinical

psychologists, aimed to change the dialog around medication adherence from punitive to collaborative. However, there remains an ongoing challenge to normalize conversations on medication adherence and approach poor adherence as a collaborative problem to solve. Indeed, we continue to advocate for ongoing training and collaboration with our clinical psychology team to ensure that all providers receive similar training in nonjudgmental dialog.

We acknowledge the following limitations. First, we settled on a point-of-care modality for the adherence risk score. This method is still person-dependent—further work is needed to integrate this score into the EHR to ensure higher reliability. The reliability of barriers screen is also person dependent—the MA is responsible for administering the barriers screen to all liver transplant recipients at their annual visit. The use of a tablet with "firing" rules based on the EHR-coded encounter type could lead to increased reliability.[10] Last, there are important differences between the kidney and liver transplant groups at our institution. Although the kidney transplant group sees posttransplant patients every 3 months, we see patients annually. This decreased frequency may be inadequate to affect adherence behaviors. Within the kidney transplant group, all the providers (physicians and nurse transplant coordinators) meet weekly to discuss upcoming patients and their adherence risk. This practice might allow for greater standardization than point-of-care adherence risk scores. Finally, improving adherence would be expected to decrease the incidence of TCMR independent of the organ by ensuring more consistent serum immunosuppression levels.
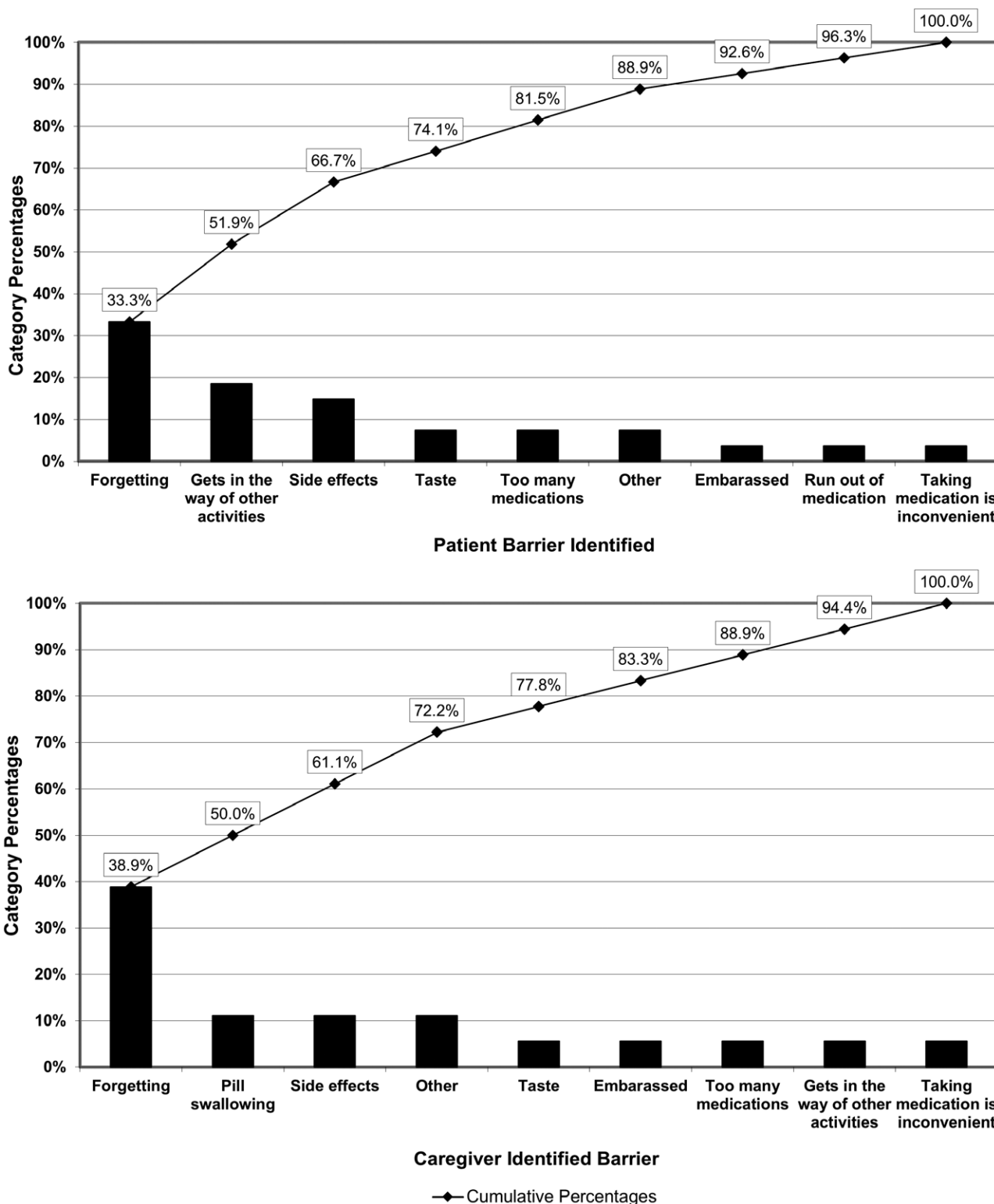
Fig. 4. Pareto charts of (A) patient and (B) caregiver identified barriers. The Pareto chart depicts identified barriers in order of most to least common. The top line indicates the cumulative percentage.

Our data demonstrate that roughly 45% of patients have MLVI > 2.0. To our knowledge, system-level interventions in this population have rarely been explored.[10,21] We adapted a successful system-level intervention for kidney transplant recipients[12] to a population of liver transplant recipients. It remains unknown whether this system-wide intervention will result in a decrease in late TCMR among our patients; however, we demonstrate that implementing such an intervention is feasible and requires minimal resources. Furthermore, we provide a

roadmap for tracking outcomes robustly to assess the utility of this process. The next phase of this improvement initiative is to determine if the process will lead to improved outcomes for pediatric liver transplant recipients.

In conclusion, we adapted and implemented a reliable systems-based, in-clinic medication adherence promotion system for pediatric liver transplant recipients. Through the use of an objective risk score, shared-decision making, and a nonjudgmental culture, we sought to improve outcomes for pediatric liver transplant recipients. By addressing perceived patient barriers, we believe patients will be less likely to experience TCMR and consequently improve allograft survival.[22]

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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