

## 12. Adherence in Solid Organ Transplantation

### 12.1 [Consensus conference reports and recommendations](#)

### 12.2 [Review articles](#)

### 12.3 [Adherence assessment tools](#)

### 12.4 [Interventions](#)

### 12.5 [Tacrolimus inpatient variability](#)

### 12.6 [Non-adherence and clinical outcomes](#)

### 12.7 [Risk factors for non-adherence](#)

#### 12.1 Consensus conference reports and recommendations

Ettenger R, et al. (2018). Meeting report: FDA public meeting on patient-focused drug development and medication adherence in solid organ transplant patients. *Am J Transplant*, 18(3), 564-573. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/?term=Meeting+report%3A+FDA+public+meeting+on+patient+-+focused+drug+development+and+medication+adherence+in+solid+organ+transplant+patients>.

- 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.

Maldonado AQ, et al. (2018). Meeting report: Consensus recommendations for a research agenda to address immunosuppressant nonadherence in organ transplantation. *Clin Transplant*, 32(9):e13362. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/30053319>

- 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.

Myaskovsky L, Jesse MT, Kuntz K. (2018). Report from the American Society of Transplantation Psychosocial Community of Practice Adherence Task Force: Real-world options for promoting adherence in adult recipients. *Clin Transplant*. 2(9). Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/30022527>

- 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

Neuberger JM, et al. (2017). Practical recommendations for long-term

management of modifiable risks in kidney and liver transplant recipients: A guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation*, 101, S1–S56. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/28328734/>

- 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

Fine RN, et al. (2009). Nonadherence consensus conference summary report. *Am J Transplant*, 9(1), 35-41. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19133930>

- 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.

## 12.2 Review articles

Sandal S, Chen T, Cantarovich M. (2021). Evaluation of transplant candidates with a history of nonadherence: an opinion piece. *Canadian Journal of Kidney Health and Disease*, 8, 1-7. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7863559/>

- This opinion piece provides a review of nonadherence in transplant, nonadherence definitions, the need for these assessments, and current practices that may be contributing to disparities in access to transplantation. The authors also review interventions to assist with nonadherence, duration of adherence assessment, and who to assess.

Kuypers DRJ. (2020). From nonadherence to adherence. *Transplantation*, 104,1330-1340. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/31929426/>

- This review provides suggestions on how different types of transplant centers can set up dedicated medication nonadherence programs according to available resource to define and achieve realistic clinical goals in managing medication nonadherence.

Lee H, et al. (2020). Effectiveness of eHealth interventions for improving medication adherence of organ transplant patients: A systematic review and meta-analysis. *PLoS ONE*, 15(11),1-18. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33152010/>

- This systematic review and meta-analysis aimed to evaluate the effects of eHealth interventions for improving medication adherence in organ transplant patients as compared to usual or conventional care alone. Results of this study suggest that eHealth interventions were similar to standard care or advanced care for improving medication adherence.

Pruette CS & Amaral S. (2020). Empowering patients to adhere to their treatment regimens: a multifaceted approach. *Pediatr Transplant*, 00, e13849. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33152010/>

- This article reviews recent literature published over the last 5 years on the topic of adherence in transplant recipients. The purpose was to highlight various insights and opportunities to promote adherence at the individual patient level, family level, healthcare system level, and community level.

Chisholm-Burns MA, Spivey C, Pickett L. (2018). Health literacy in solid-organ transplantation: a model to improve understanding. *Patient Prefer Adherence*, 12, 2325–2338. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/30464420>

- 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.

Duncan S, et al. (2018). A systematic review of immunosuppression interventions in transplant recipients: Decoding the streetlight effect. *Pediatric Transplant*, 22, e13086. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29218760>

- 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.

Kilian MO, et. al. (2018). Psychosocial predictors of medication non-adherence in pediatric organ transplantation: A systematic review. *Pediatr Transplant*, 22, e13188. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/29637674/>

- There is limited literature surrounding psychosocial predictors of non-adherence. This article sought to identify studies of the psychosocial predictors of non-adherence.

Zhu Y, et al. (2017). Efficacy of interventions for adherence to the immunosuppressive therapy in kidney transplant recipients: a meta-analysis and systematic review. *J Investig Med*, 65,1049-56. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/28483983/>

- This study investigated whether adherence interventions improve adherence of kidney transplant recipients to immunosuppressive regimens. Primary outcomes included adherence rate and score. Among participants receiving intervention, the adherence rate and score was significantly higher than the control group. Examples of interventions included inclusion of a pharmacist, continuing education, and behavior contract.

Doyle IC, Maldonado AQ, Heldenbrand S, Tichy EM, Trofe-clark J. (2016). Nonadherence to therapy after adult solid organ transplantation: A focus on risks and mitigation strategies. *Am J Health Syst Pharm*, 73(12), 909-920. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/27189855>

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

Heldenbrand S, et al. (2016). Assessment of medication adherence app features, functionality, and health literacy level and the creation of a searchable Web-based adherence app resource for health care professionals and patients. *J Am Pharm Assoc*, 56(3),293-302. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27067551>

- 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)).

Fredericks EM, Dore-Stites D. (2010). Adherence to immunosuppressants: How can it be improved in adolescent organ transplant recipients? *Curr Opin Organ Transplant*, 15(5), 614-20. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/20651598/>

- This review examined recent studies and position statements to determine current issues related to improving medication adherence in adolescent transplant recipients. The authors identify technology, such as internet and cell phones, as a promising mechanism for delivering adherence promoting interventions to this population. The authors conclude that strategies for promoting adherence in adolescent transplant recipients should incorporate health-related education, motivational and behavioral skills.

Denhaerynck K, et al. (2005). Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transplant Int*, 18(10), 1121-1133.

<https://www.ncbi.nlm.nih.gov/pubmed/16162098>

- 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.

### 12.3 Adherence assessment tools

Krause A, et al. (2021). Use of an electronic medication monitoring device to estimate medication adherence in kidney transplant patients. *Transl Behav Med*, *ibaa122*. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/33710349/>

- This study aimed to assess the effectiveness of a wireless electronic medication monitoring device, SimpleMed+, in 55 kidney transplant patients. Adherence was assessed at 98.3% over an eight week study period for the 41 patients who completed the study. Fourteen patients either stopped using the device or did not use the device >70% of the time. The study authors concluded that further assessment of the practicality of an electronic medication monitoring device is warranted.

Varnell CD, et al. (2021). Predicting acute rejection in children, adolescents, and young adults with a kidney transplant by assessing barriers to taking medication. *Pediatr Nephrol*, ePub ahead of print.

Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33501558/>

- In this 2-year observational, prospective cohort study, 98 kidney transplant recipients were assessed for barriers to adherence using a barriers assessment tool (a 14-item checklist) to determine the association with acute rejection. Kaplan-Meier analyses identified that patients were more likely to have an episode of acute rejection ( $p = 0.02$ ) than those who did not have an identified barrier via the assessment tool. Within the pediatric and adolescent kidney transplant recipients, identification of adherence barriers may assist in guiding targeted interventions to reduce risk of acute rejection.

Cushman GK. et. al. (2020). Caregivers' barriers to facilitating medication adherence in adolescents/young adults with solid organ transplants: Measure development and validation. *Pediatr Psychol*. 45, 498-508. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32374379/>

- This study evaluated the factor structure, validity, and reliability of the Caregiver Medication Barriers to Adherence Scale (CMBAS) to assess caregivers' barriers to facilitating medication adherence in adolescent and young adults with solid organ transplants.

Van Pilsum Rasmussen SE, et. al. (2020). Psychosocial factors and medication adherence among recipients of vascularized composite allografts. *SAGE Open Med*, 8, 2050312120940423. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32695395/>

- The authors studied various psychosocial factors using validated tools to assess medication adherence among vascularized composite allotransplantation recipients.

Gomis-Pastor M, et. al. (2019). Multimorbidity and medication complexity: New challenges in heart transplantation. *Clin Transplant*, 33, e13682. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/31368585/>

- This study was a single-center, observational study that included heart transplant recipients > 1.5 years from transplant and assessed multimorbidity and therapeutic complexity, which are recognized problems in heart transplant population. The patient-level Medication Regimen Complexity Index Spanish version (pMRCI-S) score was utilized and the impact of the index score on specific variables was assessed.

Gustavsen MT, et al. (2019). Evaluation of tools for annual capture of adherence to immunosuppressive medications after renal transplant. *Transplant International*, 32(6):614-625. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/30770608>

- 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.

Zhang M, et. al. (2019). Prevalence and risk factors of immunosuppressant nonadherence in heart transplant recipients: A single-center cross-sectional study. *Patient Prefer Adherence*. 13, 2185-2193. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6930119/>

- This study assessed immunosuppressant adherence based on the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS). Immunosuppressant nonadherence was categorized into five domains of contributing factors which were then compared between adherent and nonadherent patients.

Rich KL, et. al. (2018). Predicting health care utilization and charges using a risk score for poor adherence in pediatric kidney transplant recipients. *Clin Pract Pediatr Psychol*, 6, 107-116. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6910652/>

- The authors developed a novel risk score to identify patients at risk for poor adherence behaviors and evaluated whether it would predict future health utilization and charges. The score consisted of three metrics of adherence including: immunosuppression drug levels, timely laboratory monitoring, and timely clinic visits.

Williams A, Low JK, Manias E, Dooley M, Crawford K. (2016). Trials and tribulations with electronic medication adherence monitoring in kidney transplantation. *Res Social Adm Pharm*, 12(5), 794-800. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/26616159>

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

Hugon A, et al. (2014). Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. *Transplantation*, 98(2):222-228. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/24926826>

- 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

Marsicano Ede O, et al. (2013). Transcultural adaptation and initial validation of Brazilian-Portuguese version of the Basel assessment of adherence to immunosuppressive medications scale (BAASIS) in kidney transplants. *BMC Nephrol.* 14(1):108. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/23692889>

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

Dharancy S, Giral M, Tetaz R, Fatras M, Dubel L, Pageaux GP (2012). Adherence with immunosuppressive treatment after transplantation: results from the French trial PREDICT. *Clin Transplant*, 26(3), E293E299. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22686953>

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

Schäfer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. (2008). Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant*, 8(3), 616-626. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/18294158>

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

Chisholm MA, Lance CE, Williamson GM, Mulloy LL. (2005). Development and validation of the immunosuppressant therapy adherence instrument (ITAS). *Patient Educ Couns.* 59(1)13–20. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/16198214>

- 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.

## 12.4 Interventions

Marco B, et al. (2021). Adherence to, and patient convenience of, prolonged-release tacrolimus in stable kidney and liver transplant recipients after conversion from immediate-release tacrolimus in routine clinical practice in Switzerland. *Swiss Med Wkly.* 151, w20453. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/33638353/>

- This multi-center, observational, 12-month study evaluated medication adherence in liver and kidney transplant recipients converted from immediate-release tacrolimus to prolonged-release tacrolimus. Investigators utilized interview questionnaires and tacrolimus trough levels to assess non-adherence for up to 12 months post-conversion. Of the 75 patients assessed, majority of patients reported decreased pill burden and ease of remembering to take prolonged-release tacrolimus. Overall, 1-year non-adherence rates were similar before and after conversion.

Serper M, et al. (2021). Transplant regimen adherence for kidney recipients by engaging information technologies (TAKE IT): Rationale and methods for randomized controlled trial of a strategy to promote medication adherence among transplant recipients. *Contemp Clin Trials.* 103,106294. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33515781/>



- This publication dictates the proposed methods and background for the TAKE IT trial, a two-arm, patient randomized controlled trial at two transplant centers. The study plans to recruit 450 kidney transplant recipients within two years of transplant. The intervention arm will implement the TAKE IT strategy, which involves use of an adherence mobile application, self-reported adherence assessments, care alert notifications, adherence reports, and tailored adherence support tools when needed. The primary outcome will assess medication adherence through pill count. The planned follow up period after inclusion is two years.

Fedderson N, et. al. (2020). Adherence in pediatric renal recipients and its effect on graft outcome, a single-center, retrospective study. *PETR*, 00, e13922. Retrieved from: <https://onlinelibrary.wiley.com/doi/full/10.1111/pepr.13922>

- The aim of the study was to determine the intra-patient immunosuppressant variability as measured by the trough-level CoV% in a single-center study and to correlate this with biopsy-proven rejections within up to 6 years following transplantation. The authors also compared subjective adherence ratings of patient, families, and healthcare professional and correlated those with both the immunosuppressants' trough level CoV%, as well as formation of dnDSA and rejection episodes. Results of the study showed the CoV% was by-trend higher in those patients with biopsy-proven rejection. Also the psychologist's assessment correlated significantly with both rejection as well as with the formation of dnDSA. The authors concluded that medication adherence is important, but also stresses the role of a multi-disciplinary treatment approach to support pediatric renal transplant patients and their families.

Wadhvani S, et al. (2020). Implementing a process to systematically identify and address poor medication adherence in pediatric liver transplant recipients. *Pediatr Qual Saf*. 5(3), e296.

Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32656465/>

- This cohort study describes the implementation of a process to appropriately assess and address medication nonadherence in the pediatric liver transplant population. The paper describes a multidisciplinary approach transplant clinic to identify poor adherence through a barriers assessment tool, implement a patient directed intervention bundle, and assess the intervention through variability in tacrolimus trough levels and episodes of late acute cellular rejection. During the 6 month follow up period, >90% of the 85 patients received an intervention bundle. The most common identified adherence barrier was forgetfulness.

Hall CL, et. al. (2019). Improving Transplant Medication Safety Through a Technology and Pharmacist Intervention (ISTEP): Protocol for a Cluster Randomized Controlled Trial. *JMIR Res Protoc*. 8, e13821.

Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/31573933/>

- This study focused on the clinical and economic effectiveness of a pharmacist-led, technology-enabled intervention versus usual care, in veteran organ transplant recipients. This was a 24 month, prospective, parallel-arm, cluster-randomized, controlled multicenter trial. The final results of this study are expected to be submitted for publication August 2021.

Paterson TS, et. al. (2019). Impact of once- versus twice-daily tacrolimus dosing on medication adherence in stable renal transplant recipients: A Canadian single-center randomized controlled trial. *Can J Kidney Health Dis*, 6, 2054358119867993. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6699008/>

- This was a 4 month controlled medication dosing trial in adult renal transplant patients in a Canadian sample. The authors further described the relationship between tacrolimus dosing schedule and implementation adherence.

Triplett KN, et al. (2019). Digital medicine program with pediatric solid organ transplant patients: Perceived benefits and challenges. *Pediatr Transplant*. 23, e13555. Retrieved from: <https://onlinelibrary.wiley.com/doi/10.1111/petr.13555>

- This paper describes the implementation of a digital medicine program (DMP) where transplant patients' medications were co-encapsulated with ingestible sensors. Adherence was monitored via a patient mobile application and a provider portal.

Tsapepas DS, et al. (2018). Using technology to enhance medication regimen education after solid organ transplantation. *Am J Health Syst Pharm*, 75(23), 1930-1937. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/30463868>

- 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.

Abedini S, et al. (2018). Immunosuppression adherence in stable kidney transplant patients converted from immediate-to prolonged-release tacrolimus in clinical practice: A Norwegian study. *Transplantation direct*. 4(2). Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29464199>

- 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 postconversion.

Sayegh CS, et al. (2018). Cell phone support to improve medication adherence among solid organ transplant recipients. *Pediatr Transplant*, e13235. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/29920879/>

- This study investigated the potential efficacy of a 12-week cell phone support intervention to improve immunosuppressant medication adherence.

Cukor D, Ver Halen N, Pencille M, Tedla F, Salifu M. (2017). A pilot randomized controlled trial to promote immunosuppressant adherence in adult kidney transplant recipients. *Nephron*. 135(1), 6-14. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28049201/>

- 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.

Dobbels F, et al. (2017). Efficacy of a medication adherence enhancing intervention in transplantation: The MAESTRO-Tx trial. *J Heart Lung Transplant*, 36(5), 499-508. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28162931>

- 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.



Mellon L, et al. (2017). Intervention for improving medication adherence in solid organ transplant recipients. Cochrane Database of Systematic Reviews, 12, 1-15. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6486115/>

- This review aimed to look at benefits and harms of using interventions for improving adherence to immunosuppressant therapies in solid organ transplant recipients, including pediatric and adult heart, lung, kidney, liver, and pancreas transplant recipients.

Reese PP, et al. (2017). Automated reminders and physician notification to promote immunosuppression adherence among kidney transplant recipients: a randomized trial. Am J Kidney Dis. 69(3), 400-409. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27940063>

- 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.

Low JK, Crawford K, Manias E, Williams A. (2016). A compilation of consumers' stories: the development of a video to enhance medication adherence in newly transplanted kidney recipients. J Adv Nurs, 72(4), 813-824. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/26709034>

- This paper describes the design and development of a video created to educate new kidney transplant recipients about the importance of medication adherence.

Low JK, Williams A, Manias E, Crawford K. (2015). Interventions to improve medication adherence in adult kidney transplant recipients: a systematic review. Nephrol Dial Transplant. 2015, 30(5),752-761. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24950938>

- This systematic review aimed to assess the effectiveness of interventions to improve medication adherence to immunosuppressive medications in adult kidney transplant patients

Williams A, et al. (2015). Examining the preparation and ongoing support of adults to take their medications as prescribed in kidney transplantation. J Eval Clin Pract. 21(2), 180-186. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/25318842>

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

Joost R, Dörje F, Schwitulla J, Eckardt K, Hugo C. (2014). Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first posttransplant year: a quasi-experimental study. Nephrol Dial Transplant, 29(8), 1597-1607. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24914089>

- 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

Muduma G, Odeyemi I, Smith-palmer J, Pollock R. (2014). Budget impact of switching from an immediate release to a prolonged-release formulation of tacrolimus in renal transplant recipients in the UK based on differences in adherence. Patient Prefer Adherence, 8, 391-399. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24729687>

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

Srivastava K, Arora A, Kataria A, Cappelleri JC, Sadosky A, Peterson AM. (2013). Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis.

Patient Prefer Adherence,7,419-434. Retrieved from:  
<http://www.ncbi.nlm.nih.gov/pubmed/23737662>

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

Beckebaum S, et al. (2011). Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. *Transpl Int*. 24(7), 666-675. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21466596>

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

Miloh T, et al. (2009). Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging. *Pediatrics*, 124, e844–e850. Retrieved from:  
<https://www.ncbi.nlm.nih.gov/pubmed/19822583>

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

## 12.5 Tacrolimus inpatient variability

Leino AD, et al. (2019). Assessment of tacrolimus intra-patient variability in stable adherent transplant recipients: Establishing baseline values. *Am J Transplant*, 19(5):1410-1420. Retrieved from:  
<https://www.ncbi.nlm.nih.gov/pubmed/30506623>

- 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.

Van Der Veer MAA, et al. (2019). High intra-patient variability in tacrolimus exposure is not associated with immune-mediated graft injury after liver transplantation. *Transplantation*, 103(11):2329-2337. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/30801539>

- This study evaluated the impact of inpatient 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.

Shuker N, et al. (2018). Inpatient variability in tacrolimus exposure does not predict the development of cardiac allograft vasculopathy after heart transplant. *Exp Clin Transplant*, 16(3), 326-332. Retrieved from:  
[https://www.ncbi.nlm.nih.gov/pubmed/?term=Experimental+and+Clinical+Transplantation+\(2018\)+3%3A+326-332](https://www.ncbi.nlm.nih.gov/pubmed/?term=Experimental+and+Clinical+Transplantation+(2018)+3%3A+326-332)

- 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 inpatient 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 inpatient tacrolimus variability.

Shemesh E, et al. (2017). The Medication Level Variability Index (MLVI) predicts poor liver transplant outcomes: a prospective multi-site study. *Am J Transplant*, 17(10), 2668-2678. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28321975>

- 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.

Shuker N, et al. (2016). A high inpatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation. *Transpl Int*. 29(11), 1158-1167. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27188932>

- 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.

Shuker N, van Gelder T, Hesselink DA. (2015). Intra-patient variability in tacrolimus exposure: causes, consequences for clinical management. *Transplant Rev*, 29(2), 78-84. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25687818>

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

Supelana C, et al. (2014). The Medication Level Variability Index (MLVI) predicts rejection, possibility due to nonadherence, in adult liver transplant recipients. *Liver Transpl*. 20(10), 1168-1177. Retrieved from: <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.

Shemesh E, Fine RN. (2010). Is calculating the standard deviation of tacrolimus trough levels the new gold standard for evaluating nonadherence to medications in transplant recipients? *Pediatr Transplant*, 14(8), 940–943. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2992596/>

- 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.

Stuber ML, Shemesh E, Seacord D, Washington J 3rd, Helleman G, McDiarmid S. (2008). Evaluating nonadherence to immunosuppressant medications in pediatric liver transplant recipients. *Pediatr Transplant*, 12(3), 284–288. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/18331387>

- 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.

Venkat VL, Nick TG, Wang Y, Bucuvalas JC. (2008). An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. *Pediatr Transplant*, 12(1):67–72. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/18186891>

- 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.

## 12.6 Non-adherence and clinical outcomes

Lorenz EC, et al. (2018). Long-term immunosuppression adherence after kidney transplant and relationship to allograft histology. *Transplant Direct*. 4(10). Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6233670/>

- 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.

Malheiro J, et al. (2018). Correlations between donor-specific antibodies and non-adherence with chronic active antibody-mediated rejection phenotypes and their impact on kidney graft survival. *Human Immunology*. 79(6), 413-423. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29577962>

- 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.

Wiebe C, Nevins TE, Robiner WN, Thomas W, Matas AJ, Nickerson PW. (2015). The synergistic effect of class II HLA epitope-mismatch and nonadherence on acute rejection and graft survival. *Am J Transplant*, 15(8), 2197-2202. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/26095765>

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

Nevins TE, Robiner WN, Thomas W. (2014). Predictive patterns of early medication adherence in renal transplantation. *Transplantation*, 98(8):878-884. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24831921>

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

Lieber SR, Volk ML. (2013). Non-adherence and graft failure in adult liver transplant recipients. *Dig Dis Sci*. 58(3), 824–834. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/23053889>

- 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.

Sellarés J, et al. (2012). Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*, 12(2), 388-399. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22081892>

- 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.

Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. (2009). Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant*, 9(11), 2597-2606. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19843035>

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

Fredericks EM, Lopez MJ, Magee JC, Shiek V, Opiari-Arrigan L. (2007). Psychological functioning, nonadherence and health outcomes after pediatric liver transplantation. *Am J Transplant*, 7(8), 1974-1983. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/17617862>

- 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.

Vlaminck H., et al. (2004). Prospective study on late consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant patients. *Am J Transplant*, 4(9), 1509-1513. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/15307839>

- 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.

## 12.7 Risk factors for non-adherence

Ko H, et al. (2021). Association between medication adherence and inpatient variability in tacrolimus concentration among stable kidney transplant recipients. *Nature*, 11:5397. <https://www.nature.com/articles/s41598-021-84868-5>

- In this post-hoc analysis, the variability of tacrolimus trough levels were calculated using coefficient variation and mean absolute deviation in 92 kidney transplant recipients. Patients were required to have more than 5 months of medication event monitoring system (MEMS) use and more than 4 tacrolimus troughs for analysis. Between the nonadherent and adherent groups, no statistically significant differences were identified in the coefficient variation or the adherence detected by MEMS. Self-reports of adherence did not significantly affect the interpatient variability of tacrolimus.

Quast LF, et. al. (2020). Adherence barriers for adolescent and young adult transplant recipients: Relations to personality. *Pediatr Psychol*, 45:540-549. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32291448/>

- The current study examines associations between personality (i.e., agreeableness, conscientiousness, neuroticism) and adherence barriers in a group of adolescent and young adult solid organ transplant recipients.

Cossart AR, Staats CE, Campbell SB, Isbel NM, Cottrell WN. (2019). Investigating barriers to immunosuppressant medication adherence in renal transplant patients. *Nephrology*, 24(1), 102-110. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29278439>

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

Danziger-Isakov L, et al. (2019). Perceived barriers to medication adherence remain stable following solid organ transplantation. *Pediatr Transplant*, 23, e13361. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6652201/>

- This study evaluated the perceived barriers to adherence reported by pediatric and adolescent patients and their guardians and whether these would increase in severity as time from transplant increased.

Denhaerynck K, et al. (2018). Multilevel factors are associated with immunosuppressant nonadherence in heart transplant recipients: The international BRIGHT study. *Am J Transplant*, 18:1447–1460. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29205855>

- 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.

Ladin K, Daniels A, Osani M, Bannuru RR. (2018). Is social support associated with post-transplant medication adherence and outcomes? A systematic review and meta-analysis. *Transplant Rev*, 32(1):16-28. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28495070>

- 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.

Lehner LJ, et al. (2018). Evaluation of adherence and tolerability of prolonged-release tacrolimus (Advagraf™) in kidney transplant patients in Germany: A multicenter, non-interventional study. *Clin Transplant*, 32(1), e13142. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29052906>

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

Shemesh E, et al. (2018). Trajectory of adherence behavior in pediatric and adolescent liver transplant recipients: The medication adherence in children who had a liver transplant cohort. *Liver Transplant*, 24(1), 80-88. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28779546>

- 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.

Mehta P, Steinberg EA, Kelly SL, Buchanan C, Rawlinson AR. (2017). Medication adherence among adolescent solid-organ transplant recipients: A survey of healthcare providers. *Pediatr Transplant*, 21(7), e13018. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28670855>

- 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.



Nevins TE, Nickerson PW, Dew MA. (2017). Understanding medication nonadherence after kidney transplant. *J Am Soc Nephrol*, 28, 2290-2301. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/28630231/>

- The goal of this review was to provide summary of risk factors associated with medication non-adherence (MNA), the strategies to overcome MNA and the effectiveness of these approaches. Risk factors for MNA identified in this review include condition related factors, health system/healthcare provider factors, sociodemographic factors, patient-related psychosocial factors, treatment related factors.

Belaiche S, Décaudin B, Dharancy S, Noel C, Odou P, Hazzan M. (2017). Factors relevant to medication nonadherence in kidney transplant: a systematic review. *Int J Clin Pharm*, 39(3), 582-593. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28374343>

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

Brito DC, et al. (2016). Stress, coping and adherence to immunosuppressive medications in kidney transplantation: a comparative study. *Sao Paulo Med J*. 134(4), 292-299. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26648278>

- 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).

De Geest S, et al. (2014). Describing the evolution of medication nonadherence from pretransplant until 3 years post-transplant and determining pretransplant medication nonadherence as risk factor for post-transplant nonadherence to immunosuppressives: The Swiss Transplant Cohort Study. *Transplant Int*, 27(7), 657-666. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/24628915>

- 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.

Chun-Wei Su G, et al. (2013). Assessing medication adherence in solid-organ transplant recipients. *Exp Clin Transplant* 2013;6:475-481. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/24344939/>

- This was a single center, retrospective, cross-sectional cohort study that evaluated 225 outpatient lung, kidney, and liver transplant recipient's adherence to immunosuppressant medications. Surrogate markers were used to measure medication adherence. Markers included medication possession ratio (days of medication supplied/actual days) and gap in prescription refills (> 30-day lapse between expected depletion of supply and next refill). Patients were adherence to their immunosuppressant medication regimens if their medication possession ratio was > 80%. Overall, medication possession ratios were approximately 95% for kidney and lung transplant recipients and 92% for liver recipients.

Gorevski E, et al. (2013). Is there an association between immunosuppressant therapy medication adherence and depression, quality of life, and personality traits in the kidney and liver transplant population? *Patient Prefer Adherence*, 7, 301-307. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23620661>

- 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.

Rodrigue JR, Nelson DR, Hanto DW, Reed AI, Curry MP.(2013). Patient-reported immunosuppression nonadherence 6 to 24 months after liver transplant: association with pretransplant psychosocial factors and perceptions of health status change. *Prog Transplant*, 23(4), 319-328. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/24311395>

- 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.

Scholz U, et al. (2012). Predicting intentions and adherence behavior in the context of organ transplantation: gender differences of provided social support. *J Psychosom Res*, 72(3), 214-219.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22325701>

- 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.

Russell CL, Kilburn E, Conn VS, Libbus MK, Ashbaugh C. (2003). Medication-taking beliefs of adult renal transplant recipients. *Clin Nurse Spec*, 17(4), 200-208. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/12869867>

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