Adherence in Solid Organ Transplantation

Consensus Conference Reports and Recommendations

· This report highlights the need to individualize and simplify IST to mitigate short- and long-term adverse side effects, and gain clarity about optimal vs acceptable medication adherence. Participants were clear that problems with current nonspecific IST lead not only to adverse physiological health conditions, but myriad emotional health problems. As new approaches to therapy are being developed, it is critical for the drug developers and regulatory agencies to include the issues articulated by patients, such as those discussed in this conference, if the innovations are to accomplish the goal of better healthcare for solid organ transplant recipients.


· This report aimed to define non-adherence, describe its prevalence, how it can be measured, what the risk factors might be, and what clinical impacts it can have on patients using immunosuppressant medications. Additionally, this report attempted to provide recommendations for future study.


· In these consensus recommendations, members of the AST TxPharm COP met to identify unmet research needs related to medication nonadherence in transplant and presented on past, present and future directions of medication nonadherence and unmet research needs in the area. Key next steps for addressing nonadherence that were identified include development of a cost-effective, nonspecialized intervention(s) that does not require high levels of health literacy and can be adapted to multiple organs, as well as the use of tools to detect nonadherence that also address the issue as well. This meeting also resulted in the development of the AST Transplant Pharmacy Adherence Consortium (TPAC), which is dedicated to fostering development of a research agenda and connecting resources/researchers in the areas of adherence.

In these consensus recommendations, the AST Psychosocial and Pharmacy CoPs came together to develop a list of strategies using available resources, clinically feasible methods of screening and tracking adherence, and activities that ultimately empower patients to improve their own self-management.


The COMMIT group was formed in 2015 and is composed of 20 leading kidney and liver transplant specialists from 9 countries across Europe. The objective of this supplement is to provide specific, practical recommendations, through the discussion of current evidence and best practice, for the management of modifiable risks in those kidney and liver transplant patients who have survived the first postoperative year. In addition, the provision of a checklist increases the clinical utility and accessibility of these recommendations, by offering a systematic and efficient way to implement screening and monitoring of modifiable risks in the clinical setting.

**Review Articles**


This literature review developed a model to better depict factors associated with low health literacy, including adherence. The impact of these factors and their relationships to solid organ transplant recipient outcomes are reviewed.


In this literature review of 38 articles measuring nonadherence, nonadherence was associated with poor clinical outcomes, lower lifetime costs because of shorter survival, and a lower number of quality adjusted life years. Consistent determinants of nonadherence were found to be younger age, social isolation, and cognitions such as low self-efficacy, specific health beliefs. A limitation of this review is that the evidence summarized is based on older immunosuppressive regimens; further research would need to be conducted in order to characterize determinants of nonadherence in newer immunosuppressive regimens.

- This commentary comprehensively reviews current literature to identify factors that contribute to solid-organ transplant patient non-adherence and to explore potential solutions.


- This systematic review identified 41 studies that evaluated outcomes of various interventions to improve medication adherence in solid organ transplant recipients. The authors conclude that adherence interventions to date have been largely ineffective in improving transplant outcomes. Future interventions may wish to concentrate on non-adherent patients rather than using convenience sampling, use direct measures of adherence to guide the interventions, and employ strategies that are intensive and yet engaging enough to ensure that non-adherent patients are able to participate.


- This study searched for and identified 367 unique evaluable adherence applications. The results of this study included scoring of apps and inclusion of the 100 highest-scoring apps onto a searchable website for healthcare providers and patients to use to identify potential apps that may benefit them ([www.medappfinder.com](http://www.medappfinder.com)).

**Adherence Assessment Tools**


- This study assessed and validated a five-item scale that measures patients’ adherence to immunosuppression therapy. The scale included one item that was deleted due to lack of response variability, and the published results of the four-item scale are the first published and validated instrument for measurement of adherence to immunosuppressive therapy.


- This observational study evaluated patient adherence using the “compliance evaluation test” and through physician a “visual analog scale”. Determinants of adherence were then explored.

- This study evaluated tools suitable for annual routine capture of adherence data in renal transplant patients. The BAASIS© overall response rate was over 80%. Intensive BAASIS© assessment early after transplantation increased the chance of capturing a nonadherence event, but did not influence the 1-year adherence prevalence. The adherence-tools generally captured different populations. Combining these tools is feasible for annual capture of adherence status.


- This study aimed to determine whether parameters of a model adapted from the theory of planned behavior (attitudes and beliefs) could predict adherence in transplant patients


- This study aimed to validate an instrument for accurately estimating immunosuppressant nonadherence in Brazilian/Portuguese-speaking transplant patients known as the BAASIS.


- In this cross-sectional study, nonadherence was measured using electronic monitoring, assays, self-reporting and clinician reports. The findings suggested that combining multiple measures resulted in increased accuracy in diagnosing nonadherence.


- This paper outlines the challenges in measuring medication adherence using electronic medication monitoring of kidney transplant patients.

**Interventions**

This was a non-interventional, observational, multicenter study involving over 90 Norwegian kidney transplant recipients who were converted from immediate to prolonged-release tacrolimus formulations. Immediately in the first month following conversion, patients were more adherent as compared to baseline; however, the increased adherence was not sustained through 12-months post-conversion.


This study set out to determine the efficacy, safety, and adherence implications of switching patients from twice daily to once daily tacrolimus dosing.


The aim of this pilot study was to test whether a culturally sensitive cognitive-behavioral adherence promotion program could significantly improve medication adherence to tacrolimus prescription as measured by telephone pill counts among kidney transplant recipients.


In this randomized controlled trial, half of a cohort of heart, liver, and lung transplant recipients on twice daily tacrolimus-based immunosuppression regimens received patient tailored behavioral interventions over a 6-month period. Post-intervention, this group was noted to have higher-dosing adherence in comparison to the control (no intervention) group. The intervention group also trended to have better event-free survival at 5 years, with regards to mortality and retransplantation.


This prospective trial utilized a pharmaceutical intensified care program led by clinical pharmacists to see if patient adherence would improve compared to patients who only received standard care.


This paper describes the design and development of a video created to educate new kidney transplant recipients about the importance of medication adherence.
· This systematic review aimed to assess the effectiveness of interventions to improve medication adherence to immunosuppressive medications in adult kidney transplant patients

· The aims of this prospective study were to pilot-test the effects of medication reminders via text message on patients' adherence and outcomes

· This study assessed the cost differential between using a long-acting formulation of tacrolimus versus standard tacrolimus when considering the cost of non-adherence

· The aim of this randomized single center trial was to evaluate the impact of varying forms of custom reminders on tacrolimus adherence. Patients were provided wireless pill bottles containing tacrolimus which allowed for pill bottle opening recordings.

· This meta-analysis assessed the impact of reduced frequency dosing on adherence, compliance, persistence, and associated economic impact.

· In this retrospective cohort study, a digital education intervention was introduced to 282 kidney transplant recipients. Patients were able to correctly answer questions related to medication indications, dosing, and administration considerations (90%), but many (61%) had issues properly
identifying adverse effects. This study does not directly address an intervention for improving adherence, but instead focuses on optimizing medication education in solid organ transplant recipients.


This paper examines how adult transplant recipients are prepared and supported by transplant coordinators and pharmacists to take their medications as prescribed.

**Tacrolimus IntraPatient Variability**


This study evaluated a cohort of adherent liver and kidney transplant recipients and sought to determine the intra-patient variability of tacrolimus. In this retrospective analysis of 96 patients, results suggested that monitoring standard deviations of routine tacrolimus blood levels can be of utility in detecting non-adherence to immunosuppressant medications prior to clinical rejection and allow for earlier intervention.


An editorial addressing standard deviation of tacrolimus trough levels as a standard for addressing nonadherence. In this, the author(s) state that while medication level variation has promise as a procedure to evaluate nonadherence, more data must be conducted in larger, prospective studies before implementation on a large-scale occurs.


In this prospective, multicenter study that studied the Medication Level Variability Index (MLVI) as a means for detecting nonadherence, results demonstrated that a higher MLVI pre-rejection predicted rejection as well as had significant association with other secondary outcomes. The results of this larger study suggest that MLVI is a marker that can use clinically-derived information in order to predict rejection.

This retrospective study evaluated the impact of tacrolimus IPV on CAV and acute cellular rejection after heart transplant in 86 patients. Results suggest a high intrapatient variability in tacrolimus exposure does not appear to influence heart transplant outcomes, unlike its influence on kidney transplant function. A higher immunosuppression exposure after heart transplant, including the use of prednisone often in a combination of 3 immunosuppressive drugs, may protect against the effects of high intrapatient tacrolimus variability.


This retrospective cohort study evaluated the impact of high IPV in tacrolimus exposure on a composite endpoint of graft failure, late BPAR, histologically confirmed transplant glomerulopathy, or doubling of serum creatinine concentration in the period between month 12 after the transplantation and the last follow-up.


Review article presenting the evidence for intra-patient variability in tacrolimus pharmacokinetics in the use of optimizing transplant outcomes and gauging nonadherence.


In this retrospective analysis of 96 patients, results suggested that monitoring standard deviations of routine tacrolimus blood levels can be of utility in detecting non-adherence to immunosuppressant medications prior to clinical rejection and allow for earlier intervention.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4177441/

In this study, a retrospective chart review sought to validate previous findings that a higher MLVI may predict rejection and found that the MLVI was both associated with rejection as well as may predict its occurrence in adult liver transplant recipients.

This study evaluated the impact of intrapatient variability on immune-mediated graft injury after month six in 326 liver transplant recipients. Secondary outcomes were the association between tacrolimus IPV on loss of renal function per year follow up and CMV after month 6. They concluded that high IPV in tacrolimus exposure beyond month 6 post-liver transplantation was not associated with immune-mediated graft injury.


In this retrospective cohort study, variation in calcineurin inhibitor levels was studied after a protocol for immunosuppression management was introduced at a single center. The study group found an increase in the risk of rejection with a single unit increase in the standard deviation of tacrolimus blood level. They also found that despite standardized management certain patients may have had significant variability in tacrolimus levels, indicating potential nonadherence and area for intervention.

Non-Adherence and Clinical Outcomes

This study assessed relationships between adherence, HRQOL, psychological function, and family function in pediatric liver transplant recipients and parents in order to characterize the relationship between adherence and health outcomes in children who were within 5 years of their liver transplantation. The results not only related nonadherence to frequency/duration of hospitalizations, liver biopsies, and rejection episodes, but also suggested that empirically based assessment of HRQOL, parenting stress, and family functioning may help identify patients at risk for nonadherence.


A sample of 444 patients were reviewed to determine pre-transplant predictors of non-adherence and clinician report of non-adherence. Nonadherence was found in nearly a quarter of the patient population, with factors such as a history of substance abuse and a past history of nonadherence found to be significant independent predictors of nonadherence. The study also found significant predictors of higher deviation of tacrolimus levels as well as an independent association between SD of tacrolimus levels and graft failure over time.


This retrospective analysis of over 500 renal allograft recipients at a single-center evaluated the influence of non-adherence on long-term allograft histology and survival.
- A secondary objective in this study was to evaluate chronic-active antibody-mediated rejection (CAABMR) phenotypes between adherent and non-adherent renal transplant recipients found to have CAABMR.

- This study quantified individual medication adherence patterns in kidney transplant recipients through electronic medication monitoring.

- This paper describes factors associated with compliance to immunosuppressive medications and examines relationships between compliance with allograft outcomes and costs.

- This prospective multicenter cohort study reviewed 315 renal transplant recipients that underwent biopsies for clinical indications. The authors aimed to understand the causes of kidney transplant failure, including nonadherence.

- In this study, patients were categorized as either compliant or non-compliant based on self-reported adherence interviews. Investigators sought to compare rates of late acute rejections between these two groups.

This study explored the relationship between class II HLA epitope-mismatch and patient medication non-adherence and how it relates to graft survival.

**Risk Factors for Non-Adherence**


This systematic review of 37 studies aimed to identify factors associated with non-adherence.


This single-center, cross-sectional study compared stress and coping mechanisms between fifty Brazilian renal transplant recipients classified as either adherent and non-adherent using the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS).


This was an analysis of 161 kidney transplant recipients who completed surveys comprising of 5 validated questionnaires. The survey helped identify barriers leading to non-adherence - with forgetfulness and skipped doses being the most prominent reasons.


This prospective nationwide cohort study described the evolution of medication non-adherence from pre-transplant through 3 years post-transplant among more than 1500 Swiss kidney, liver, heart, and lung transplant recipients.


This cross-sectional study identified multilevel factors associated with implementation phase immunosuppressant nonadherence in adult heart transplant recipients across 4 continents, 11 countries, and 36 centers.

- This cross-sectional study aimed to determine the relationship between patient characteristics (e.g., depression, personality, and quality of life) and immunosuppressant medication adherence in kidney and liver transplant patients.


- This meta-analysis reviewed 32 studies to identify the influence of social factors (e.g. marital status and social support) on post-transplant medication adherence and other post-transplant clinical outcomes.


- This study reports rates of adherence over an 18-month period among patients receiving a prolonged-release tacrolimus formulation.


- A cohort of pediatric solid organ transplant providers were administered an anonymous online survey to capture provider perspectives on barriers to medication adherence and recommendations for interventions.


- Investigators retrospectively reviewed the influence of pretransplant sociodemographic and psychosocial variables on nonadherence rates post-transplant in a cohort of over 200 liver transplant recipients at two different transplant sites.

This paper aimed to describe medication taking beliefs of renal transplant recipients through comprehensive interviews


This study examined the determinants of intention formation and adherence behavior in transplant patients. Further, this study attempted to characterize the role of a patient’s support system (gender dependent) and how it impacts adherence.


This publication takes the results from the original MALT study that validated MLVI and evaluated variance in adherence behavior. Results of the study identified potential risk factors for worsening adherence, suggested good baseline adherence does not guarantee adherence, and that monitoring of MLVI be computed frequently in order to characterize nature of nonadherence with MLVI as it may fluctuate over time.