



# Evaluation of Transplant Candidates With a History of Nonadherence: An Opinion Piece

Canadian Journal of Kidney Health and Disease  
Volume 8: 1–7  
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DOI: 10.1177/2054358121990137  
journals.sagepub.com/home/cjk



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## Keywords

transplantation, nonadherence, compliance, disparity, solid organ transplantation

Received September 15, 2020. Accepted for publication January 3, 2021.

## Key Points

1. Pretransplant nonadherence is recognized as a relative or absolute contraindication to transplantation as it is associated with posttransplant nonadherence, which can lead to graft loss, and patient morbidity and mortality.
2. A psychosocial assessment may help assess transplant candidates with nonadherence and identify interventions to help them.
3. In the fields of liver and kidney transplantation, there is a lack of standardized guidelines on whom to perform this assessment on and a lack of objective methods to define, quantify, and measure the risk of nonadherence.
4. Some of the current practices are at risk of implicit bias in healthcare, and this might be contributing to disparities in access to transplantation.
5. Standardized and validated measures followed by pragmatic interventions and support for transplant candidates with a history of nonadherence are needed.
6. Patient engagement should be sought to ensure transparency in allocation practices and promote mutual accountability.

## Introduction

The transparency and validity of assessing the candidacy of a patient for a solid organ transplant have recently been called into question by the media.<sup>1</sup> Transplant centers perform a lengthy medical, surgical, and psychosocial evaluation on candidates with organ failure. This process ensures that there are no contraindications to surgery and to the use of long-term immunosuppressive medications. In addition, it helps ascertain if transplant candidates are likely to benefit from the transplant surgery over long term.

Pretransplant nonadherence to prescribed therapy, medications, investigations, and clinical visits, is recognized as a relative or an absolute contraindication by transplant programs. For example, the Canadian Society of Transplantation states,

given the use of immunosuppressive agents with a narrow therapeutic window, the impact of nonadherence to therapy on the risk of acute rejection and premature graft loss, and the scarcity of donor organs, nonadherence is a contraindication to kidney transplantation.<sup>2</sup>

This echoes the recommendations of some of the other major transplantation societies as summarized in Table 1.<sup>2–8</sup> Most recommend delaying transplant surgery until patients have demonstrated adherence to therapy for 6 months.

## Why Is a Nonadherence Assessment Needed?

There is a chronic shortage of donors and demand for organs is far greater than the supply. In Canada, more than 4,000 people are waiting for an organ transplant and more than 200 die annually waiting for one.<sup>9</sup> Also, transplanted organs are considered a gift to society from donors and their families, and allocation decisions are made on policies that

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**Table 1.** Current Guidelines in the Assessment of Transplant Candidates With a History of Nonadherence.

<b>Heart and lung</b>	
Society for Cardiothoracic Surgery in Great Britain and Ireland (2011)	A history of prior nonadherence to treatment or follow-up needs further evaluation and may represent a relative or absolute contraindication. Such patients need psychological/psychiatric evaluation
International Society for Heart Lung Transplantation (2016)	Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant. Psychosocial assessment should be performed before listing for transplantation. Evaluation should include an assessment of the patient's ability to give informed consent and comply with instruction, including drug therapy, as well as assessment of the support systems in place at home or in the community
<b>Kidney</b>	
American Society of Transplantation (2001)	Delay transplantation for patients who, despite interventions, are not able to improve life-threatening, noncompliant behaviors.
Canadian Society of Transplantation (2005)	Nonadherence to therapy is a contraindication. Kidney transplantation should be delayed until patients have demonstrated adherence to therapy (attendance for dialysis and compliance with medications) for at least 6 months. All patients should have a psychosocial evaluation
Lisbon conference (2007)	Psychosocial stability and the financial, family, and community resources necessary to be compliant with medical recommendations. Avoid kidney transplantation in those with difficult psychosocial circumstances, compliance, or communication. To prevent nonadherence, it is essential to identify patients at risk
<b>Liver</b>	
American Association for the study of liver disease and American Society of Transplantation (2013)	Candidates should be evaluated for and meet reasonable expectations for adherence to medical directives and mental health stability as determined by the psychosocial evaluation
European Association for the Study of the Liver (2015)	Social, psychological and, when indicated, psychiatric evaluation should be performed to evaluate adherence of the recipient, and potential risk factors for nonadherence

attempt to maximize the expected net amount of overall good achieved with each organ.<sup>10</sup> Current allocation practices balance the ethical principles of utility, justice, equity, and respect for persons.<sup>10,11</sup> To establish equipoise between these ethical principles, a nonadherent patient is not considered to be a suitable transplant candidate. There is empirical evidence to support these practices as well. Pretransplant nonadherence is predictive of posttransplant nonadherence in transplant recipients, and nonadherence with immunosuppressive medications after a transplant is a significant risk factor for graft loss, and patient morbidity and mortality.<sup>2-8,12</sup> Also, losing a graft to nonadherence can have a significant economic impact. In the United States, it is estimated to be \$15 to \$100 million annually.<sup>13</sup> Nonadherence rates are reported to be 36 cases per 100 patients per year in kidney transplant recipients and 7 to 15 cases per 100 patients per year in other solid organ transplant recipients.<sup>14</sup> Thus, a non-adherence assessment is needed for ethical, medical, and economic reasons.

### How Is a Nonadherence Assessment Performed?

To assess the risk of nonadherence in transplant candidates, a psychosocial evaluation is performed by a multidisciplinary

team of social workers, mental health professionals, and/or other specialty physicians (Table 1). These assessments help determine a patient's candidacy for solid organ transplantation but more importantly help identify educational and behavioral interventions to implement prior to transplantation. Following this, many centers enforce a minimum 6-month demonstrated adherence to therapy as recommended by the Canadian Society of Transplantation and other organizations (Table 1).<sup>2</sup>

### Contemporary and Controversial Issues With Current Clinical Practice

We now summarize our opinion on some of the contemporary and controversial issues with current practice. For the purposes of this article, our opinions pertain to kidney and liver transplant candidates only.

#### How Is Nonadherence Defined?

Adherence is defined as "the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."<sup>15</sup> Both from a research and clinical perspective, definition of adherence in

transplant candidates and recipients is not standardized.<sup>14</sup> In general, one tends to focus on taking medications alone; however, there are several other domains to adherence, such as clinic visits, exercise, and blood tests that can affect patient outcomes.<sup>12,14</sup> Nonadherence is a lack of adherence to a long list of medically necessary regimens and interventions that goes beyond taking medications. For example, in a study of veterans who were kidney transplant recipients, posttransplant nonadherence with clinic appointments (defined as patient with no shows to both clinic and laboratory visits) was associated with a 65% higher risk of graft loss.<sup>16</sup> Importantly, the risk of nonadherence to one domain of a medical regimen may not correlate across all.<sup>14</sup> For instance, nonadherence to dialysis might be due to the inherent difficulties of dialysis, such as transportation.<sup>17</sup> This may or may not be associated with nonadherence to medical regimens and interventions posttransplantation.

In addition, compliance is used interchangeably with adherence. Compliance with a treatment plan implies a paternalistic stance by the provider with the patient playing a more passive role, while adherence underlines the collaborative nature of the therapeutic relationship between the 2 parties. Many clinicians may expect compliance and not adherence when evaluating a transplant candidate. Thus, adherence and the domains of adherence which are most relevant to liver and kidney transplant candidates and recipients needs to be better defined in the scientific literature as well as clinical practice.

### *How Is Nonadherence Quantified?*

Similar to the definition, measurements of adherence in transplant candidates and recipients are not standardized.<sup>14</sup> What level of adherence is considered acceptable is not known; some state 100% adherence is not realistically possible.<sup>13,18</sup> In one study of kidney transplant recipients, posttransplant compliance was measured using insurance claims electronically submitted to obtain reimbursement for dispensed medications.<sup>19</sup> Compared to those with excellent compliance, those with good compliance did not have higher odds of death or graft failure, while those with fair and poor compliance had a graded increase in this risk. Thus, what level of nonadherence is acceptable needs to be better quantified, and whether that measure is applicable to all domains of adherence needs to be determined.

### *In Whom to Assess for the Risk of Nonadherence?*

Due to resource limitations, and/or lack of qualified personnel, some programs may choose to perform a nonadherence risk assessment on selective transplant candidates who are identified as “high-risk.” Often these “high-risk” candidates are identified subjectively. Sometimes, psychosocial factors, such as pretransplant substance abuse, mental health

disorders, and poor social support, are used to identify them.<sup>18,20,21</sup> These practices are not completely supported by current evidence. A review of 147 studies in the field of solid organ transplantation summarized that factors, such as poor social support, had little correlation with nonadherence in transplant recipients.<sup>14</sup> Yet, lack of social support pretransplant was deemed to be an absolute contraindication to liver transplantation by 50% of Canadian and 70% of U.S. centers; the remaining indicated it to be a relative contraindication.<sup>22</sup> While some psychosocial measures, such as pretransplant substance use, are associated with posttransplant nonadherence,<sup>14</sup> objective and valid tools on how to use these variables in determining who to perform a nonadherence risk assessment is needed.

### *How to Assess for the Risk of Nonadherence?*

Prior to a liver or kidney transplant, there is a lack of an objective and universal tool to assess for the risk of nonadherence posttransplant. At 79 centers across the United States, about half state that they have a protocol to evaluate medication adherence before transplant listing.<sup>17</sup> When such a protocol existed, it was rarely in the form of a formal questionnaire.<sup>17</sup> Some centers, instead of a protocol, may rely on the referring or evaluating health care teams’ perception alone in determining the risk of nonadherence. However, a clinicians’ perception has not been consistently demonstrated to predict certain domains of nonadherence such as medication adherence.<sup>23,24</sup> Some tools to assess for the risk of nonadherence have been developed and validated but only in the posttransplant setting and mostly pertain to medication adherence.<sup>18,25-28</sup> Some of these studies are limited by their single-center and retrospective design, and small sample size.

### *Can Interventions Help With Nonadherence?*

Performing a risk assessment pretransplant can identify multifaceted and individualized interventions to help a transplant candidate and develop a treatment plan prior to the transplant. The vast majority of the current literature, however, focuses on interventions in patients posttransplant. In the kidney transplant literature, for example, we found 3 systematic reviews that have shown that educational and behavioral interventions can increase adherence in kidney transplant recipients.<sup>29-31</sup> Applicability to the pretransplant setting is unclear. Also, the follow-up period in most studies was 1 year or less, and all 3 reviews concluded that studies are at high risk of bias (Table 2). Concerns have been raised with respect to convenience sampling that leads to selection bias and Type II error.<sup>27</sup> Many only look at process outcomes, such as adherence behaviors, and robust outcomes, such as graft survival, have not been adequately evaluated.<sup>27</sup> These interventions require significant resources, such as technological infrastructure and ancillary staff, which can

**Table 2.** Summary of Three Systematic Reviews to Assess the Effectiveness of Interventions to Improve Medication Adherence in Kidney Transplant Recipients.

Author, Journal (Year)	Methods of the review	Inclusion and follow-up	Studies included	Risk of bias	Results	Conclusion/s
Low et al, Nephrol Dial Transplant (2015) <sup>30</sup>	Eight electronic databases; multiple designs; adult only; English language only	Behavioral, educational, and combination for 3 to 12 months Follow-up following intervention was >3 months in some but not all	12 studies: 8 RCTs, 2 retrospective cohort studies, 2 no paired-comparison data	Quality of RCTs: average score 52.7% Using the TREND checklist: average score 60.7% Lack of blinding, lack of transparency during randomization	Medication adherence rates were greatly enhanced when multidimensional interventions were implemented whereas one-off feedback from a nurse and financial assistance programs offered little improvement. Dose administration aids when used in conjunction with self-monitoring also improved adherence.	An intervention targeting behavioral risk factors or a combination of behavioral, educational, and emotional changes is effective in enhancing medication adherence.
Mathes et al, Systematic Reviews (2017) <sup>29</sup>	Four electronic databases; multiple designs; all age groups; 4 different languages	Educational, behavioral, and reminder intervention for 8 weeks to 1 year Follow-up period $\leq 1$ for all except 10 years for 1 study	12 studies: 8 RCT, 2 retrospective cohort studies, 1 nonconcurrent cohort study, 1 nonrandomized trial	High: inadequate allocation sequence, lack of blinding	All studies showed an effect direction in favor of the intervention. Intervention effect was only moderate. Studies that combined educational and behavioral intervention components showed larger effects. All studies that were statistically significant were multimodal. Studies that included an individualized component and more intensive interventions showed larger effects. A reminder system intervention showed no statistical significant difference.	Adherence-enhancing interventions can increase adherence. However, because of the small effect, the high risk of bias, and the invalidity of adherence measures, the actual benefit of adherence interventions for an unselected patient population seems limited.
Zhu et. al. J Investig Med (2017) <sup>31</sup>	Four electronic databases; multiple designs; age, and language not specified	Any type of intervention that reported adherence rate or adherence score Follow-up 3 to 15 months	Eight studies: 6 RCTs, 2 prospective studies	5/8 studies had unknown or high risk in allocation concealment and blinding of outcome assessment All high risk for lack of blinding	The adherence rate (pooled odds ratio = 2.37, 95% CI: 1.22-4.58, $p = .01$ ) and adherence score (pooled standardized difference in means = 1.71, 95% CI: 0.35-3.06, $p = .01$ ) were significantly higher than the control group. Sensitivity analysis indicated that findings for adherence rate were robust. However, for adherence score, the significance of the association disappeared after removing one of the studies.	Intervention programs designed to increase immunosuppressive adherence in patients with kidney transplant improve adherence.

Note. CI = confidence interval; RCT = randomized control trials; TREND = Transparent Reporting of Evaluations with Nonrandomized Designs.

be challenging in resource-limited settings. Two other systematic reviews in all solid organ transplants that included liver transplant recipients reported similar findings.<sup>27,32</sup> More importantly, sustained improvement with these interventions has not been demonstrated in the medical literature. A Cochrane review of 182 randomized controlled trials conducted in all fields of medicine suggested that even the most effective interventions did not lead to large improvements in adherence or clinical outcomes.<sup>33</sup> Thus, after a patient is determined to be at-risk for nonadherence pretransplant, a long-term plan to support them posttransplant needs to be provided.

### ***How Long Should a Transplant Candidate Demonstrate Adherence?***

The 6-month time observation period recommended by various organizations is derived from the alcohol abstinence literature.<sup>34</sup> In liver transplant candidates with severe acute alcoholic hepatitis or alcohol-related end-stage liver disease, this is done to ensure the nonreversibility of the disease and to obtain a better control of alcohol use disorder.<sup>5,6</sup> Although shorter pretransplantation period of abstinence is a risk factor for relapse,<sup>21,35</sup> the 6-month rule was chosen arbitrarily.<sup>34</sup> Evidence favoring this recommendation in the adherence assessment is scant. Also, setting time cut-offs for assessing a transplant candidate without long-term support are not ideal as there are temporal changes in adherence patterns.<sup>13-15</sup> Last, any time period chosen for the patient to demonstrate adherence is at risk of the Hawthorne effect, that is, transplant candidates may modify their behavior as they are being observed.<sup>36</sup>

### ***Are These Methods Contributing to Disparities in Access to Transplantation?***

Some practices in the adherence assessment of liver and kidney transplant candidates are subjective and at risk of implicit bias. Implicit bias can happen due to varying socioeconomic backgrounds, racial demographics, motivations, and experiences of the evaluating health care professionals.<sup>12</sup> Research suggests that it can shape the behavior of health professionals and can result in differences in medical treatment along the lines of race, ethnicity, gender, sex, or other characteristics.<sup>37</sup> This may contribute to health care disparities.<sup>37</sup> For example, a well-validated tool, called the Implicit Association Test, was used to measure implicit bias in physicians.<sup>38-41</sup> A significant pro-Caucasian bias has been reported by all. Physicians have been shown to associate non-Caucasian race with uncooperativeness, nonadherence, and noncompliance.<sup>38,39,42,43</sup>

While no specific study has assessed for implicit bias in the nonadherence assessment of liver or kidney transplant candidates, some have raised concerns in the field of lung transplantation.<sup>44</sup> Also, as mentioned above, some of the current practices are subjective and potentially at risk of

being biased. When certain psychosocial factors are used to determine “high risk” candidates subjectively, implicit bias can affect practice. A correlation between these very psychosocial factors and decreased access to transplantation is widely reported in the transplant literature. For example, poor health literacy is considered to be a risk factor for nonadherence,<sup>22</sup> and candidates with limited health literacy had a 30% decreased likelihood of being wait-listed for a kidney transplant.<sup>45</sup> Also, in the absence of objective and universal tools to assess for the risk of nonadherence, the evaluating team’s implicit bias can impact who is determined to be a suitable candidate for transplantation. Thus, current practice patterns in the adherence assessment may be contributing to disparities in access to transplantation, but further work is needed to determine this.

## **Research and Practice Implications**

We propose the following measures to address the concerns we have raised. We first recommend that the term nonadherence be better defined and quantified in liver and kidney transplantation. Objective, valid, and standardized criteria on whom to perform a nonadherence risk assessment on need to be established; if resources allow a practice of universally performing a risk assessment on every transplant candidate could be considered. Following this, appropriate pretransplant tools to assess for the risk of nonadherence posttransplant need to be developed and validated in different patient populations. Studies evaluating their efficacy should avoid convenience sampling and consider meaningful outcome measures such as, graft and patient survival. Once a candidate has been determined to be at risk for nonadherence posttransplant, pragmatic, individualized, and long-term interventions to support them should be developed. Community resources and support systems should be engaged to ensure that patients receive long-term support based on their personal, cultural, and religious beliefs. Also, attention could be directed toward provider- and system-related factors when addressing interventions to improve adherence.<sup>13</sup> Finally, patient engagement and consultation with patient partners should be sought when making practice and policy decisions. This may strengthen the decision-making process, promote mutual accountability, and ensure transparency in allocation decisions.

## **Conclusion**

Pretransplant nonadherence is recognized as a relative or absolute contraindication to transplantation as it is associated with posttransplant nonadherence, which can lead to graft loss, and patient morbidity and mortality. A psychosocial evaluation is performed to help assess the candidacy of transplant candidates who are nonadherent and to identify interventions to help them. We have raised some contemporary issues with current clinical practice in the fields of liver and kidney transplantation. We also express our opinion that some



of the current practices are at risk of implicit bias in health care and this might be contributing to disparities in access to transplantation. We offer measures to address some of the concerns we raised including patient engagement to help make practice and policy decisions. This is needed to ensure transparency and continued faith in the current transplant allocation systems, which has recently been questioned by the media and the public.

### Ethics Approval and Consent to Participate

Not applicable.

### Consent for Publication

All authors provided consent for publication.

### Availability of Data and Materials

Not applicable.

### Acknowledgments

The authors wish to acknowledge Andrea Herrera-Gayol, MD, MSc, PhD for her critical review of the manuscript.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Sandal has received an education grant from Amgen to increase living donor kidney transplantation. The other authors declare no conflicts of interest.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The publication costs are supported by an education grant that Dr. Sandal received from Amgen Canada. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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