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Medical adherence in pediatric organ transplantation: what are the next steps?

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Abstract

Purpose of review—Adherence within pediatric transplantation has gained importance as the complexities of long-term medical management of these patients are identified and knowledge regarding the negative consequences of nonadherence accumulates. We review recent findings to highlight gaps in the literature and make suggestions for future directions.

Recent findings—Most research has focused on medication nonadherence, and a recent meta-analysis indicates that nonadherence is more prevalent in adolescent transplant recipients than in younger children. Nonadherence to other areas of the regimen (e.g. clinic attendance) may be even more common than medication nonadherence. However, work to date is based primarily on kidney and liver pediatric transplant patients, with a paucity of research on heart, lung and intestinal recipients. Risk factors for nonadherence after pediatric transplantation include poor family and child functioning. Intervention research remains rare. Challenges include the need for clearer definitions of what constitutes clinically significant nonadherence, longitudinal and prospective assessment of a wider range of potential risk factors, and the development and evaluation of interventions to treat or prevent nonadherence.

Summary—Adherence research in pediatric transplantation is in its infancy. Significant opportunities exist to advance the field and create standards for effective identification, measurement, and treatment of nonadherence.

Keywords

adherence; medical management; nonadherence; pediatric transplantation

Introduction

Adherence to the medical regimen is widely considered to be critical in order to avert late rejection episodes, graft loss, patient death, and decrease medical costs following solid organ transplantation [1-3,4•]. Rates of nonadherence in pediatric transplantation have been reported to be as low as 3% and as high as 71%, with the highest incidence of nonadherence

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Conflicts of interest

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reported among adolescent kidney transplant patients [5,6••,7•]. Despite the associated risks of nonadherence after transplantation, limited research has been undertaken to systematically examine adherence among pediatric patients [8••] with the majority of studies being carried out among adult patients [9]. In the present review we discuss current definitions of adherence, rates and risk factors associated with nonadherence, treatment of nonadherence, challenges in this area, and next steps for this field. Our intent is to inspire researchers and clinicians to work toward the identification, prevention, and treatment of nonadherence among pediatric solid organ transplant patients.

Defining adherence

Medical adherence has been defined by the World Health Organization (WHO) as ‘the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider’ [10]. In pediatric transplantation, the posttransplant immunosuppressive regimen has been the primary focus of medical adherence research and clinical activity. A recent national consensus conference on adherence in transplantation [8••] considered adherence to be ‘satisfactory’ as long as ‘... the gaps between the recipient’s dosing history and the prescribed dosing regimen have no effect on [the] therapeutic outcome’ (p. 36).

Although these statements provide starting points for discussion and exploration, to date there are no standard metrics that identify the specific degree of nonadherence to post-transplant immunosuppressive medications that best predict adverse outcomes [11-14]. Moreover, beyond medication adherence, there are other elements of the medical regimen to consider (e.g. diet, exercise, and clinic attendance), and strategies to systematically assess adherence to these elements remain underdeveloped. In addition, defining adherence in pediatric transplantation is challenging because the definitions of adherence suggest an ‘agreement’ between the patient and the medical provider. Agreement regarding medical care may not be fully possible in a pediatric setting in which the patient may have limited understanding and rely on a parent to make decisions and concur with recommended care [15]. Therefore, when considering adherence in children it is more appropriate to refer to ‘family adherence’, and this concept has yet to be effectively defined [6••].

Assessment, rates, risk factors and treatment of nonadherence

There have been four areas of key focus within recent adherence research in pediatric transplantation. In the following sections, we summarize the major issues and principal findings from recent investigations in these areas.

Assessment of nonadherence

We conducted a recent meta-analysis examining 61 studies of nonadherence in pediatric transplantation [6••]. We found that the majority of studies focused on medication adherence, and most studies were conducted with kidney (49%) or liver (30%) transplant patients. Fewer studies considered heart or lung recipients, and none involved intestinal or multivisceral transplant patients. Most of the studies used cross-sectional or retrospective designs (as opposed to prospective examination) and used single rather than multiple methods for data collection (i.e. adherence data were collected from a single source such as parent or child report or chart review). We found that nonadherence rates tended to be underestimated in studies with poor methodological quality including reliance on a single measure of adherence.

Rates of nonadherence

Across the 61 studies, rates of nonadherence for completing clinic appointments and medical tests (e.g. biopsies, laboratory draws to monitor immunosuppressants) were highest (12.9 cases per 100 patients per year). Nonadherence rates to diet, exercise, substance use restrictions (e.g. recommendations not to smoke or drink alcohol), and other requirements were slightly better (8 cases per 100 patients per year), although the findings are based on only a handful of studies that examined these elements of the medical regimen. The rate of nonadherence to the medication regimen was lowest (six cases per 100 patients per year).

Risk factors of nonadherence

Several important correlates of nonadherence were found in the meta-analysis, including poorer family functioning (increased parental distress, poor family cohesion) and poorer child psychological functioning (poor child behavioral functioning, increased child distress). These findings reinforce the notion that adherence in pediatrics should be seen as a ‘family matter’ that requires attention to family context, dynamics, and relationships.

Most importantly, our meta-analysis and a number of subsequent studies [7•,16-20] showed that older children (>10 years) were significantly more likely to experience poorer adherence. For example, we found that 7.1 of every 100 adolescent recipients per year were nonadherent to medications, compared to only 2.4 of every 100 younger children. This is an important issue, particularly in light of recent Organ Procurement and Transplantation Network (OPTN) pediatric data as of 1st of May 2011 that show that patient and graft survival rates decrease over time and more dramatically among adolescents. Of the nearly 2000 children who receive an organ every year in the USA, 45% are adolescents (aged 11–17 years old). In this age group, by 5 years post-transplant patient survival rates range between 39% for lung and 96% for kidney, whereas graft survival rates range between 35% for lung and approximately 68% for kidney, heart, and liver. In contrast, graft survival for recipients aged 6–10 years is better at 41% for lung, 75% for heart and liver, and 82% for kidney at 5 years. Research in the general pediatric arena supports the association between older age and poorer adherence and notes the difficulties that adolescents experience adhering to chronic illness regimens [6••,8••,21,22].

Several recent studies have examined additional risk factors for nonadherence in pediatric and adult transplant patients [20,23,24•,25-27]. The adult literature is relevant insofar as the behavior of parents of pediatric recipients may be affected by the risk factors. Findings from a review of qualitative studies [25] in the adult kidney transplant literature suggest that attitudes regarding medication taking, disruptions in schedules, medication side effects, and financial constraints such as being unable to cover medication co-pays are associated with nonadherence to the medication regimen. Findings from the pediatric kidney transplant literature [20,24•,26,27] suggest that patients who report greater perceived adversity associated with their medical treatment needs, and who identify such barriers as having difficulty swallowing medications and keeping a consistent schedule are at higher risk of nonadherence and demonstrate poorer long-term outcomes. Adolescents’ competence in self-management, self-care autonomy, and maturity level is known to be associated with their overall ability to manage and participate in medical care [28-31], raising significant concerns regarding the risks of transitioning adolescents to adult care [7•,17,28,32]. In addition, confusion regarding ‘who’ (e.g. adolescent or parent) is primarily responsible for completing tasks associated with medication adherence (e.g. calling in refills, filling the pill box, keeping track of the dosing schedule) is associated with a higher likelihood of nonadherence [23]. In contrast, parental supervision of medication administration and parental reminders to take medications were associated with better medication adherence [27].

Adherence interventions

A recent review [33••] shows that targeted treatments for medication nonadherence in adult and pediatric transplantation have included behavioral interventions, educational interventions, and system level interventions focused on patient–provider interaction. The review highlights the scarcity of research specific to transplantation and pediatric transplantation in particular [33••]. Only four intervention studies [2,28,34,35] specifically targeted pediatric transplant patients. Three of these studies [28,34,35] evaluated educational interventions among liver and renal pediatric transplant patients, with an emphasis on teaching patients regarding their transplant, their medical care needs, and medications. One of the three studies [35] also used peer modeling and parent rewards for participation in medical care to enhance outcomes. These three studies yielded mixed results with regard to improving adherence. The fourth study [2] evaluated the impact of an individually tailored, medication adherence-support intervention on medication adherence. This study identified some improvement, but no statistically significant differences. More recently, a study [36•] examining the impact of texting medication-taking reminders to patients or parents showed promise in improving tacrolimus blood levels and reducing the incidence of rejection episodes.

Challenges of adherence research

In order for adherence research in pediatric transplantation to advance, several challenging issues must be resolved more effectively in ongoing studies. These include measurement concerns, design limitations in intervention studies, and limitations in knowledge of risk factors for nonadherence.

Measurement of nonadherence

The WHO and the Fine *et al.* consensus study [8••] discuss the challenges of adherence research which include the wide variability in the methods utilized to measure adherence and problems with the interpretation and accuracy of adherence measurement. For example, should nonadherence to immunosuppressive medications be defined as less than 80% adherence to all required doses during a given time period, or is it better defined as any late or missed medication dosages?

Multidimensional assessment of medication nonadherence, utilizing combinations of both observer-reported (e.g. self and clinician report) and indirect or biologic (e.g. pill counts, tacrolimus blood levels) measures has been touted to have the most sensitivity and specificity for identifying nonadherence [6••,7•,8••]. However, a gold standard method to assess medication nonadherence has yet to be identified. Several studies [2,37•,38] have found that patients whose blood serum immunosuppressant levels were more than two standard deviations from their target range had a higher likelihood of demonstrating nonadherence among other measures and experiencing late rejection. A recent study [26] provides evidence that even small variations in blood levels of immunosuppressants may increase the potential for graft loss in children, leading some researchers to suggest that measuring immunosuppressant blood levels [38,39] might soon be considered the most reliable measure of medication nonadherence. However, to date no prospective longitudinal studies exist exploring a causal relationship between these factors. In addition, adherence to other medications (e.g. antibacterial and antifungal medications) is not measured through serum blood levels and other important elements of the medical regimen (e.g. diet) have been largely ignored in the literature.

Interventions for nonadherence

Recognition of the prevalence and consequences of nonadherence to the medical regimen has led to an increased focus on developing interventions to treat nonadherence particularly among adolescent patients [2,33•,36•,40]. However, most of the studies undertaken to date are primarily educational in nature, lack a clear theoretical basis, include small samples, and include no long-term follow-up of effects after intervention termination.

Knowledge of risk factors for nonadherence

Although a growing number of studies have examined risk factors for nonadherence [6•] – particularly in relation to medication-taking – limited knowledge is available regarding how risk factors might work together to affect adherence. For example, little is known regarding how patient age and other family relationship factors (e.g. parental distress or perceived burden) might interact to affect nonadherence rates. In general, taking stock of overall family dynamics in combination with patient-specific factors (e.g. maturity level of the patient, parental expectations, unspoken family rules) might be of particular importance.

The next steps

In the following section, we will offer suggestions regarding how to address the existing gaps in adherence research. We believe that addressing these gaps will ultimately allow research in this field to be significantly advanced, as well as enhancing clinical opportunities to improve patient outcomes.

Improving standards for determining nonadherence

We believe that achieving consensus regarding how to define and measure ‘medication nonadherence’ is of primary importance. Previous studies have used a variety of cut points to operationalize nonadherence and most studies have specifically focused on immunosuppressants. Work is needed to determine whether newer metrics for examining nonadherence based on variability in serum blood levels of immunosuppressants have predictive validity (i.e. are associated with clinical events such as graft rejection).

In addition, clearer definitions are needed for nonadherence to other components of the medical regimen. Thus, research examining patterns of attendance at clinic, participation in required medical care (e.g. laboratory blood draws, biopsies), and home monitoring are necessary to develop a more global understanding of pediatric transplant adherence. Further, understanding engagement in risk-taking behaviors by adolescent solid organ transplant patients is necessary as little is known regarding patterns of drug, alcohol and tobacco use in these populations and the relationship between these behaviors and medical outcomes.

Examining nonadherence in under-researched patient groups

The majority of adherence studies in pediatric transplantation have focused on kidney patients. Although much can be learned from kidney transplant groups, findings from these studies may not generalize to other pediatric organ transplant groups (heart, lung, and intestinal transplant patients) who have not been widely investigated and present a significant gap in the existing adherence literature.

Identifying strong risk factors for nonadherence

A more systematic examination of factors known to be associated with adherence across the lifespan of the patient needs to be undertaken. In particular, identification of pretransplant factors that raise risk for post-transplant nonadherence [40] could suggest areas for intervention and allow time (if feasible) to intervene prior to transplant. Preventive work

may help reduce instances of nonadherence post transplantation and the associated negative medical outcomes.

Developing family-centered interventions for nonadherence

Interventions to treat nonadherence in pediatrics, whether in transplant or other populations, would benefit from more fully recognizing that adherence occurs within the context of the developing child and family. Ideally, interventions to improve adherence would become part of standard care such that strategies meant to support family adherence are implemented prior to transplantation and evolve over time as needed. Much can be learned about family-centered adherence interventions from the literature regarding other chronically ill pediatric groups [41,42]. Two recent meta-analyses of adherence interventions [41-43] found promising results, in terms of improvements in adherence and health outcomes following interventions, particularly for interventions that were multidimensional in nature (e.g. behavioral components with education). In addition, studies of adherent families who have effectively negotiated complex medical regimens [27] might pinpoint ways of successfully handling the transition of care from the parent to the child.

Mobile health technology (e.g. cell phones, pocket personal computers) is an emerging area of investigation for researchers interested in supporting adult patients' engagement in self-care behaviors, including adherence [36•,44-47,48•], and it holds promise for pediatrics [36•]. Mobile health technologies provide a novel avenue for reinforcing the principles and requirements of healthcare while promoting engagement and active participation by patients burdened with highly complex regimens. Because rates of electronic and mobile media usage (e.g. texting, cell phone, and the Internet) are highest among adolescents [49], and given the severe consequences associated with nonadherence, interventions that marry technological communication among adolescents with self-care behaviors may help provide the needed edge to improve long-term outcomes in transplantation [36•]. Recent interest in utilizing mobile health technologies to support and promote adherence among transplant populations has shown initial promise among pediatric liver transplant recipients [36•]. Consistent with the concept of 'family adherence', we are currently developing a mobile health application to support adolescent transplant patients and their parents in tracking and monitoring healthcare behaviors while enhancing dyadic communication and interaction regarding completion of these tasks [50].

Conclusion

This is an exciting time in pediatric transplantation. We are in a unique position to advance the field of adherence research in this population. By taking steps to standardize the assessment of adherence to various aspects of the medical regimen and across the lifespan of the patient, investing in the prospective investigation of risk factors, and developing effective interventions to prevent and treat nonadherence we may be able to limit the number of patients who engage in behaviors that negatively impact their graft and overall quality of life.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

•of special interest

••of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 561).

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Key points

- Most adherence research has focused on medication adherence with limited research examining adherence to other areas of the medical regimen.
- Adherence research has been primarily carried out with kidney and liver pediatric transplant patients, with a paucity of research on heart, lung and intestinal recipients.
- Several challenges exist in adherence research including the need for clearer definitions of what constitutes clinically significant nonadherence, longitudinal and prospective assessment of a wider range of potential risk factors, and the development and evaluation of interventions to treat or prevent nonadherence.