

Adherence in Adolescent and Young Adult Kidney Transplant Recipients

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Abstract: Poor adherence to immunosuppressive medications may be the most important barrier to long term graft survival. An understanding of medication adherence and its determinants is critical to addressing this important problem. In this paper, we will review the different ways in which adherence may be compromised, summarize the evidence that young people constitute a particularly high risk group, and consider the consequences and impact of poor adherence. We will also review the determinants of adherence, including characteristics of the patient and family, the treatment regimen, the healthcare team and its organization, and the healthcare system. We will highlight the most common barriers to adherence identified by young people, and consider different methods of measuring adherence, along with the advantages and limitations of each. Finally, we will consider possible intervention strategies to improve adherence in young people.

Keywords: Adherence, adolescence, compliance, emerging adulthood, pediatric, renal transplant.

INTRODUCTION

Poor treatment adherence is one of the most important obstacles to graft longevity in kidney transplantation [1-3]. Effective immunosuppressive medications cannot prevent rejection if they are not consumed every day on a strict schedule. Similarly, graft dysfunction signalling possible rejection cannot be detected and treated early without regular monitoring of serum creatinine. Although transplant recipients of all ages may have difficulty adhering to a strict treatment plan, adolescents and young adults are at particularly high risk for poor adherence [4-6]. Not coincidentally, young people also have the highest risk for graft failure of any age group [7].

Adherence is defined as the extent to which an individual's behavior coincides with medical or health advice [8]. This definition underscores the socially constructed nature of adherence by focusing on the correspondence between patient behaviors and the prescriptions, recommendations, and/or advice from health care providers. As such, the interchange between patients and providers is critical to optimizing adherence. The World Health Organization (WHO) definition, emphasizes the need for the patient and provider to have an *agreed upon* treatment plan [9]. Although, we concur that the patient's agreement is ideal, this is difficult to objectively verify. Therefore, the alternate definition is used for the purpose of this review. Of course the goal of any treatment plan is to optimize outcomes. With this in mind, *satisfactory adherence* has been defined as sufficient concordance between the prescribed treatment plan and the patient's behaviour such that outcome is unaffected by any deviations

from the plan [9]. We will focus primarily on medication adherence, but recognize that poor adherence to other aspects of treatment, including attendance at clinic visits and blood testing are also very common [10] and impact outcomes.

In this paper, we will review the different forms of poor adherence, show that young people constitute a particularly high risk group, and consider the consequences and impact of poor adherence. We will also review factors that influence adherence, highlighting the most common barriers to adherence identified by young people, and consider different methods of measuring adherence. Finally, we will consider possible intervention strategies to improve adherence in young people.

COMPONENTS OF ADHERENCE

Excellent medication adherence requires taking the correct dose of medication, at the correct time of day, every day, for as long as the condition is being treated. There may be problems with any of these components of adherence (Table 1).

Dosing Adherence. Failure to take the correct dose of medication may occur for two possible reasons: dosing errors or deliberate modification of the dose by the patient. Dosing errors occur for a variety of reasons, including physician prescribing error, pharmacist dispensing error, poor communication between the patient and the physician or pharmacist, or misunderstanding on the part of the patient. Once identified, dosing errors are usually easily corrected. Deliberate dose modification by the patient is a more difficult problem to correct. Patients may reduce the dose of medication because they believe that the medication is too strong, because of unpleasant side effects, or because of financial constraints [11-13]. Patients who cannot afford a medication may take a lower dose of medication in an effort to make the supply last longer [14]. Dose reductions of more

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than 50% were associated with a 70% higher risk of graft failure compared with no reduction [15]. A dose higher than prescribed may also be consumed in an effort to make up for prior missed doses. Determining appropriateness of dosing requires open communication between the treating team and the patient, with the treating team directly acknowledging with the patient that patients may sometimes modify their doses, and that they want to understand when and why the patient may have done this.

Timing Adherence. Taking medications on schedule is referred to as ‘timing adherence’. Incorrect timing of medication doses is the most common form of poor adherence; 76% of kidney transplant recipients between 11 and 20 years old indicated they had taken medications at least 1 hour late at least once in the prior week [16]. Some 46% of 250 adult kidney recipients had adherence issues, with 28% of those who had taken medications more than 2 hours late reporting that this happened more than once per week [17]. The consequences of off-schedule dosing, in terms of graft outcomes, are unknown. However, even minor deviations from the prescribed medication schedule were associated with significantly higher late acute rejection rates in heart [18] and kidney [19, 20] transplant recipients. It is unrealistic to expect that patients will always take their medications at exactly the same times every day. Most healthcare professionals are willing to accept a window of 1-2 hours around the expected dosing time [21, 22]. It is important, however, that physicians, nurses and pharmacists discuss the intended dosing schedule with transplant recipients and agree upon set dosing times. This approach will emphasize the importance of correct dose timing.

Taking Adherence. The proportion of prescribed doses of medication that are taken each day is referred to as ‘taking adherence’ [23]. In a study of 33 kidney transplant recipients 11-20 years old, 27% reported missing at least one dose of medication within the prior week [16]. Poor taking adherence has been linked to higher acute rejection and graft failure rates [20, 24]. Like with timing adherence, there is no known safe level of taking adherence. More risky still than occasional missed doses are ‘drug holidays’, defined as missing ≥ 2 consecutive doses [20, 23]. Again, it is important that patients be made to feel comfortable disclosing missed doses of medications to the treating team to accurately inform clinical decision-making.

Persistence. Appropriate dosing, timing, and taking adherence are all examples of *implementation* or *execution* of the recommended treatment regimen [21, 22]. Continuing the medication regimen for as long as the condition being treated is present constitutes *persistence* [25]. Perhaps not surprisingly, complete discontinuation of immunosuppressive medications by transplant patients is not very common. Most studies showed persistence with immunosuppressive medications over the period of observation. However, discontinuation of study drug at 6 months after randomization was reported in 18.5% of patients taking once daily tacrolimus and 28% of patients taking twice daily tacrolimus in a trial of once daily versus twice daily tacrolimus dosing [21]. Discontinuation of medication was associated with an 8.3 times higher risk of graft failure among patients recorded in the USRDS covered under Medicare [15].

Multiple methods of assessing adherence should be used whenever feasible for optimal assessment of adherence in clinical and research settings as well as the advancement of scientific understanding of adherence.

ADHERENCE AMONG YOUNG TRANSPLANT RECIPIENTS

Adolescents and young adults with a broad range of chronic conditions, including diabetes, rheumatologic disorders, and organ transplantation have been shown to have poorer adherence to both medication and to general care (e.g., clinic appointments, routine blood monitoring) compared with other age groups [26-30]. This deterioration in adherence is likely related to the increasing independence afforded young people as they mature, with less time spent under direct adult supervision, and increasing responsibility placed on the young person for tasks related to medication taking and overall management of their condition [31-34].

Many prior studies of medication adherence in pediatric transplant recipients classified patients as either adherent or non-adherent. Different studies used different methods of measuring adherence, and slightly different definitions of non-adherence. In a systematic review of studies of immunosuppressive medication adherence, Dobbels estimated the prevalence of non-adherence at 30.7% overall [5]. When patient age was taken into account, the prevalence of non-adherence was estimated at 43.2% among adolescents (≥ 10 years old), compared with 22.4% among younger children or a mixed younger and adolescent population. Dew and colleagues also found older age to be associated with poorer adherence in a meta-analysis of studies examining medical regimen adherence among pediatric solid organ transplant recipients, with non-adherence rates three times higher in adolescents than in younger children [4].

Although adolescents have shown a higher risk of poor adherence than younger children in the majority of studies, this finding is not universal. An American study of pediatric kidney transplant recipients found greater adherence, as measured using Medicare prescription claims data, among older patients than among younger ones [24]. This finding may have been influenced by the very select sample of eligible patients (only 22% of pediatric kidney transplant recipients are insured by Medicare) and/or by the method used to assess adherence. Compared with older kidney transplant recipients, those under 24 years old had a higher prevalence of poor adherence and a lower prevalence of high adherence in one U.S. study [6]; in another study the risk of poor adherence 12 months post-transplant was 1.7 times higher among those 0-18 years and 1.6 times higher in those 19-24 years than among those 25-44 years old [15]. The evidence overall suggests that adolescents and young adults have the highest risk of poor adherence of any age group. This is also corroborated by clinical experience, and by the strong association between adolescent age and poorer graft outcomes [7, 35]. Graft failure rates begin to rise at about 11 years of age, peak in the interval between 17 and 24 years, and decrease thereafter [7]. As illustrated in Fig. (1), the age at which graft failure rates are highest corresponds with the period during which adherence is likely poorest.

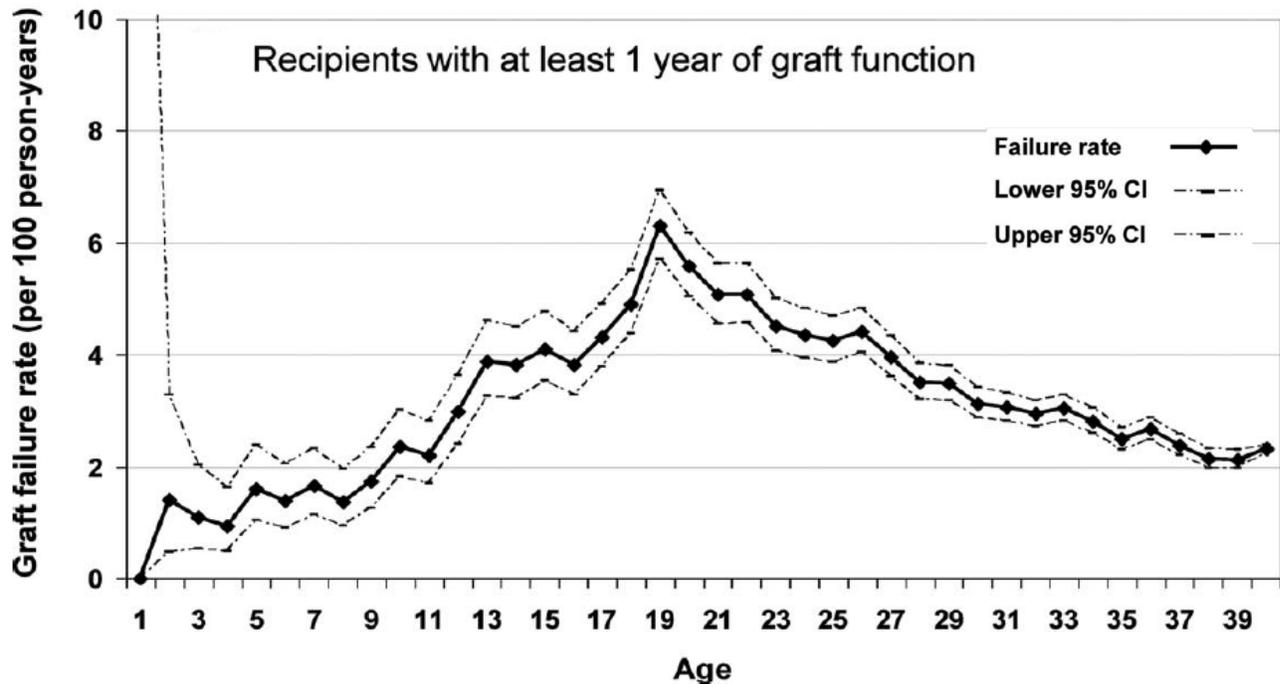


Fig. (1). Crude age-specific death-censored graft failure rates (failures per 100 person-years) in each 1-year age interval are shown with 95% confidence intervals for kidney transplant recipients with at least 1 year of graft function (reproduced from [7]).

There is little information on how adherence behaviour prior to transplantation is used to assess transplant readiness or to identify patients at higher risk for poor adherence post-transplant. A recent survey of centers with membership in the United Network for Organ Sharing (response rate 44%) found that only about half of respondents assessed adherence in any way before listing for transplant, and 94% used no formal questionnaire to assess medication adherence prior to listing [36]. The ability of medication adherence during dialysis to predict adherence behaviour post-transplant is also unknown. This may be particularly challenging in children and adolescents, whose behaviour is likely to change over time. More research is needed in this area.

CONSEQUENCES AND IMPACT OF POOR ADHERENCE

Numerous studies showed a strong association between poor adherence and adverse graft and patient outcomes. Among pediatric kidney transplant recipients for whom adherence was assessed using Medicare prescription claims, each 10% decrement in adherence was associated with an 8% higher hazard of graft failure [24]. Poor adherence was also associated with higher hospitalization and mortality rates in pediatric kidney transplant recipients [37]. There is growing evidence that poor medication adherence may be the most important mediator of late acute rejection and graft failure - especially among young people [2, 3, 5, 19, 38, 39]. Antibody-mediated rejection is increasingly recognized as a major cause of graft failure among those whose grafts have survived for at least one year [3]. Sellarés and colleagues hypothesized that chronic poor adherence leads to donor-specific antibody formation and subsequent antibody-mediated rejection - with a high risk of failure. In an

observational study of 315 adult kidney transplant recipients, 60 experienced graft failure, of whom 47% had antibody-mediated rejection on their last biopsy. The medical records contained concerns about poor adherence ten times more frequently among those whose grafts failed (32%) than among those whose grafts did not fail (3%) [3]. Another study of 628 adult kidney transplant recipients found that 48% of graft failures (death censored) that occurred ≥ 2 years post-transplant could be attributed to poor adherence [2]. Of the 37 patients with evidence of poor adherence, 78% subsequently experienced graft failure, compared with only 7.8% of the 591 with good adherence. Younger age was significantly associated with a higher risk of graft failure due to poor adherence; among those < 50 years old at transplant, 2/3 of death censored graft failures were due to poor adherence [2].

Not all studies have shown a significant association between adherence and graft outcomes. A study of 243 adult kidney transplant recipients, in which adherence to a single immunosuppressive medication was monitored electronically during the first 6 months post-transplant, found no association between adherence and any of acute rejection, decline in glomerular filtration rate, or graft survival [40]. The authors hypothesized that sustained effects of immunosuppression induction agents may have protected patients from poor adherence during the study period. In addition, relatively good adherence in the period immediately following transplantation, large variability in causes of graft failure in this interval, and relatively low acute rejection rates may all have contributed to this finding. Another study of 121 prevalent adult kidney transplant recipients in whom adherence to a single immunosuppressive medication was monitored electronically for 12 months also found no association between adherence and any of acute rejection, decline

in glomerular filtration rate, or graft loss [22]. However, poor outcomes were extremely uncommon in this cohort, suggesting that the study may have been underpowered to detect such associations.

Most agree that poor immunosuppression adherence is a major risk factor for graft failure. Graft failure has profound implications for both quality of life and patient longevity. Quality of life is significantly poorer for patients treated with dialysis than for those with a functioning transplant [41, 42]. Pediatric renal transplant recipients who returned to dialysis therapy following graft failure had a 4.4 times higher mortality rate than those who maintained graft function [43]. Individuals who lose a renal graft are not assured of receiving another; organ shortages and potential antibody sensitization related to the failed graft substantially limit opportunities for repeat transplantation.

In addition to the medical and quality of life costs associated with non-adherence, there are also substantial economic costs. The median annual cost per patient with graft function was estimated at \$16 844, compared with \$82 765 in the year of graft failure and \$70 581 per year during dialysis therapy [44]. Another study estimated that persistent poor adherence is associated with a \$12 840 increase in individual 3-year medical costs [6].

DETERMINANTS OF ADHERENCE

Fig. (2) illustrates the factors proposed by the World Health Organization (WHO) to determine treatment adherence [42]. These include patient-related factors (e.g. health beliefs, self-efficacy, knowledge, and perceived barriers to adherence), social and economic factors (e.g., family functioning, social supports, and medication costs), therapy-related factors (e.g., treatment side effects, duration of treatment, and regimen complexity), condition-related factors (e.g. symptoms, comorbidities, psychiatric conditions), and health care system-related and health care team-related factors [45]. Table 2 summarizes how the factors identified by the WHO fit into the framework proposed by Berben *et al.* to conceptualize the determinants of adherence at different “levels” [46]. Berben’s framework

emphasizes the fact that an individual patient’s adherence is influenced not only by factors unique to that particular patient, but by the patient’s interactions with those around him or her, and by the environment in which he or she is living. This framework includes patient-level (WHO patient-, condition-, and therapy-related factors), “micro”-level (social factors and interactions with the care team), “meso”-level (organization and expertise of the healthcare team and care processes), and “macro”-level (high-level healthcare systems factors, including care and medication cost coverage, and overall care environment) factors. When considering ways of improving adherence, clinicians often focus on what the patient must do; this framework helps highlight the things clinicians, and the healthcare system at large, may do to help support better adherence.

Table 1. Components of adherence.

Component		Potential Problems
Persistence		<ul style="list-style-type: none"> Discontinuing medication
Implementation/ Execution	Taking	<ul style="list-style-type: none"> Missing doses intermittently or consistently Drug holidays
	Timing	<ul style="list-style-type: none"> Off-schedule dosing intermittently or consistently
	Dosing	<ul style="list-style-type: none"> Dosing errors Deliberate under- or over-dosing

Macro-level/Financial factors: International comparisons of adherence and graft outcomes may shed some light on the impact of health care systems factors on adherence. A meta-analysis comparing European with American kidney transplant recipients found significantly poorer adherence among American patients [47]. The inability of some patients to pay for medications may have an important effect on adherence. In a survey of 254 American kidney transplant programs, 87% of adult programs and 67% of pediatric programs indicated that patients frequently contacted them with concerns about the high cost of immunosuppressive medications, and 75% of adult and 56% of pediatric

Table 2. Determinants of adherence.

Level	Factor	Examples
Patient	Sociodemographic	Sex, age, race, socioeconomic status
	Individual	Health beliefs, self-efficacy, condition and treatment knowledge, perceived barriers to adherence
	Condition-related	Nature of condition being treated, symptoms, comorbidities, psychiatric conditions
	Treatment related	Taste of medication, treatment side effects, duration of treatment, regimen complexity, number of doses per day
Micro	Social	Family structure, family functioning, social supports, economic factors
	Care team	Quality of interactions with healthcare team, trust in care providers
Meso	Care organization	Accessibility to care and to care providers
	Care team composition	Expertise of individuals on care team; inclusion of pharmacists, psychologists, nurses, physicians, surgeons
	Care processes	Methods of communication with care team; language barriers; clinic structure; frequency of visits; frequency of monitoring
Macro	Insurance	Medication and care coverage
	Healthcare system	General ‘culture’ of care; organization of healthcare

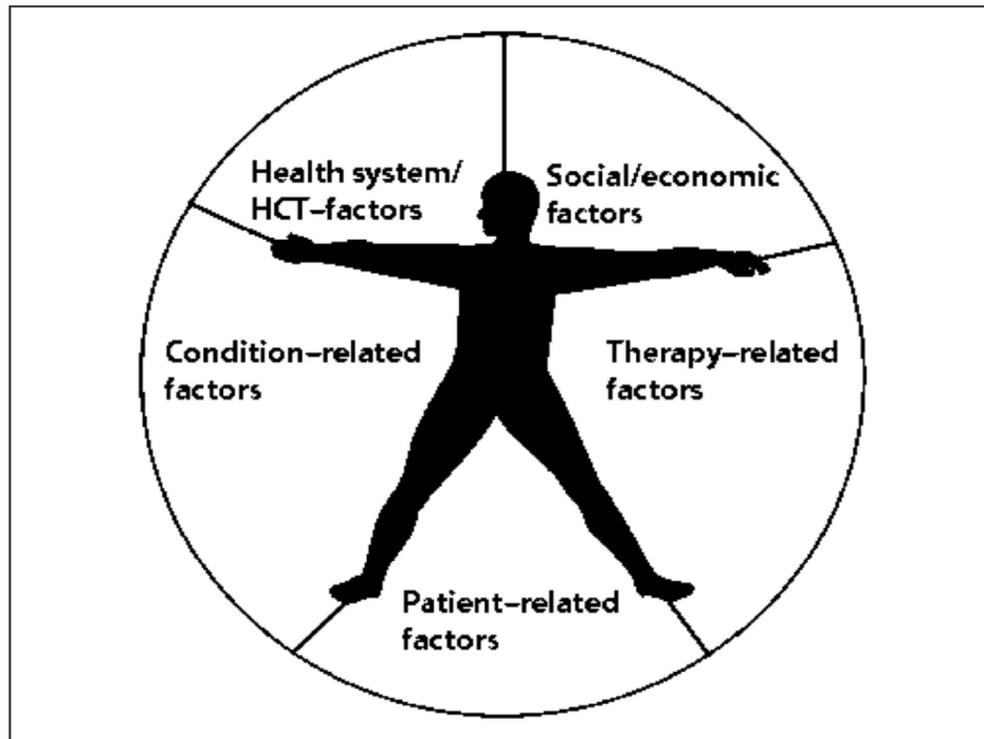


Fig. (2). Interacting factors influencing treatment adherence as identified by the World Health Organization (reproduced from [45]).

programs indicated that > 20% of their patients had trouble paying for their medications [13]. Furthermore, 43% of programs reported that > 10% patients do not take their medications as prescribed due to inability to pay for them. Some patients admit to reducing their doses to allow a prescription to last longer [14]. Inability to pay for medications appears to be more common among adults than children, likely due to additional options for medication cost coverage available to children. Loss of insurance coverage may be a contributing factor to the lower levels of adherence seen among young adults [48].

Meso-level factors: The role of healthcare processes and structures in adherence is just beginning to be explored. There is some evidence that adult-oriented healthcare processes may be poorly matched to the developmental needs of adolescents and young adults, contributing to poorer adherence in this group. There was a 2-fold increased risk of graft failure during the period following transfer of Canadian pediatric kidney transplant recipients to adult care [49]. In a study of American pediatric kidney transplant recipients, the negative effect of transfer depended on age at transfer: individuals transferred at < 21 years old had a 57% higher risk of graft failure than individuals of the same age who had been transferred at \geq 21 years old [50]. Transfer results not only in a change in care provider, but usually involves a major change in the care philosophy, practices, and resource availability. There are several important differences between the pediatric and adult care environments. Autonomy is expected in the adult care context, with emphasis being placed on the responsibility of the patient for their own health. In contrast, a more family-centered and paternalistic approach is common in the

pediatric setting. In addition, the volume of patients per care provider is typically substantially higher in the adult versus pediatric care setting, resulting in less availability of adult care providers [51, 52].

Micro-level factors: Whereas social support has not been consistently identified as a significant determinant of adherence among adults [11, 22], lack of parental supervision and support, poor parent-patient communication, and poor family functioning have been identified as barriers to adherence among children and adolescents [4, 5, 51]. Family efficacy, defined as the family's ability to accomplish tasks needed to function, was associated with fewer perceived barriers to adherence [53]. Poor communication between the patient and the physician has also been shown to have a negative impact on adherence [54].

Patient-level factors: When considering patient-level determinants of adherence, it should be recognized that poorly adherent patients will each have a different combination of reasons for their poor adherence. Most poor adherence is 'unintentional' [14], and believed to be related to inadequate organizational skills and/or problem-solving abilities, or to complexity of the medical regimen. Forgetting was the most commonly stated reason for missing medications (56%) in one study of adolescent renal transplant recipients [30], and the second most common (29%), after organizational problems (58%) in another study [55]. Breaches in adherence were most common when people were outside their normal routines [12, 14]. Evening doses were missed or late more frequently than morning doses [21, 22]. Other modifiable risk factors for poor adherence in adolescents with transplants include poor

medication and disease knowledge and lack of a pillbox [4, 5, 9, 30, 51, 56]. Depression has not been consistently identified as a significant determinant of adherence [11, 57]. Interestingly, higher levels of anxiety were associated with better adherence among pediatric kidney and liver transplant recipients [57]. Self-efficacy, defined as a sense of control over one's environment and behaviour, has a positive influence on adherence, and was estimated to explain 9% of the variability in adherence in a study of 121 adult kidney transplant recipients [22].

Intentional poor adherence frequently relates to health beliefs, and may be more difficult to change. The Health Belief model suggests that people adhere to a treatment if they (i) perceive that they are susceptible to disease, (ii) believe that the disease has serious consequences, and (iii) believe that the benefits of taking action outweigh the costs associated with action and the barriers to taking action [11]. A survey of 558 adult kidney transplant recipients found that patients with good adherence had a stronger belief in the necessity of immunosuppressive medications than those with poorer adherence [11]. A study of kidney transplant recipients 11-20 years of age examined patients' perceptions of adversity associated with transplantation, hypothesizing that greater perceived adversity may tip the cost-benefit equation, favouring poor adherence. They found that those who received a transplant at ≥ 16 years of age and those who had not experienced an interval of dialysis before transplantation perceived greater adversity with transplantation; however, there was no significant association between perceived adversity and adherence [16]. Among adolescents, poor adherence may reflect attempts to 'be normal' - though this represents less than 5% of reasons given for poor adherence [55].

Factors related to treatment may also influence adherence. Complexity of the medication regimen, multiple doses per day, and multiple pills per dose have all been identified as barriers to good adherence [5, 30, 58]. Some comparisons of the once-daily with the twice daily formulation of tacrolimus, including in a randomized trial [21], found greater satisfaction [59] and superior adherence with the once-daily formulation [21, 60, 61]. However, the proportion of patients who missed medication for at least one full day (i.e. a single dose for those on once-daily dosing or 2 consecutive doses for those on twice-daily dosing) was higher (62%) among those on once-daily dosing than for those on twice-daily dosing (40%). The consequences of missing a dose may be more serious with single daily dosing in terms of total drug exposure [62]. Furthermore, other studies found no difference in adherence between those taking once daily versus twice daily tacrolimus [62, 63].

Levels of adherence are also dynamic over time; it is common for adherence to decrease as time since transplant increases. Two studies of adult kidney transplant recipients found significant declines in adherence over time [20, 64]. However, the independent effect of time since transplant is more difficult to assess in pediatric recipients, who are also moving into adolescence and young adulthood concurrently with increasing time since transplant.

METHODS OF MEASURING ADHERENCE

There is no perfect method of measuring medication adherence. Each method has advantages and disadvantage. Methods of measuring adherence, summarized in Table 3, can be divided into 'direct' and 'indirect' methods.

Direct Methods: Direct methods of measuring adherence include direct observation of medication taking - which is clearly impractical outside a hospital setting - and blood drug levels. Single trough levels of the immunosuppressive medications tacrolimus, cyclosporine, mycophenolate, and sirolimus that are low or undetectable may provide evidence of very recent poor adherence, but provide no information about adherence patterns over longer periods. Variability in trough levels of tacrolimus, as quantified by the standard deviation, is gaining popularity as a direct method of quantifying adherence among transplant recipients. High tacrolimus level standard deviation, which reflects erratic dosing, was strongly associated with number of acute rejections in adolescent liver transplant recipients [65], and decreased following an adherence-promoting intervention [66, 67]. A study of 144 heart, liver, kidney, and lung transplant recipients 8 to 18 years old found higher tacrolimus level standard deviations to be associated with a significantly higher risk of late acute rejection, and each 1 unit higher standard deviation of tacrolimus levels to be associated with a 1.58 times higher risk for graft loss [68]. Graft survival was better when the standard deviation was < 2.0 .

It has been suggested that the coefficient of variation may provide a better measure of variability in tacrolimus levels than standard deviation since higher standard deviation may reflect higher absolute levels of tacrolimus [69]. A study of 46 kidney transplant recipients < 22 years old found that a coefficient of variation of tacrolimus levels greater than 41% was associated with a higher risk of rejection (odds ratio 9.7, $p=0.005$). Some have suggested that it may be more appropriate to consider the proportion of tacrolimus trough levels outside the target range, or the mean deviation from target [70] rather than the standard deviation. This suggestion stems from the fact that target tacrolimus trough levels may change over time; if the dose is modified to reach a new target, and the level changes accordingly, the standard deviation will increase even in the face of excellent adherence.

There is some early evidence that standard deviation of sirolimus trough levels is also a reasonably good marker of adherence [71]. A composite of variability in tacrolimus or sirolimus trough levels and self-report, such as the 'system for integrated adherence monitoring' may also provide adherence information [71]. Unfortunately, the variability in the levels of other immunosuppressive medications are less useful. Variability in cyclosporin levels reflects adherence poorly [72]. Mycophenolic acid levels and azathioprine metabolites are not routinely monitored, and have not been studied. Although tracers may be added to medications in the research setting to provide a means of monitoring adherence directly, this is expensive and impractical for clinical purposes [73].

Table 3. Methods of measuring adherence.

Method		Advantages	Disadvantages
Direct			
Observation	Medication consumed under direct observation	Very accurate	Impractical
Drug levels	Measure serum trough levels	Objective measure	Only provides information on very recent adherence
	Calculate variability in tacrolimus trough levels (standard deviation or coefficient of variation)	Objective measure; easily obtained, relatively inexpensive	Need multiple levels to calculate variability; changing target levels will increase variability even if adherence is good; alternative reasons for variable levels; not useful for all types of medications
Biomarkers/ tracers	Measureable tracer consumed with drug	Objective measure	Expensive, impractical
Indirect			
Electronic monitoring	Electronic pill bottle cap records opening of a bottle for a single medication	Portable, easy to use, provides information on both taking and timing; provides information about each dose so can see changes over time	Assumes medication is consumed when bottle is opened; unattractive to people who use a multi-dose pillbox; requires adherence to use of the device; requires user to download data; relatively expensive; requires expertise in using and interpreting data
	Multi-dose electronic pillbox (available with real-time web-based data storage) records opening of compartment where pills are stored	Easy to use, provides information on both taking and timing; provides information about each dose so can see changes over time; data stored securely on internet in real-time; can be used to provide dose reminders only when needed	Assumes medication is consumed when compartment is opened; not very portable; requires adherence to use of the device; relatively expensive; loss of internet connection results in loss of data; requires expertise in using and interpreting data
Pill counts	Patient brings pill supply to have pills counted and number remaining compared with number expected to be remaining if adherence was perfect, based on number dispensed	Simple, relatively inexpensive	Requires patients to bring pills for counting; provides no information about timing of missed doses or about times of day that medications are taken
Pharmacy records	Compare number of pills dispensed over a given interval with number expected to be consumed within that interval	Simple, relatively inexpensive	Estimates may be compromised by pill 'stockpiles' at patients' homes; if patient uses more than one pharmacy, may miss refills; provides no information about timing of missed doses or about times of day that medications are taken
Self-report	Various self-report tools may be used with different time windows	Simple, inexpensive	Poor recall; overestimates adherence; the most accurate reporting is only for brief time windows
Collateral report	Report of parents, other caregivers, members of care team	Simple, inexpensive	Poor recall; biased reporting; may correlate poorly with other methods

Indirect methods: Electronic monitoring is considered an indirect method, and makes the assumption that the medication is consumed every time the electronic device is opened. Medications may be monitored using a bottle with an electronic cap that records a date and time 'stamp' each time the bottle is opened (such as the Medication Event Monitoring System, MEMS) or using a multidose electronic pillbox such as the Vaica Simplemed device. Bottle devices have the advantage of being portable, but may be unacceptable to people who use a multidose pillbox to organize their medications [73], and require the user to bring the cap to the center for reading, or at least place it on a reader at home. Multidose electronic pillboxes are not very portable, and may depend on a reliable internet connection. However, they have several advantages, including real time storage of adherence data on a web-based system requiring no action on the part of the user, providing an organizational

system that may itself promote adherence, and the option of providing reminders to users only if the device is not opened on time. All electronic monitors provide rich adherence information, allowing tracking of patterns of missed and late doses, and changes in adherence over time.

Pill counts are fairly simple, but require patients to bring pills for counting, and provide no information about the timing of missed doses or about times of day that medications are taken. Counts also assume that missing pills have been consumed. Pharmacy records can be used to estimate the number of pills consumed, knowing timing of refills and amount of medication dispensed at each refill. A significant limitation of pharmacy refill records is that patients may have 'stockpiles' of medication at home, left over after dose changes, making it difficult to accurately determine the amount of medication consumed.

A variety of tools exist to capture adherence by self-report. In general self-report tends to overestimate adherence. However, self-report does have moderate correlation with other methods, such as electronic monitoring [70]. The accuracy of self-report can be improved by remaining neutral and non-judgmental when questioning, and by limiting recall of adherence to a relatively short time period. Collateral report from parents or from members of the healthcare team may also be used. However the accuracy of collateral reports in diagnosing poor adherence is very limited [70].

POTENTIAL INTERVENTIONS TO IMPROVE ADHERENCE

Interventions to improve adherence may be applied at a program level, to all patients in the program, or at an individual level, targeted to patients identified to be at high risk. Program level interventions recognize that poor adherence is often unrecognized, and may include components targeting meso-, micro-, and patient-level factors influencing adherence. The goal of program level interventions is to improve the adherence of all patients in the program. The most effective intervention strategies likely include both program-level and targeted interventions. Prior work suggests that interventions administered repeatedly at regular intervals offer better sustained treatment effects than interventions delivered in single session or concentrated formats [74-78]. Repeated intervention sessions allow the opportunity to provide anticipatory guidance, recognizing that adherence barriers may change over time (e.g. during coming holidays or following a major change of routine such as leaving home for college) [23, 73].

An effective program-level intervention must address the most common, and most powerful, determinants of poor adherence. Prior studies of adult transplant recipients [38] and children and adolescents with other chronic illnesses [79-84] indicate that effective interventions include education in conjunction with some combination of adherence monitoring, promotion of problem-solving [82, 85-87], goal-setting, development of routines, and/or adherence support. There is some evidence suggesting that motivational interviewing techniques may also improve adherence [88, 89]. Other potential interventions at a program level include blood drug level and graft function monitoring at a higher frequency, and inclusion of a clinical pharmacist in the care team. Even something as simple as consistently asking about medication adherence at every clinic visit may have a positive effect on adherence. Given that organizational problems and ‘forgetting’ are two of the most commonly identified barriers to adherence, recommending and teaching use of a multidose pillbox may also help [30, 55]. Routinely recommending a system of dose reminders, such as a watch or cellphone alarm, or an adherence system that provides phone or text message reminders, is another potentially useful strategy. A variety of smartphone applications and web-based tools to promote better self-care and medication adherence have become available in recent years. These include applications such as MyMedSchedule and the companion website MedAction

Plan (<https://secure.medactionplan.com/ped/>), and MyMeds (<http://about.my-meds.com/>), among others. A recent review of smartphone applications compares the features of many available products [90]. These applications provide features such as medication lists, adherence self-tracking, and text message dose reminders.

For adolescents and young adults, who are beginning to take over responsibility for their own care, it may also be useful to clearly identify who is responsible for each task related to medication taking, using a tool such as the Allocation of Responsibility for treatment regimen tasks questionnaire [34]. Tools designed to identify personal barriers to adherence, such as the Adolescent Medication Barriers Scale, may be used to tailor interventions to address the most relevant barriers [56]. Adherence support from a key person from outside the healthcare team - called a ‘personal trainer’ [83, 84] has also shown promise in improving adherence as did a ‘continuous self-improvement’ intervention approach with adult kidney transplant recipients [91].

In order to effectively apply targeted interventions, high risk patients must first be identified. This may be done using adherence monitoring systems (such as electronic monitoring), following drug levels, using self-report tools, or based on prior behaviour (known poor adherence, rejection episodes). More frequent visits and bloodwork for patients at high risk may improve adherence [67]. Adherence ‘contracts’ have also demonstrated some efficacy in adult kidney transplant recipients [92].

SUMMARY

Adherence to immunosuppressive medications is essential to long term graft survival. However, long-term medication self-management and maximizing adherence is complex and difficult due to multiple and often interrelated factors. Categorizing these factors as patient (e.g., multiple medications, changes in routine), micro (e.g., poor family functioning), meso (e.g., changes in providers,) and macro (e.g., insurance coverage) factors provides a useful heuristic for guiding adherence assessment and intervention with patients. Optimizing graft survival and adherence in young people requires integrated and comprehensive care programs that include assessment, monitoring and intervention that directly considers factors on all of these levels (i.e., patient-, micro-, meso- and macro-). A number of empirically based intervention strategies focused on optimizing adherence are emerging in the literature. It will be essential that the dissemination of these tools occur as rapidly as possible to optimize the outcomes for young adults receiving transplants now and in the future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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