Optimizing Medication Adherence: An Ongoing Opportunity To Improve Outcomes After Kidney Transplantation

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Nonadherence of transplant recipients to prescribed medical regimens has been identified as a major cause of allograft failure. Although recent studies offer new insight into the clinical phenotypes of nonadherence, advances in defining risk factors and appropriate interventions have been limited because of variable definitions, inadequate clinical metrics, and the challenges associated with healthcare delivery. Significant nonadherence is estimated to occur in 22% of renal allograft recipients and may be a component of allograft loss in approximately 36% of patients. It is associated with increased incidence of rejection (acute and chronic) and, consequently, shortened renal allograft survival, requiring reinstitution of costly chronic renal replacement therapy with an incumbent effect on morbidity and mortality. The economic effect of nonadherence approaches similar magnitude. Identification of risk factors, coupled with measures that effectively address them, can have a positive effect at many levels—medically, socially, and economically. Further advances are likely to be dependent on improving interactions between patients and caregivers, broadening immunosuppressant availability, and newer therapeutics that move toward simpler regimens.

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"I will prescribe dietetic measures for the benefit of the sick according to my ability and judgment" (1). So stated Hippocrates in 400 BC when most treatments prescribed seem unlikely to have resulted in significant healing regardless of whether they were implemented. With the unprecedented efficacy of modern medicine, a new challenge has arisen: the benefits of prescribed therapy cannot be realized unless that therapy is actually applied. Medical adherence, a reflection of the degree to which a patient follows directions regarding treatments, medications, and clinical surveillance as prescribed by their caregiver, is now a significant predictor of outcome, particularly among those for whom chronic therapies are required. Nonadherence results in disease progression, increased health care costs, and even premature death (2–7). In the United States alone, the cost of these undesirable outcomes is estimated to be in excess of $100 billion per year (2,4,8,9). Pinsky *et al.* identified a $12,840 increase in individual 3-year medical costs for patients with persistently low compliance (10).

Among transplant recipients, nonadherence is a major risk factor for rejection and allograft loss (7,10,11). A recent report from a "consensus conference" on nonadherence to immunosuppressive agents soberly concluded that nonadherence is more prevalent than previously assumed, is difficult to measure accurately, confers worse outcomes, occurs for a variety of reasons, and is hard to change from a behavioral perspective (12). Nonetheless, Cleemput and colleagues, when comparing hemodialysis to renal transplantation, concluded the latter to be cost-effective, even if patients were nonadherent posttransplantation (13). They also found that renal transplantation offers improved quality of life and increased survival, although lifetime costs for an adherent renal transplant recipient are potentially higher than lifetime dialysis costs, as these patients live longer. Although nonadherence is a complex and challenging problem, understanding its basis, with appropriate remedies, has the potential to dramatically improve transplant outcomes.

Effect of Nonadherence

Adherence rates have been quantified in several ways: as a percentage of prescribed doses taken, timing accuracy, or the number of drug holidays in a given period of time. Adherence rates, higher in acute illness, fall dramatically after 6 months (14–16). In clinical trials, nonadherence rates as high as 43 to 78% have been reported (14,17). Accurately quantifying nonadherence in transplant recipients can be difficult because of inconsistent methodology. Many studies are based on patient self-reporting with highly variable response rates likely to underestimate nonadherence (18,19). Approximately 20% of American kidney recipients demonstrate significant nonadherent behavior posttransplantation, with surprisingly similar rates of nonadherence documented in recipients of essential cardiac, lung, and hepatic allografts (20–22).

Prospective studies of nonadherence linked to clinical outcome are few. Nevins *et al*. prospectively monitored medication adherence in 180 newly transplanted patients using electronic Medication Event Monitoring System technology (MEMS bottle cap) for 4 years, with a subsequent 4.7-year follow-up to determine the relationship between nonadherence and clinical outcome (23). Patients were subdivided into tertiles based on ad-

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herence patterns to daily azathioprine dosing established in the first 6 months posttransplantation: Tertile A missed <1.5% of doses, tertile B missed >1.5 to <5% of doses, and tertile C was nonadherent with ≥5% of doses. Nonadherence appeared early with ≥50% patients missing ≥1 day between day 0 and day 90. Adherence in all groups declined over time, but maintained rank order. Clinically, tertile C fared worst with earlier and more frequent rejections ($P = 0.025$), longer interdose intervals ($P = 0.005$), and more drug holidays ($P < 0.001$). Authors identified a subgroup ($n = 23$) that skipped medication ≥2 days in the second posttransplant month. The late acute rejection rates ($P < 0.001$) and graft loss before death rates ($P < 0.001$) were higher in this group compared with those in the other patients studied. The authors concluded that even minor medication adherence infractions have significant predictive value for worse clinical outcomes in transplant recipients. Chisholm *et al.*, analyzing data from the United States Renal Data System, found greater adherence to be more significantly associated with long-term robust clinical outcomes in pediatric renal transplant recipients than in adult recipients (24). Denhaerynck and colleagues measured nonadherence in adult renal transplant recipients by a number of different methods in patients whose immunosuppression included mycophenolate mofetil, sirolimus, or tacrolimus (25). Interestingly, no association was found between nonadherence and allograft function and survival, leading these authors to postulate that newer immunosuppressants might allow less stringent adherence margins than older agents (azathioprine or cyclosporine).

There may also be a phenotype in which nonadherence is linked to chronic allograft nephropathy. At our institution, we retrospectively examined 83 patients of renal allograft loss attributed to chronic rejection in a cohort of 1005 renal allograft recipients with functioning grafts 6 months posttransplant (26). Of the 83 patients with chronic rejection, 48 were noncompliant. Conversely, among patients deemed compliant, graft loss attributable to chronic rejection was infrequent. Vlaminck *et al.* also monitored adherence in 146 adult kidney recipients. Twenty-one percent experienced a late acute rejection compared with 8% in the adherent group at 5 years ($P < 0.05$) (27). Nonadherent patients demonstrated progressive worsening of renal function over time, even in the absence of acute rejection ($P < 0.001$). They were also more likely to demonstrate markers of antibody activation at biopsy than adherent patients with renal dysfunction, and the histology in nonadherent patients revealed substantially more interstitial fibrosis and tubular atrophy (28). Antibody-mediated rejection is common among nonadherent patients, and with donor-specific antibody a marker for poor outcome, it seems likely that antibody development might link chronic nonadherence with late allograft failure (29,30).

Measuring Nonadherence

The gold standard for measuring adherence remains electronic medication monitoring with a microdevice that records each time a pill bottle is opened (31,32). Limitations include lack of certainty that the medication or correct dose was ingested and lack of availability in clinical practice (33). Nonetheless, studies based on electronic monitoring provide the most reliable insight into patient behavior. Patient self-reporting of nonadherence has inherent limitations; patients may not be willing to disclose shortcomings even in nonthreatening circumstances (34). Pill counts are likewise considered unreliable. Prescription refill rates correlate with adherence, but may be difficult to monitor in clinical practice, and reveal nothing about timing of ingestion. Clinical response may also be an indication of adherence, although other factors can affect this parameter.

A potentially useful adjunct to otherwise subjective metrics is drug level monitoring as a surrogate for compliance. Indeed, monitoring drug/metabolite levels in blood or urine would appear to provide direct evidence of adherence, but is subject to significant variability (31). It may potentially be confounded by white-coat compliance, a known phenomenon whereby adherence increases 5 days before a medical visit, and wanes thereafter, contributing to the unreliability of drug levels or pill counting as a measure of compliance (17). Utilizing objective parameters of adherence, one study reported that 75% of nonadherent patients were found to have low calcineurin inhibitor levels compared with 24% of adherent patients with subtherapeutic drug levels (35). Kahan *et al.* addressed the consequence of variability in cyclosporine levels over a 5-year period in adult renal transplant recipients (36). The incidence of chronic rejection was 24% in the less variable cohort *versus* 40% among the variable cohort. Additionally, medical costs were significantly greater in the variable cohort.

Others have documented a combination of methods to detect nonadherence to have a more accurate yield. Simons *et al.* proposed combining subjective patient reporting and objective drug data to determine rates of adherence (37). In another study, Butler and coworkers tested the reliability of patient reporting and physician identification of nonadherence to electronic monitoring, finding both to be severely flawed (34). In a cohort of 249 kidney transplant recipients with prospective electronic monitoring that documented 17% of patients as nonadherent with medications, Schafer-Keller and coworkers found self-reporting to underestimate and variation in immunosuppressant blood levels to overestimate nonadherence. These investigators proposed combining measures to increase diagnostic accuracy (31).

Understanding Nonadherence Behaviors

Understanding patient behaviors, perceptions, experiences, and responses to immunosuppressive-related treatment posttransplantation should provide insight and opportunity to develop mechanisms to affect nonadherence.

Urquhart describes six patterns of medication compliance (as documented by electronic monitoring) (38). One sixth take nearly all doses; one sixth take nearly all doses with some timing infractions; one sixth miss an occasional single-day's dose, with some timing irregularity; one sixth take drug holidays 3 to 4 times a year; one sixth have monthly or more frequent drug holidays with frequent dose omissions; and the final sixth take few or no doses. Greenstein and colleague

identified three groups of noncompliers—accidental noncompliers (47%), invulnerable noncompliers who had a belief of invincibility (28%), and decisive noncompliers (25%), each of which has different origins and will require different interventions (18). Other common reasons cited for nonadherence were oversleeping, work-related barriers and forgetfulness, forgetting to refill medications, changes in prescription, busyness, and traveling without medication (39).

It is well documented that increasing frequency of drug doses increases nonadherence (40). Richter *et al.* found that reduced dosing frequency resulted in overall improvements in adherence, patient satisfaction, quality of life, resource use, and costs (41). Adverse side effects from immunosuppressive agents also contribute to nonadherence (33). Patients sometimes avoid corticosteroids because of the effect on appearance with the female gender consistently related to higher levels of symptom occurrence and distress (42). However, Drent *et al.* prospectively assessed compliance with prednisolone in liver transplant recipients using electronic monitoring and found an overall high level of compliance (43). Glander *et al.* found that correct recall of number of medications was associated with better renal function in renal transplant recipients (44). These patients had greater variability in calcineurin inhibitor levels. Incorrect recall increased with increasing number of medications and was found to be a more important determinant of clinical outcome than self-reported compliance.

Access to immunosuppressive agents is also a prerequisite to adherence, with the convoluted reimbursement system in the United States (with loss of drug coverage after 3 years for patients reliant on Medicare ESRD benefits) posing a major impediment for many. However, Nevins and colleagues found nonadherent behavior evident within weeks of transplantation, when access to medications is not an issue, and indeed adherence patterns that are persistent begin early in the posttransplant period (45). Nonetheless, there are patients for whom nonadherence is solely the result of financial distress. Woodward and colleagues documented a direct relationship between loss of insurance coverage and allograft failure: analysis of renal transplantation outcomes according to zip code demonstrated a significantly greater risk of late allograft loss in lower income areas (46). Patients without private health insurance, more often African American, are also at increased risk for allograft loss (47). At our institution, noncompliance and late allograft loss are closely linked, especially among African Americans (48). In the military, with identical access to healthcare, racial differences in allograft survival contradict this finding. Butkus *et al.* also found that nonadherence was a significant predictor of allograft loss in renal transplant recipients and was more common among African Americans than Caucasians (47). Racial differences disappeared when data analysis was corrected for socio-economic status, which may be regarded as a surrogate for a number of variables including education, financial status, health care coverage, availability of reliable transportation, and self-efficacy, suggesting that the answer may lie in the sustained capacity of the patient to adhere to complex medical regimens rather than factors intrinsically related to race.

Age predicts adherence patterns. Greenstein and colleague found that age is positively associated with compliance—likelihood increased 1.6-fold per year (18). Other studies had previously shown that increasing age was associated with better compliance (10,49), although the greatest absolute and relative benefits of kidney transplantation accrue to younger patients. Pinsky *et al.* found that adolescent recipients aged 19 to 24 years were more likely to have persistent noncompliance compared with patients aged 25 to 44 years (10). Chisholm-Burns *et al.* found, in contradiction to previous literature, that pediatric renal transplant recipients were more nonadherent than adolescent renal transplant recipients (24). A delay in transplantation in the pediatric population may carry untoward effects. Adolescents seem to be at greatest risk (20,50). In a meta-analysis of pediatric allograft recipients, Dew *et al.* found that older aged children, greater family dysfunction, and poor psychologic status are significantly correlated with nonadherence (51). Adolescent immaturity may lead to conflict and nonadherence, as a misguided assertion of independence. Finally, in the United States, insurance coverage for immunosuppressive medications changes as the child transitions to adulthood, and with it adds a requirement for navigating the vagaries of adult health care. The effect of each of these factors on medication adherence is substantial.

Older patients may have lower verbal memory skills and cognitive impairment that may affect compliance. Stoehr *et al.* found better verbal memory to be independently associated with the use of medication schedules and that better executive functioning was strongly associated with adherence to prescription instructions in elderly patients (52). Older patients also place more trust in their physician and pharmacist (rather than other sources) to provide information regarding medication (53). In elderly patients, regimen complexity and type of caregiver assistance are independent correlates of medication nonadherence (54).

Vasquez *et al.* identified a number of factors that affect medical nonadherence in renal transplant patients (19). Ten percent of those surveyed had received living donor kidneys, and neither donor source nor employment status was associated with nonadherence. Lack of knowledge regarding immunosuppression and number of medications were the only two factors associated with noncompliance ($P < 0.05$). Patient's perception of their risk of rejection did not affect compliance. Education, employment, and country of origin (United States *versus* non-United States) were also significantly associated with compliance. Patients with diabetes mellitus were 50% more likely to be compliant than patients without diabetes. Predictors of nonadherence included greater period of time since transplantation and having a living donor allograft, which may reflect a belief that histocompatibility confers less need for immunosuppression. Lower self-efficacy has also been found to be associated with nonadherence (32).

Identification of important variables in adherence is complicated by inconsistency with the technique used to define nonadherence and the population studied, and also the behavior itself. Indeed, some studies have yielded conflicting results, with higher educational levels and job status as both positive

and negative influences on adherence. Nonetheless, several important variables recur as significant in multiple studies and may be highly relevant in the clinical arena (Tables 1 and 2).

Dealing Effectively with Nonadherence

As a threat to optimal outcomes after kidney transplantation, nonadherence is worthy of attention and intervention. Successful intervention to improve adherence must be multidimensional. One approach is to use identified risk factors to avoid transplantation in high-risk candidates. Pretransplantation, there is a relative absence of evidence-based guidelines for screening adherence. Medical criteria for transplantation are well established, and a psychosocial assessment is recommended without any definite guidelines. Dobbels *et al.* addressed this issue in a prospective analysis describing heart, lung, and liver recipients in the first posttransplant year, where they defined pretransplant psychosocial and behavioral predictors of transplant outcomes (late acute rejection/allograft loss) (55). Patients were evaluated according to a number of pretransplant characteristics, controlling for comorbid factors. Forty percent reported adherence issues posttransplantation. Independent predictors of medication nonadherence were pretransplant nonadherence ($P = 0.0009$, with an eightfold higher risk), higher education (to 12th grade) ($P = 0.021$), lower social support ($P = 0.026$), and lower conscientiousness ($P = 0.014$). Being single was the only significant predictor of allograft loss 6 to 12 months posttransplantation ($P = 0.037$). Pretransplant medication nonadherence was also a predictor of late acute rejection.

As nonadherence to dialysis regimens may predict similar behavior posttransplantation, it is not unreasonable to delay transplantation until a patient demonstrates adherence to his or her dialysis regimen. However, the limitations of such an approach are demonstrated by the incidence of recidivist substance abuse posttransplantation and the number of nonadherent dialysis patients who do well posttransplantation (56). As noted, other risk factors, such as youth, do not lend themselves to use as a selection criterion. Likewise, the adverse effect on outcomes of increasing time on dialysis stands in stark contrast to the old saw that delaying transplantation improves adherence (57).

Dunn *et al.* reviewed nonadherence in re-transplant patients, comparing those with a history of renal allograft loss due to nonadherence with patients who underwent re-transplant because of allograft loss due to other reasons (58). Authors concluded that prior allograft loss to nonadherence is associated with increased risk of graft loss after re-transplant, although the majority of the nonadherent group did well and recommended consideration of patients with a history of nonadherence for re-transplantation, in addition to aggressive intervention to prevent repeat nonadherent behavior.

Education regarding the importance of immunosuppressive

Table 1. WHO classification of risk factors for nonadherence (64)

Socio-economic factors	Age, gender, nationality, live alone/with others, employment status, perceived adequacy of one's financial situation, level of education
Patient-/disease-related factors	Health beliefs/behaviors, vaccination status, smoking history, alcohol use, depression
Treatment-related factors	Patient symptoms, side effects of medications
Health care system/health care worker factors	Lack of health insurance or health benefits

Table 2. Risk factors associated with adherence and nonadherence with immunosuppression

Adherence	Nonadherence
Older patient (>40 yr); female gender; Caucasian; good social support	Younger patient (<25 yr); male gender; non-Caucasian; non-United States resident; poor social support
Good insight into illness; positive perception of treatment benefits; education regarding illness/treatment; absence of psychological or psychiatric illness	Poor illness insight; poorly perceived treatment benefits; lack of education about illness and treatment; presence of psychological or psychiatric illness
Good provider-patient rapport; simpler medication regimens; lower medication toxicity/side effects; lower symptom distress	Poor provider-patient rapport; complex medical regimens; higher medication toxicity/side effects; high symptom distress
Health care coverage; access to health care; available transportation	Lack of health care coverage; impediments to cost of medication, including unemployment/copayments; greater geographic distance to travel; poor transportation access
Diabetes mellitus; shorter time since transplantation	Patient without diabetes; increased period of time since transplantation

agents in ensuring optimal outcomes must be an ongoing effort. Gordon *et al.* emphasize the importance of a medication schedule and use of cues, pillboxes, and reminders from others (39). Pinsky *et al.*, finding that less than perfect compliance predicts allograft loss and increased costs, emphasize the need to maximize compliance rather than discourage low compliance (10). Many transplant centers use repetitive teaching to promote adherence. Open-ended questions regarding compliance may elicit honest replies and lead to appropriate solutions. Currently available options in immunosuppression allow some flexibility for the patient experiencing intolerable adverse effects. Dosing regimens can be simplified to improve adherence. A new once daily preparation of tacrolimus has been shown to provide equal efficacy to Prograf in kidney and liver recipients (59,60). Clinical investigation of biologics as maintenance agents is now underway. If proven effective, these agents may offer the potential for significant improvement in adherence (61,62). Availability of social workers to help access benefits including use of indigent drug programs all can enhance adherence. De Bleser *et al.*, in a recent systematic review of 12 intervention studies in solid organ transplant recipients, found that only 5 used randomized control designs (63). Five found a statistically significant improvement on one medication-adherence outcome with intervention. Eight studies had intervened at the level of the health care provider, health care setting, or system level with limited improvement in adherence. No single intervention was found to be superior, although authors suggest that a combination of interventions via team approach may be the most helpful long-term strategy.

Conclusions

Given its potentially devastating consequences, adherence deserves attention. It is irrelevant which immunosuppressive medications are prescribed if the patient simply does not, or cannot, take them. The reasons for nonadherence are complex and sometimes of a nature that makes assessment and intervention difficult. The result of these interventions should be improved allograft and patient survival.

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