REVIEW ARTICLE

Drugs 2007; 67 (10): 1463-1481
0012-6667/07/0010-1463/$49.95/0

Medication Noncompliance and its Implications in Transplant Recipients

Paul E. Morrissey,[1] *Michelle L. Flynn*[2] and *Sonia Lin*[2]

1 Brown Medical School, Rhode Island Hospital, Providence, Rhode Island, USA
2 University of Rhode Island, Kingston, Rhode Island, USA

Contents

Abstract

The transplant patient's therapeutic regimen consists of a lifelong drug therapy, including immunosuppressive drugs, prophylactic antimicrobials and often medications for the treatment of hypertension, diabetes mellitus and other comorbid diseases. Regular clinic appointments are required to monitor for signs and symptoms of immunological injury, recurrent disease and adverse drug effects. Patients are instructed to avoid risk factors for cardiovascular disease and cancer (e.g. diet, exercise, sun protection and not smoking). Noncompliance with all aspects of this regimen is substantial. Medication noncompliance leads to an increased incidence of acute rejection, chronic rejection and graft loss. Undoubtedly, many practitioners fail to appreciate the extent of noncompliance as the signs are often subtle and most patients are unwilling to disclose deliberate or widespread disregard for medication use. Newer immunosuppressive agents,

particularly once-daily medications and long-acting antibody preparations offer convenience and monitoring that may improve compliance. This review focuses on the prevalence, correlates and consequences of medication nonadherence after organ transplantation. Current recommendations to enhance adherence are discussed.

Organ transplantation is currently accomplished with a high rate of success. The vast majority of solid organ transplant recipients survive the first year with a functioning allograft. Kidney allograft survival exceeds 90% at most centres and 1-year acute rejection rates under 10% are routine at our centre and many others. This improved success rate is largely attributable to the use of newer immunosuppressive drugs.

Following solid organ transplantation, immunosuppressive medications must be taken indefinitely to prevent graft loss caused by acute and chronic rejection. Unfortunately, these medications are associated with numerous complications and adverse effects.[1,2] In addition to the potentially devastating effects of long-term immunosuppressive therapy (heightened risk of infection and certain cancers), these medications have other adverse effects that include pain, nausea, diarrhoea and altered cosmesis (table I). The majority of these 'nuisance' effects are managed with additional medications. Continued expert monitoring and oversight is required to achieve an appropriate threshold between efficacy and toxicity. This further increases the complexity of the medical regimen, making adherence difficult. Moreover, against this background of success, medication nonadherence is increasingly recognised as a cause of allograft dysfunction and failure.

This article reviews aspects of noncompliance after solid organ transplantation. The vast majority of the noncompliance literature in transplantation is based on research and experience with kidney transplant recipients. However, the lessons are widely applicable in solid organ transplantation. Our primary emphasis is on medication noncompliance (as defined in section 1). Research in this area and broad suggestions for improving patient compliance are discussed.

Table I. Maintenance immunosuppression and common adverse effects of specific agents

Corticosteroids (prednisone, solumedrol)
Hypertension
Sodium and fluid retention
Psychosis, emotional instability
Delayed growth, amenorrhoea
Osteopenia, avascular necrosis
Muscle weakness (myopathy)
Glaucoma, cataracts
Centripetal obesity (Cushingoid appearance)
Metabolic: glucose intolerance, hyperlipidaemia
Cosmetic: oedema, Cushingoid features, petechiae and ecchymoses, increased sweating
Azathioprine
Bone marrow suppression
Mycophenolate mofetil
Bone marrow suppression: leukopenia (common), anaemia, thrombocytopenia
Gastrointestinal disturbances: gastritis, diarrhoea
Ciclosporin
Nephrotoxicity (acute and chronic renal dysfunction)
Hypertension
Neurotoxicity (tremor, paraesthesias, headache)
Post-transplant diabetes mellitus
Metabolic: hyperuricaemia, hyperkalaemia, hyperlipidaemia
Cosmetic: excess hair growth, gum hyperplasia
Tacrolimus
Nephrotoxicity (acute and chronic renal dysfunction)
Hypertension
Neurotoxicity
Post-transplant diabetes mellitus
Metabolic: hyperkalaemia, hypomagnesaemia
Sirolimus
Bone marrow suppression: thrombocytopenia, leukopenia, anaemia
Delayed wound healing, lymphocele formation
Arthralgia, bone pain
Pneumonitis
Metabolic: hyperlipidemia
Cosmetic: acne, aphthous mouth ulcers

1. Definition of Noncompliance/ Nonadherence

Noncompliance is the failure or refusal to conform and adapt one's actions to a rule, to necessity or to another's wishes. It follows that medication noncompliance is the failure to follow the medication regimen prescribed by the physician.

Successful organ transplantation requires compliance with a complex medical regimen, which includes immunosuppressive drugs, prophylactic anti-infective medications, anti-ulcer medications and others, as well as laboratory and medical follow-up. Many patients with end-organ disease requiring transplantation also have systemic diseases that require ongoing drug therapy and monitoring. The details of these complex regimens should be discussed prior to transplantation with potential recipients and their families. There is an implicit contract for compliance when the patient agrees to listing for organ transplantation. This understanding differentiates adherence from compliance;[3] adherence requires the patient to understand and agree to the physician's recommendations. Prior to solid organ transplantation, patients should be informed of the likely regimen after transplantation, understand the potential risks and benefits of immunosuppressive medications, recognise the ongoing need for other maintenance medications and agree to follow the prescribed regimen (adherence). Transplant recipients should be aware of the lifelong need for immunosuppression and in agreeing to transplant listing also agree to medication adherence. Therefore, in transplantation, the terms 'compliance' and 'adherence' can be applied interchangeably.

In the field of medicine, the term 'noncompliance' is used particularly in regard to a patient not taking a prescribed medication or following a prescribed course of therapy. Overt noncompliance is the willful and explicit refusal to comply with an established or recommended regimen. This should rarely be encountered in transplantation, having addressed such attitudes in the pretransplant evaluation. However, covert noncompliance as a result of forgetfulness, a fundamental denial of clinical reality, irrational fears of adverse effects or the medical environment, adverse reaction to authority, feeling of powerlessness, anger at caregivers or others, belief in unsubstantiated alternative therapies, depression, mania, psychosis, arrogance or countless other reasons remains problematic.

Two related terms, 'persistence' and 'concordance', are less frequently applied to medical compliance. 'Persistence' refers specifically to the concept of continuous therapy: the patient filling the initial prescription, refilling the prescription on schedule and taking the medication until it is discontinued. Some authors consider adherence to have two components: (i) compliance (taking the medication as directed); and (ii) persistence (staying on the medication).[4] The term 'concordance' was proposed by the Royal Pharmaceutical Society of Great Britain in 1997 to emphasise the shared decision-making between provider and patient.[5] While compliance describes the degree to which the patient follows the prescribed regimen of medicines, concordance describes an agreement between a patient and a healthcare professional about whether, when and how medicines are to be taken. Concordance produces an agreement that respects the beliefs and wishes of the patient, rather than the authoritarian instructions of the doctor.

'Adherence' is particularly suited to the agreement or contract that begins with the pretransplant evaluation and is inherent in the process of listing for deceased donor transplantation. In specifying that the patient's behaviour correspond with agreed recommendations from a healthcare provider, adherence recognises the shared role between provider and patient in decision making. Additionally, the term 'nonadherence' will refer to inconsistent or wrongful use of medications. The behaviour of a patient persistently missing medication doses is termed 'nonadherent'. This review is primarily concerned with covert nonadherence with medications prescribed for the prophylaxis of allograft rejection. Noncompliance in transplantation is any behaviour including nonadherence to medication used for the prophylaxis of allograft rejection that threatens allograft histology of function.

2. Scope of the Problem

Six months after being given prescriptions for drugs to lower blood pressure and cholesterol, only one patient of three was still taking the two medications. This was demonstrated in a retrospective cohort study that examined 8406 enrollees in a US managed care plan who initiated treatment within a 90-day period.[6] Patients were considered adherent if they had filled prescriptions sufficient to cover at least 80% of days with both lipid lowering and blood pressure medications. The percentage of patients who were adherent with both therapies was just 45%, 36% and 36% of patients at 3, 6 and 12 months, respectively. Patients were more likely to be adherent if they had a history of symptomatic heart disease or took fewer other medications.

The benefits of treating hypertension and normalising blood lipids are well established in the medical community, but are manifest over the long term. Therefore, the consequences of noncompliance are rarely immediate or of serious consequence. Many medications are taken to relieve symptoms, and the benefits are quantifiable and apparent to the patient. Transplant immunosuppressive medications, on the other hand, are taken for the prophylaxis of rejection. The therapeutic benefit derives from avoidance of an adverse event (acute rejection), rather than improvement of a physical derangement. However, stopping or markedly underdosing immunosuppression, even once for an extended period of time, may precipitate acute or chronic rejection leading to permanent allograft damage or loss. Unfortunately, once this process begins, even if compliance is perfect thereafter, the process is not likely to be reversible (figure 1 and figure 2).

What constitutes nonadherence varies from one study to another with a range of definitions from a single delinquent or missed dose of medication to arbitrary numbers of missed doses or a pattern of erratic drug taking including delinquent and absent intervals. Some investigators have defined nonadherence as missing, forgetting, altering or delaying a dose at least once per month.[7-10] Others have used a definition of missing at least 10% of doses (6 doses/month).[11,12] Still others have used missing at least 20% of doses (12 doses/month).[13] The absence of a uniform standard complicates research in this area.

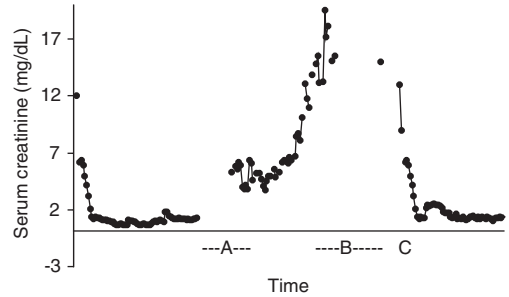

Fig. 1. Plot of renal function (serum creatinine) over time. This patient, an 11-year-old boy, underwent a pre-emptive living-related renal transplant (time zero). His father was the donor. The kidney functioned immediately and he enjoyed normal renal function for 3 years. At age 15 years, he was lost to follow-up for a period of 4 months (A). He missed scheduled clinic appointments and laboratory testing. He failed to respond to telephone reminders and was not seen until he presented with a serum creatinine of 4.9 mg/dL. A biopsy showed acute rejection with moderate vasculitis (Banff classification IIa). He admitted to nonadherence, which he attributed to carelessness. He received pulse corticosteroids followed by muromonab CD3 (OKT3) with modest improvement in his renal function and after 21 months he returned to haemodialysis. After 3 months, he was re-listed for transplantation, but considered unavailable pending psychological evaluation, counselling by social work and a 6-month period (B) of documented compliance with dialysis sessions, medications (monitored by prescription refills) and clinic appointments. He received a second kidney transplant from a deceased donor (C) and continues to do well 2 years later.

3. Extent of the Problem in Renal Transplantation

It would seem intuitive that after the gift of organ donation, whether from a living or cadaveric donor, transplant recipients would comply with the transplant team's prescriptions for successful long-term outcome. While most patients do experience a good long-term result, nonadherence is surprisingly common and not infrequently contributes to allograft loss. Estimates of medication noncompliance varies widely in the literature based upon several factors, including medication-specific factors (number of medications, dosage), patient-specific factors (age, education) disease-specific factors (acute vs chronic disease) and the authors' operational definition of compliance.[14] Despite methodological problems inherent in defining and measuring medication compliance, studies indicate that 15% to 30% of trans-

plant recipients exhibit nonadherence[7-17] and that this percentage is likely to be considerably higher in some groups.[18-20] A summary of these studies is given in table II.

Butler et al.[22] reviewed and organised the literature on medication noncompliance after renal transplantation. Their systematic literature search identified 325 studies published from 1980 to 2001 reporting the frequency and impact of nonadherence in adult renal transplant recipients. Thirty-six studies meeting predefined inclusion criteria (>5 patient samples and paediatric recipients comprised <10% of sample) were analysed by meta-analysis to estimate the impact of nonadherence on graft failure. Cross-sectional studies (n = 15) described the prevalence of nonadherence in a clinic population with functioning transplants. They tended to rely on self-report questionnaires, which were usually poorly described. A median of 22% (range 18–26%) of recipients were nonadherent. Cohort studies (n = 10), which included patients from a defined time period, indicated that nonadherence contributed substantially to graft loss. A median of 36% (range 14–65%) of graft losses were associated with prior nonadherence. In case studies (n = 12) of patients with failed transplants, a median of 15% of graft failures were ultimately attributed to nonadherence.

Naturally, there are varying degrees and patterns of nonadherence. These may include delaying a twice-daily dose by a few hours, occasionally skipping a dose, or stopping a drug altogether for days or weeks at a time. Because of the variety of nonadherent behaviours, compliance is best considered as a continuous variable, not a discrete entity. Chapman[23] classified compliance after transplantation relative to timing (early or late), frequency (occasional, intermittent, persistent or complete), psychology (aetiology) and diagnostic certainty.

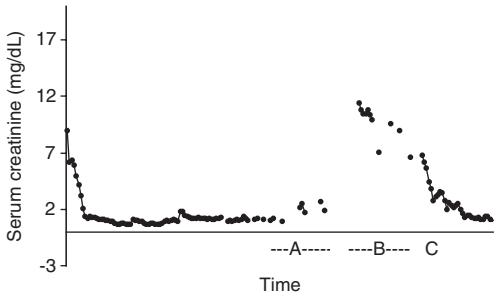

Fig. 2. Plot of renal function (serum creatinine) over time. This patient, a 32-year-old female, underwent a living-related renal transplant (time zero). Her brother was the donor. She enjoyed normal renal function for 5 years. She became increasingly busy at work and complacent with follow-up. Laboratory studies were obtained with decreasing frequency (A). After several months without laboratory studies, she presented with a serum creatinine of 11 mg/dL. A biopsy showed acute rejection (Banff classification Ib) along with extensive interstitial fibrosis and tubular atrophy. She admitted to occasional nonadherence, which she attributed to forgetfulness. She received pulse corticosteroids with no effect and returned to haemodialysis. After 2 months, she appeared at the clinic with her sister who wished to serve as a living donor. At this time, the recipient admitted significant noncompliance leading to the prior acute rejection. She had a history of depression treated with escitalopram. She agreed to undergo psychological evaluation, including a 6-month period of bimonthly counselling sessions (B). Compliance was documented by attendance at these sessions, dialysis and clinic appointments. The sister was informed that the previous allograft loss was related to noncompliance. She agreed to proceed with kidney donation. The recipient received the second kidney transplant (C) and continues to do well 1 year later.

4. Clinical Implications of Noncompliance in Renal Transplantation

Nonadherence with immunosuppressive medications can lead to acute rejection and graft loss.[10,11,24] With the present availability of more potent and specific immunosuppression, acute postoperative rejection is uncommon and medication noncompliance has emerged as an increasingly important factor in the ongoing clinical management of organ transplant recipients; noncompliance has been clearly demonstrated to play a role in acute rejection, chronic rejection, and graft loss.[24] The odds of graft failure increase 7-fold (95% CI 4, 12) in nonadherent compared with nonadherent individuals, confirming the association between medication noncompliance and graft failure.[22] A retrospective analysis of patient behaviour suggestive of noncompliance (i.e. missed appointments, fluctuating drug concentrations) found that noncompliance accounted for over half of the renal allograft loss that had previously been attributed to ostensibly unavoidable chronic rejection.[10]

The impact of nonadherence may be sudden and dramatic as with acute rejection, or indolent even

Table II. A summary of incidence of nonadherence with immunosuppressive medication in kidney transplant recipients in selected studies

Study	Year	Nonadherence (% patients)	Comments
Beck et al.[21]	1980	43	Assessed by pill counts
Kiley et al.[15]	1993	26	105 patients assessed by questionnaires
Hilbrands et al.[12]	1995	23	113 patients assessed by pill counts
Siegal and Greenstein[8]	1997	18	Assessed by surveys (519 patients) and chart reviews (397 patients)
Greenstein and Siegal[7]	1998	22	Multicentre survey of 1547 recipients
Raiz et al.[9]	1999	26	Mail-in survey at a single centre (357 responders)
Chisholm et al.[13]	2000	52	Free medications provided from clinic to 18 study patients
Nevins et al.[11]	2001	18	Prospective study with electronic monitoring in 180 patients
Shaw et al.[17]	2003	32	112 paediatric patients assessed by drug levels
Vlaminck et al.[16]	2004	23	146 adult patients assessed by interviews

subtle. The link between subclinical noncompliance and decreased graft function was recently documented in a prospective study of late consequences of nonadherence with immunosuppressive therapy in renal transplant patients.[16] Patients were prospectively classified as noncompliant based on screening interviews. Over 5 years, 21% of nonadherent kidney transplant recipients had late acute rejection versus 8% of adherent patients. Serum creatinine levels were similar at baseline, but at 5 years there was a difference of almost 1 mg/dL between compliant and noncompliant groups ($p < 0.001$). The incidence of noncompliance in this study was comparable with findings in other transplant and nontransplant populations (table II).

The costs of nonadherence are enormous. In transplantation, nonadherence leads to acute rejection, the treatment of which requires hospital admission, diagnostic evaluation (biopsy) and expensive anti-rejection therapies. Furthermore, the required augmentation of immunosuppression necessitates additional courses of prophylactic anti-infective medications and predisposes recipients to infectious complications, post-transplant lymphomas and other conditions. Finally, immunological injury usually leads to reduced allograft survival, ultimately resulting the recipient's need for retransplantation, organ replacement therapies (if available) or death.

Given the obvious and serious nature of nonadherence to immunosuppressive medications, one wonders how such behaviour could be so prevalent. However, for some patients, transplantation amounts to trading one set of problems for another.[18] The problems may include ongoing symptoms, a complex and burdensome medication and follow-up schedule, adverse effects of drugs as well as financial pressures. These stressors may cause patients to deviate in a number of ways from the plan of care outlined by the transplant team. Complaints of medication regimens, adverse effects and cost are common. Weight gain, tremors, cosmetic perturbations, laboratory abnormalities and a host of other symptoms following transplantation are often attributed to medications. Patients who are not faring well after transplantation sometimes announce "I was better off on dialysis".

5. Extent of the Problem in Extrarenal Transplantation

Optimal outcome after heart, lung and heart-lung transplantation can only be obtained if patients are supported in adhering to a lifelong therapeutic regimen. Information on the prevalence and correlates of pretransplant medication nonadherence in extrarenal transplantation is limited. Most studies confirm features of nonadherence similar to renal transplantation including social and financial factors. Noncompliance with life-saving medical regimens both before and after transplantation is surprisingly high. One study explored self-reported pretransplant medication nonadherence before heart, liver or lung transplantation in 174 patients by survey.[25] The prevalence of pretransplant nonadherence was

16.7% and was comparable among the three groups. Multiple logistic regression revealed that higher educational level ($p = 0.008$), lower social support ($p = 0.013$) and lower conscientiousness ($p = 0.023$) were independent predictors of pretransplant medication nonadherence.

Even after a lifesaving transplant (heart, lung, liver) compliance is difficult for many patients. A cohort of 101 heart recipients underwent detailed interviews at 2, 7 and 12 months after transplantation.[26] Potential predictors of noncompliance were obtained from medical record reviews and from initial patient interviews. While the degree of noncompliance varied across timepoints, the following rates of persistent noncompliance were observed during a period of 1 year: exercise (37%), monitoring blood pressure (34%), medications (20%), smoking (19%), diet (18%), having blood work completed (15%), clinic attendance (9%) and heavy drinking (6%). Compliance in most areas worsened significantly over time. In contrast to a study of pretransplant adherence,[25] sociodemographic characteristics showed no significant influence on any area of compliance after transplantation.

Electronic monitors permitted De Geest et al.[27] to link medication noncompliance with later outcomes in cardiac transplant recipients. The investigators monitored ciclosporin compliance prospectively for 3 months in 101 patients. Medication compliance rates were high, with only nine patients classified as 'moderate subclinical non-compliers'. However, those patients with even modest decreases in compliance experienced more frequent acute rejections, and one noncompliant patient rejected and lost the cardiac transplant. Similar findings were reported after liver transplantation where nonadherence to medications is recognised as a cause of organ dysfunction especially in children and adolescents.[28] The authors developed an adherence-monitoring programme including standardised assessments by patients, parents, clinicians and standard measures of drug blood concentrations. Adherence was further assessed by electronic monitoring of medication use and azathioprine metabolite concentrations. Importantly, interventions improved compliance.[29]

6. Nonadherence Patterns

Three distinct kinds of nonadherence patterns have been described: accidental, invulnerable (immortal) and decisive.[7] 'Accidental' non-compliers forget to take their medications. They are disorganised to the extent that taking their medications is not a high priority. They need help with organisation and formation of habits that will improve daily adherence. 'Invulnerable (immortal)' non-compliers believe that missing medications will not hurt them. They hide their noncompliance and are guided by unrealistic beliefs. Their ill-conceived beliefs may be reinforced, at least initially, by the prophylactic nature of immunosuppressive medications, which lack an immediately perceivable benefit. Observing the lack of harmful effects from missed or reduced drug doses the patient assumes that they will not experience any adverse events such as allograft rejection. 'Decisive' nonadherence is brought about by an active and independent decision to ignore the need for medications. This decision is usually covert. These patients often have well considered rationales for their noncompliance. Recognition and treatment are difficult in patients who exhibit this pattern of nonadherence.

An anonymous survey of 1547 transplant recipients[7] revealed the following frequencies of noncompliance patterns: accidental non-compliers (47%), invulnerable non-compliers (28%) and decisive non-compliers (25%). Accidental non-compliers were, on average, older than other noncompliant patients and the group included the highest proportion of recipients with diabetes. Despite their nonadherence, accidental non-compliers expressed strong beliefs in the efficacy of immunosuppressant drugs. In contrast, a much smaller proportion of invulnerable non-compliers believed in the efficacy of immunosuppressant drugs. Fewer than 20% strongly agreed that they needed to use these drugs and just over one-third strongly agreed that they should never delay their medications. Invulnerable non-compliers were, on average, younger and less

educated (37.5% had at least some college education). Decisive non-compliers, although more educated, often had misconceptions about how immunosuppressive drugs worked. The distributions of sex were similar across clusters. Proportions of African Americans were similar across groups, whereas the largest proportion of Caucasian patients was found among accidental non-compliers; Hispanics were disproportionately represented in the invulnerable cluster.

Medication nonadherence may be a sign or result of a psychiatric problem such as depression, severe anxiety, oppositional-defiant disorder or post-traumatic stress disorder (PTSD). A recent study demonstrated a strong correlation between PTSD and nonadherence.[30] Pediatric liver transplant recipients with a high PTSD Reaction Index were significantly nonadherent compared with those patients who had a negative PTSD Reaction Index score. Importantly, the nonadherent patients became adherent when the symptoms of PTSD were treated. Similarly, a review of 112 paediatric renal transplant recipients reported medication nonadherence in 32.5% of individuals based on erratic immunosuppressant concentrations.[17] Nonadherence correlated with rejection and graft loss ($p < 0.001$). Nonadherence was also related to the presence of comorbid psychiatric illness ($p < 0.001$). Adolescents had significantly higher rates of nonadherence compared with younger patients ($p < 0.001$), suggesting that lack of parental supervision and parent-child conflict may be contributing to the dilemma.[17]

7. Special Concerns in Adolescents

Children make up 7% of patents receiving kidney transplants each year in the US; approximately 45% of those are adolescents (children aged 11–17 years). There is evidence that long-term graft survival rates for this group are far lower than for other groups. When compared with transplant recipients of all ages, adolescents enjoy the best 1-year graft survival. However, long-term transplant outcome in adolescents is disappointing. The 5-year unadjusted graft survival rate from deceased donor (not extended criteria donors) and living donors in the year 2004 for the age groups 1–5 years, 6–10 years and 11–17 years were 75% and 73%, 65% and 91%, and 87% and 79%, respectively.[31] The causes of poor long-term outcome in adolescents remain unclear; however, nonadherence is considered to play a major role.[20,32] Medication nonadherence was identified as the cause of graft failure in over 12% of adolescents, a rate that is more than four times greater than in adults.

Medication noncompliance is a leading cause of morbidity in paediatric transplant recipients; however, there is no uniformity and little certainty in detecting, predicting or improving medication noncompliance in this unique patient population. In a study of 21 paediatric renal transplant recipients, 43% were found to be noncompliant by pill count, interview and assessment of medical knowledge.[21] About half remained noncompliant after extensive counselling. Parental involvement and voluntary medication logs improved outcomes, but patient education did not, nor did it improve compliance with the most important medications.

The effect of nonadherence on long-term graft survival is especially significant in the African-American population.[19] One transplant centre based in Chicago reported the observation that of 44 paediatric kidney transplants, 12 were African-American, 14 were Caucasian and 18 were Hispanic. Thirty-one were cadaveric and 13 were living donor transplants. Compliance was evaluated based on trends in ciclosporin concentrations, attendance to clinic visits, individual interviews and unexplained late graft dysfunction. After 5 years, African-American recipients had a significantly higher rate of graft loss when compared with both Hispanic and Caucasian recipients (42 vs 95 vs 71%, respectively). Non-compliance was the main factor, accounting for 71% of cases of late graft loss.

Noncompliance arises from general psychosocial characteristics of this age group: preoccupation with body image (which is adversely affected by hirsutism, Cushingoid appearance, gum hyperplasia and weight gain), stress, resistance to authority, poor cognitive skills and inability to conceptualise future

consequences of present actions. Willful nonadherence stems from the intention to defy established limits. Other contributing factors in this age group include emotional problems, anxiety, hostility, avoidant behaviour, depression, poor coping skills, substance abuse, feeling of lack of control, negative interactions with healthcare providers, and a feeling of 'safety' (i.e. it won't happen to me) when acute rejection episodes did not occur early in the post-transplant course.[33] Medication nonadherence was associated with overall number of drugs prescribed, depression, feeling of lack of control, Black race, and lack of financial and social resources. A belief that health problems are beyond one's control was highly correlated with noncompliance.

Longitudinal studies further suggest that most adolescents who are consistently nonadherent could be identified at an earlier point of time.[33] An appreciation of the relevant psychological and social issues can identify adolescents at high risk for noncompliance.[20] Nonjudgmental questioning about current or previous behaviour best identifies noncompliance. Intervention techniques based on educational and psychological principles can be successfully applied by the physician to improve compliance and can improve the teenager's sense of mastery. Continuous multidisciplinary support, frequent follow-up and education are necessary to cope with this problem. However, it is unclear to what extent noncompliance in the adolescent can be prevented or improved. Modest improvements have been demonstrated after interventions in adolescents in general and particularly in adolescents with liver[29] and kidney transplants.[21] However, personal characteristics of the physician may determine whether he or she can work productively with the noncompliant adolescent.[34]

8. Role of the Transplant Team

Patients cannot be made entirely responsible for their compliance. After transplantation, the patient must assume a new and complex medical regimen. The number and frequency of medication doses is enormous. The medications are uniformly associated with unpleasant adverse effects. There is no physiologically perceived benefit to compliance with the regimen, only the knowledge that compliance reduces immunological risk. Transplant recipients require expert supervision to assist with scheduling medication doses, understanding the need for immunosuppressive drug therapy and the consequences of nonadherence and recognising adverse effects related to these medications. An assessment for nonadherence should be standard practice during all patient appointments. Indeed, the importance of doing so has been emphasised by appeals to assess compliance as the 'sixth vital sign'.[35]

Implementing effective methods to improve patient adherence to medication should take into consideration its multifactorial nature and incorporate an evaluation of patient-specific barriers and preferences. Maintenance of a positive relationship and good communication between the patient and their physician is imperative to facilitate identification of these variables.[18,34,36] Patients should be encouraged to participate in the design of their treatment regimen, as those who take an active role in their health management are more likely to be adherent to therapy.[18] Ancillary healthcare professionals should be utilised to improve medication adherence through patient education, facilitating patient access to medications, encouraging family support, facilitating mentorship programmes with previously transplanted patients and arranging follow-up.[37,38]

8.1 Pretransplant Assessment

There are some patients with end-stage renal disease who are not transplant candidates. These patients may be excluded because of extreme medical risk, uncontrolled psychiatric conditions or obvious noncompliance. An appropriate candidate must be medically fit for transplantation surgery, able to tolerate chronic immunosuppression and able to comply with all aspects of follow-up including laboratory studies, clinic appointments and medication adherence. The patient must have an appropriate support system to ensure transportation for follow-up, financial arrangements to purchase medications, psychological stability and comprehension of the

need for immunosuppression. Patients with severe psychiatric problems or limited comprehension (mentally challenged) should not be denied transplantation if adequate support systems are in place to meet the aforementioned requirements. Patients with a history of noncompliance, high-risk behaviour, drug or alcohol abuse should have appropriate counselling prior to transplantation. Ideally, a period of observed compliance with health clinic visits and medical regimens should be obtained.

The assessment of pretransplant behaviour should be made at the initial evaluation by an experienced multidisciplinary transplant team, using the records and observations of the referring caregivers as well as their own evaluations.[20] The observations from referring physicians, dialysis nurses, social workers and dietitians are all critical to the assessment of the appropriateness of the patient for transplantation. Since these assessments are subjective, considerable discussion, investigation and judgment are required prior to listing (table III). Some patients who are poorly compliant with haemodialysis, for example, become model transplant recipients. Nonetheless, it is important to address nonadherence when it is discovered. Additional teaching or counselling may be indicated prior to listing for transplantation.

8.2 Pretransplant Education

One of the most important factors in patient noncompliance is poor communication by healthcare providers.[34,35] Doctors pressed to care for too many patients in the time available may fail to adequately explain the reasons for their recommendations and drug prescriptions, the possible adverse effects and what to do about them, and the potential consequences of not following the prescribed regimen. Language and cultural barriers magnify the problem of understanding the regimen. Follow-up by members of the transplant team, be it the doctor, nurse or other healthcare professional is important to find out how the patient is faring and whether there are any problems with following the prescribed regimen. Regular medical contact, encouragement and advice are especially helpful when patients have to make major changes in the way they live. The relationship between the patient and the healthcare provider must be a partnership that draws on the abilities of each. An atmosphere in which alternative therapeutic means are explored characterises effective treatment relationships, the regimen is negotiated, adherence is discussed, and follow-up is planned.

Table III. Common factors that predispose to medication nonadherence in transplant recipients

Nonadherent behaviour prior to transplantation
Psychiatric illness: depression, anxiety
Personality disorders
Poor social support/oversight
Substance abuse and high-risk behaviour
Adolescence
Higher education level
Time since transplantation
Inadequate follow-up
Inadequate pre-transplant education
Multiple adverse effects from medications
Complex regimen: greater than twice-daily administration

Educational approaches are essential in preventing and managing nonadherence.[3] All transplant recipients must be informed about the life-long necessity of taking immunosuppressive medications. Patients should demonstrate a good understanding of the medications they are currently taking, and the dose and schedule they are expected to follow. The adverse effects of these medications should be discussed, as well as practical suggestions for ways to deal with or minimise those adverse effects. Without compromising optimal medical care, physicians should make an effort to choose medications that have fewer adverse effects. In addition, the simplest drug administration regimen should be chosen.

During regular visits, caregivers should encourage patients to express their concerns. Open-ended inquiries should be made about the patient's medication schedule, drug doses, understanding and ultimately adherence. The discussion should be nonjudgmental.[3,20] Specific concerns may be addressed by members of the transplant team with expertise, including: nurses or coordinators who foster education and adjust medications; social workers

skilled in financial assistance, pharmacy programmes and counselling; pharmacists with specialised knowledge in the area of immunosuppressive drug therapy and its optimal use; and if necessary psychiatrists to improve mental health and adherence. Enlisting the support of family members is generally, but not always, helpful. Patients can easily become victims of other people's biases that medications are harmful, addictive or unnecessary. Inadequate involvement and counselling by the transplant team may precipitate nonadherence as a result of the patient's lack of understanding or lack of confidence. The worst consequence of such a poor relationship is that the recipient loses his or her renal graft because of a lack of knowledge, not because of deliberate noncompliance.

8.3 Identifying the Nonadherent Transplant Recipient

Most cases of nonadherence after transplantation become known based on subjective techniques or unexplained alterations in drug concentrations, which trigger the transplant team's clinical suspicion. Late acute rejection episodes, marked fluctuations in immunosuppressive drug concentrations, or absences of medication adverse effects (e.g. the loss of Cushingoid features without prescribed reduction in corticosteroids) may indicate nonadherence and should prompt a discussion with the patient or family. Whole blood immunosuppressive drug concentration monitoring may be helpful when a given patient's trough drug concentration is either inexplicably low or high. A marked variation in recipients' trough blood concentrations was reported as a reliable sign of medication nonadherence.[28] These authors compared subjective measures of adherence to an objective measure of trough blood concentrations, calculated by examining the standard deviations of tacrolimus levels over time in paediatric liver transplant recipients. The standard deviation calculation for tacrolimus trough concentrations was highly correlated with adverse outcomes including acute rejection. The subjective measures used in this study bore no relationship to the clinical outcomes. This group then implemented a research programme consisting of an electronic monitoring device (MEMS-caps) and measurement of azathioprine metabolites as predictors for nonadherence. Again they confirmed that subjective clinical impressions from the medical team were unreliable in the assessment of medication nonadherence in paediatric transplant recipients.[29] Nonetheless, outside of research protocols, transplant centres are usually alerted to noncompliance via subjective measures and drug concentrations. Compliance with medical follow-up (laboratory tests and clinic visits) also serves as a surrogate for medication adherence (figure 2).

9. Methodologies Aimed at Measuring Medication Adherence

9.1 Pill Counts

Medication adherence can be measured via the use of pill counts, electronic monitoring devices, patient medication diaries, patient questionnaires, and any number of subjective techniques (table IV). Adherence is highest in research studies that used pill counts as a monitoring technique.[28] Pill counting is widely used in clinical drug trials; however, wide application of pill counting is labour intensive and not practical for the transplant clinic. This technique enlists the cooperation of the patient, which may be more easily achieved in those who are enrolled in clinical trials. Assessment of prescription refill rates is possible if the patient is using a pharmacy associated with the transplantation programme or mail-in services. Some health maintenance organisations become partners in medication adherence by monitoring prescription refills and

Table IV. Assessment of medication compliance (ranked by complexity of measurement)

Self-reporting by patient
Collateral reporting by friends or relatives
Patient diaries
Questionnaires
Laboratory tests (drug or metabolite levels)
Medical record review, clinical outcomes
Track prescription refills
Monitored pill counts
Electronic monitoring devices (detecting opening of pill bottle)

notifying healthcare providers when prolonged lapses in refills occur. Pharmaceutical companies have also adopted strategies designed to promote adherence and, in their self-interest, continued purchasing of medications. The industry provides these services through call centres augmenting the team's efforts at monitoring adherence.

9.2 Electronic Devices

Several research studies directed at measuring compliance used an electronic monitoring device called the Medication Event Monitoring System (MEMs). This device consists of a microprocessor, usually set into the cap of each medication container, which records the time and date each time a patient opens and closes the bottle to presumably dispense a dose of medication.[39] Data are stored in the microprocessor and can be uploaded into a computer for analysis and printing. The software is capable of reporting the data in tables or plots. These data are utilised to assess the overall adherence to the dosage regimen with records the proportion of doses taken and/or missed, as well as the timing precision of each dose. Data using this device have been reported in kidney[11,40,41] and heart[26] transplant recipients.

Nevins et al.[11] studied a prospective cohort of 180 renal transplant recipients who permitted electronic monitoring of their azathioprine use with the MEMs cap. These authors showed that kidney transplant recipients begin missing drug doses early after transplantation, even during the first week after hospital discharge. Half of all patients studied showed evidence of nonadherence during at least 1 of the first 6 months after transplantation. Only 21 patients (16%) did not miss any doses of azathioprine during the first 180 days after discharge; the average patient adherence rate during this interval was 92% (range: 16–100% of doses). When patients were divided into quartiles based on azathioprine compliance during the first 90 days, there was a clear dose response with increasing acute rejection rates associated with worsening compliance ($p = 0.006$). Furthermore, eventual graft loss was increased in the quartile with the poorest compliance ($p = 0.002$). Conversely, for patients in the best quartile for compliance, there were no rejections or graft losses during the next 2–4 years of follow-up. Nonadherent patients were 4–5 times more likely to experience allograft loss, even within the first 6 months of transplantation. For individuals whose early compliance decreased sequentially during the first 3 months of follow-up, there was an increased risk of acute rejection (relative risk = 13.9; $p = 0.001$). Early patterns of noncompliance were sensitive predictors of later adverse outcomes.

Electronic monitors also permitted researchers to characterise medication adherence in heart transplantation, as well as link medication nonadherence with later outcomes.[26] Ciclosporin compliance was prospectively monitored for 3 months in 101 cardiac transplant recipients who were stable for 1–6 years post-transplant. Although medication compliance rates were high, those patients with even modest decreases in compliance experienced more frequent acute rejections, and one noncompliant patient rejected and lost the cardiac transplant. Clearly, adverse outcomes are highly associated with carefully documented noncompliance. Gross nonadherence was demonstrated in a short-term study using electronic monitors to examine azathioprine compliance after kidney transplantation. Even under compliance monitoring, only a minority of patients were 100% compliant.[40]

Data generated by MEMs can successfully identify nonadherence in transplant recipients, which may carry through late post-transplant period. This method is thought to provide the most accurate way to detect nonadherence. Unfortunately, this methodology is expensive and difficult to implement in clinical practice because of the large number of different medications in a transplant patients' regimen. Its greatest use has been in clinical trials examining the incidence, outcome and possible interventions for medication nonadherence.

9.3 Patient Questionnaires

In another study, adherence to immunosuppressant medications was measured in 153 adult renal transplant recipients using self-report question-

naires, interviews, clinician rating, and ciclosporin concentrations.[41] The sensitivity and specificity of these measures were determined by comparison with electronic monitoring of prednisolone in a randomly selected sample of 58 individuals. Fifteen individuals missed at least 10% of their medication doses. None of the subjective measures of adherence correlated well when tested against electronic monitoring. Self-report at a confidential interview was the best measure of adherence for the detection of both missed doses and erratic timing of medication; however, the use of a confidential interview is not practical in the clinical setting. The authors recommended further research to establish reliable measures for medication adherence in the clinic.

Data generated by MEMs can successfully identify nonadherence in transplant recipients, which may carry through late post-transplant period. This method is thought to provide the most accurate way to detect nonadherence. Unfortunately, this methodology is expensive and difficult to implement in clinical practice due to the large number of different medications in a transplant patients' regimen. Its greatest use has been in clinical trials examining the incidence, outcome and possible interventions for medication nonadherence.

10. Devices to Promote Adherence

Forgetfulness is one of the most common reasons that patients give for missing doses of their medications.[41] Patients should be counselled about various cueing methods to integrate their medication administration times around daily routine activities. Some basic cues include meal times, upon waking in the morning or at bedtime and brushing ones teeth. Additional strategies for overcoming forgetfulness include placing medications in an obvious place, following a medication calendar, enlisting family reminders, using post-it notes, setting alarms and pharmacy refill reminders.

Pillboxes, otherwise known as daily dosing dispensers or medisets, assist patients in organising their medications. They are useful for complex regimes consisting of multiple drugs with multiple daily dose administration schedules. The size and setup of a pillbox can differ. Patients may choose to organise their medications by the day of the week, time of day or both. Medications are sorted into individual compartments by the patients (or healthcare provider), typically according to a written schedule. A pillbox may be advantageous in the transplant population given the large number of prescribed medications. However, its use may be limited when transitioning or adapting to constantly changing dosage regimens.

Electronic compliance devices are also available for improving medication adherence. The MEMs cap, which is primarily used to assess medication adherence, can also be utilised to determine patterns of adherence, specifically when doses are taken in relation to each other and the designated time. However, the MEMs cap may not be a practical solution for increasing adherence in the transplant population; the MEMS caps are primarily research tools and only promote adherence by identifying problems for the transplant team. More advanced electronic compliance devices integrate reminders to patients when a dose is due to be administered. This can be done by digital voice message, watches set with multiple daily reminders or online pager systems.

The disease management assistance system (DMAS) is a portable, battery-powered device that delivers a programmed voice message reminder at set times. The device prompts the patient to take their medication dose. After the patient does so, they are able to press a response button and the device will record the date and time for the dose taken. Most DMAS devices can store up to 3 months of data for up to 25 medications. When using the DMAS device, adherence rates to antiretroviral therapy in HIV patients were comparable with that of patients who received monthly adherence counselling.[42] Use of the DMAS device resulted in a significantly greater proportion of patients with undetectable HIV viral loads (38% vs 14%, $p = 0.014$) at 12 weeks. Viral loads are a more objective measure of the apparent efficacy of the antiretroviral regimen. Patients with memory impairment associated with HIV disease appeared to derive the most

benefit from the DMAS device, with adherence rates of 77% compared with 57% in patients who only received adherence counselling ($p = 0.001$). In contrast, the adherence rates between the two strategies were similar in patients with intact memory (83% vs 77%, respectively).

Multi-alarm pill reminder wristwatches are a variation of the DMAS device, but somewhat more discrete. The two products available are the MeDose Vibrating Alarm Watch and the HealthWatch 100 Medical Reminder Watch. These watches can store up to 6-8 reminders per day. The HealthWatch is programmed to scroll the medication name on its display and is capable of storing the time the medication was taken for up to 42 days.

Finally, an online pager system may improve adherence to medication regimens. A patient's daily dose administration schedule is programmed online into software that is linked to a web-based pager service. Information includes the medication name, number of pills, timing of dose and any specific instructions or restrictions regarding administration. In some instances, reminders for meals or follow-up clinic appointments may also be incorporated. A text message page is sent to the patient at the designated time. Use of this system also improved adherence to antiretroviral medications in HIV patients.[43] A significant improvement in adherence was seen in patients using the paging system compared with patients who were assigned to use MEMs caps. Adherence rates were 70% and 56% at 2 weeks ($p < 0.01$) and 64% and 52% at 12 weeks ($p < 0.03$), respectively.

11. Drug Regimens that May Favour Adherence

Do some drugs or drug schedules lend themselves to better compliance, and if so, does it make a significant difference? A complex medical regimen logically predisposes to noncompliance. Studies have shown that the number of prescribed medications and dosing frequency have a direct effect on adherence rates.[12,14] When a regimen is extremely complex, forgetfulness becomes a contributing factor to noncompliance.[9]

Medication regimens after the transplant procedure are complex and consist of immunosuppressive agents, prophylactic antibacterials and antiviral medications, in addition to medications required for treatment of their underlying disease states such as hypertension and diabetes mellitus. Transplant recipients typically receive 5–15 different medications, with many requiring multiple doses throughout the day. The complexity of a medication regimen is inversely proportional to the rate of adherence with an increasing number of prescribed medications favouring nonadherence.[15] The frequency of medication administration also affects adherence. In a review of 76 studies published between 1986 and 2000, adherence to medications that were administered once daily was significantly greater than those that needed to be administered three or four times a day. Similarly, medications requiring twice daily administration resulted in greater adherence than those administered four times daily.[44]

Medication regimens can be simplified or streamlined to decrease the pill burden using various strategies. Pharmacological agents that are available as a controlled-release formulation requiring less frequent administration or a transdermal patch may be prescribed in place of its immediate-release counterpart. Agents with a longer duration of action (>24 hours) within the same pharmacological drug category may be preferred over a shorter-acting agent. Use of weekly or monthly drug formulations, as well as combination drug products, will also lessen the daily pill burden, thus improving overall adherence. However, it is important to remember that newer formulations may be more expensive than the original product and/or not be covered by prescription drug plans. Although these strategies primarily focus on the reduction of the total daily number of doses, adequate patient counselling regarding the appropriate timing of the drug dose needs to be emphasised. Medications should be taken at approximately the same time every day to avoid periods of inadequate drug exposure. Thus, medications with a longer duration of action are more forgiving in terms of pharmacological coverage in the event that a

patient does forget to take a dose.[45] A clinical pharmacist may be incorporated as a member of the transplant team to provide comprehensive patient education regarding the benefits and adverse effects of their medications and specific instructions on how to properly take their medications. Pharmacists can also provide longitudinal follow-up to ensure adequate patient understanding and optimise adherence. A significantly greater proportion of patients were ≥80% adherent with their immunosuppressive medications at 1-year post-transplant procedure when a pharmacist was involved.[46] These patients were also more likely to have drug concentrations that were within the target range.

Immunosuppressive regimens obviously need to be effective. Nonetheless, the availability of several effective drugs for transplant immunosuppression means that individualised regimens can be tailored for better palatability and ease of administration. Individualised selection of immunosuppressive regimens that involve fewer medications, fewer doses and reduced adverse effects can translate to increased satisfaction, improved compliance and maintenance of graft function. In a study of 105 patients with hypertension (83% Black), compliance with blood pressure medication increased from 59% with a thrice-daily regimen to 83.6% with a once-daily regimen.[47] Ciclosporin and tacrolimus can be given once daily at almost double the twice-daily dose. Although the data are limited for once-daily administration of ciclosporin, the safety and efficacy of daily administration with tacrolimus has been documented in phase III trials.[48,49] A slow-release form of tacrolimus that can be given once daily is under development.[50]

Currently, ciclosporin and tacrolimus are usually prescribed twice daily. Sirolimus has more than a 3-fold longer half-life and is prescribed once daily.[51] Sirolimus can be used adjunctively with reduced-dose ciclosporin or tacrolimus or by itself as the 'primary' agent. However, children may metabolise sirolimus more rapidly and require twice-daily administration,[51] although these data were derived from pharmacokinetic studies in paediatric liver transplant recipients. Because of its long half-life, once a steady state is achieved with sirolimus, drug concentrations are more predictable.

It is easy to understand how difficult it is for most teenagers to accept the cosmetic adverse effects of corticosteroids (e.g. weight gain, acne, Cushingoid features). Similarly, it is difficult for adolescents to accept the hypertrichosis and gingival hyperplasia associated with ciclosporin. This often makes tacrolimus a better choice for adolescents. Corticosteroid-free immunosuppression has been advocated to avoid corticosteroid-related adverse effects. An open-labelled, prospective study of complete corticosteroid avoidance immunosuppressive protocol in 57 paediatric recipients employed an extended course of daclizumab, in combination with tacrolimus and mycophenolate mofetil and no corticosteroids. Daclizumab, a monoclonal antibody to the interleukin (IL)-2 receptor, was given as a once-monthly infusion for 6 months. Acute rejection was observed in 8%, and patient and graft survival were 98% at a mean follow-up time of 20 months (range 4.5–41 months). Protocol biopsies revealed four instances of subclinical rejection and no chronic rejection, although mild tacrolimus toxicity was present in all patients after 1 year. The corticosteroid-free group had significantly less hypertension requiring treatment, and essentially no body disfigurement. The authors concluded that this protocol avoided the morbid adverse effects of corticosteroids without increasing infection, and could contribute to improved compliance.[52]

More studies with larger numbers of patients will be required before the safety of long-term use of intravenously administered humanised or chimeric anti-CD25 monoclonal antibodies (basiliximab and daclizumab) will be known. It has been suggested recently that the early use of a humanised monoclonal antibody to the pan-lymphocyte surface antigen CD52 (Campath 1H or alemtuzumab) may one day allow the withdrawal of all oral immunosuppressive agents or use of minimal maintenance immunosuppression.[53] The application of such a protocol, if safe and efficacious, has obvious implications for compliance that are being considered by paediatric transplant professionals in the design of

future trials.[31] However, the benefits of induction therapy as well as the use of tacrolimus in minimising other maintenance immunosuppression must be countenanced by a potentially greater risk of post-transplant lymphoproliferative disorder reported with these agents.[54]

12. Prevention of Nonadherence: Summary

Since nonadherence to medications after solid organ transplantation is common and a major cause of allograft injury a strategy must be in place to prevent or minimise its occurrence. Two meta-analyses of interventions to improve medication adherence in chronically ill patients demonstrated that educational strategies alone are not effective; an aggressive combination of educational, behavioural and social support interventions provides the best results.[55,56] A team approach consisting of education, monitoring, recognition and intervention is essential to the secure the benefit of transplantation (table V). Simplified drug regimens, pillboxes to organise medications, adapting a medical regimen to the patient's lifestyle, cueing medication administration with routine activities (brushing teeth, meals, etc.) and electronic devices (alarms and alerts) can all contribute to improved adherence. More complex patterns of covert nonadherence require further insight and energy to have a successful impact on nonadherence. Recognising the root cause of nonadherence is a necessary first step.

13. Re-Transplantation after Graft Loss Due to Nonadherence

Equitable allocation of organs for transplantation maximises the chances for allograft and patient sur-

Table V. A summary of interventions aimed at improving medication adherence

Education and medical interventions
Ensure that the patient knows their medications by name, dosage and reason for prescription; reinforce these points during every clinic visit
Inform about the adverse effects of drugs
Provide written instructions for each change in medication dose or frequency
Reduce the number and frequency of medications. Where possible, medications should be given either once or, at most, twice daily
Develop the understanding that the patient needs to take immunosuppressive agents even if the transplanted organ is functioning well
Teach patients that chronic rejection is insidious in onset, hard to diagnose in its early stages and often not reversible once established
Attempt to treat adverse effects by means other than dose reduction
Inquire about problems during every clinic visit, and address specific patient concerns
Monitor compliance with laboratory work, clinic visits and prescription refills
Behavioural and psychosocial approaches
Establish adherent behaviours and tasks in preparation for transplant
Demonstrate a track record of medication adherence and knowledge
Individual team members develop rapport with patient
Identify and involve a backup support system (family or friends)
Treat depression, anxiety or other psychological issues
Elicit a personal promise of adherence (e.g. a written contract)
Use a non-judgmental approach to the discussion of adherence
Address social problems such as insurance changes or difficulties at school or work
Tailor interventions for nonadherence to the root cause
Integrate taking medication into the daily routine
Consider reminders such as digital alarms or alerts
Provide ongoing education, discussion and easily accessible counselling
Ensure that the patient knows their medications by name, dosage and reason for prescription; reinforce these points during every clinic visit
Inform about drug-induced adverse effects
Provide written instructions for each change in medication

vival, and should take into account the ability and desire of the recipient to comply with prescribed therapies directed at maintaining the allograft. However, noncompliance after transplantation is not predictable and the reasons for noncompliance are multifactorial. Furthermore, noncompliance is also a matter of degree, such that with clear evidence of overt noncompliance it is reasonable to withhold future transplantation; however, subtle suggestions of noncompliance usually predominate and these are inaccurate. As noted previously, subjective assessments of adherence applied in the clinic setting are frequently erroneous.

Although noncompliance is frequent in paediatric patients, particularly adolescents who are transitioning to independence, it should not prevent them from receiving a second transplant after a period of counselling and documented medical compliance (figure 1). Even adults who have been noncompliant after their first kidney transplant have received a second transplant with a high degree of success.[57]

Living organ donors should be aware of the team's concerns regarding recipient compliance, because it may impact the benefit that the donor anticipates for the recipient. This might occur in a combined donor-recipient-staff conference where adherence concerns are openly discussed and the recipient can publicly acknowledge their commitment to adhere. The team must also address the fundamental rationality of the donor who wishes to donate to a noncompliant patient (figure 2); transplant professionals have a well recognised responsibility not to countenance irrational donation. The consent for living donation should include the medical uncertainties, including the expected outcome of transplantation for the recipient. The disclosure process should permit a 'cooling off period' between consent and the scheduled donor operation, to provide the potential donor ample time to reconsider the decision to donate. It should be made clear to the donor that they are free not to donate and some individual in the evaluation process should serve as an independent, confidential resource for the potential donor to express hesitations or concerns that the donor may not wish to disclose in the presence of a family member. Living donors may feel pressured by their families into donating an organ and guilty if they are reluctant to go through with the procedure. Feelings of resentment may also occur if the recipient rejects the donated organ, particularly if noncompliance contributed to the allograft loss. Potential donors should be encouraged to discuss their feelings and concerns with a transplant professional, social worker or other informed advocate.

14. Future Directions to Reduce Nonadherence

Future research should seek to identify the root causes of medication nonadherence after transplantation and develop effective interventions to reduce noncompliance. Potentially effective strategies to detect and reduce noncompliance include the following:

- listening carefully to patient concerns;
- tracking prescription refills with insurers and pharmacies;
- promptly following up missed appointments;
- investigating inconsistent drug concentrations;
- improving patient education;
- adding resources for patient support;
- design and validation of compliance-friendly regimens.

The contribution of any or all of these policies is unknown. Nonadherence is widely acknowledged by the transplant community and most programmes have an infrastructure that already addresses these strategies. Given the enormity of this problem, the associated costs and the scarcity of organs for transplantation, it seems reasonable to fund further research to identify those patients at greatest risk for noncompliance and those strategies that best improve medication adherence.

15. Conclusion

Nonadherence with immunosuppressive medication is pervasive after solid organ transplantation. Clinicians must possess a heightened awareness of this behaviour and anticipate its emergence. Given the serious consequences for medication nonadherence, successful interventions will significantly re-

duce costly, adverse events (table V). Effective tolerance protocols or newer immunosuppressive agents requiring less frequent administration or associated with fewer adverse effects may improve adherence, but none are imminently available. However, as Nevins and Matas[58] so succinctly stated, effective strategies for the prevention of allograft loss due to rejection "are available today and do not require the development of a single new drug, rather they only require patients to consistently take the medications already available!" Appropriate longitudinal follow-up by a team of skilled transplant experts is warranted to accomplish this task and optimise long-term allograft function.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004 Dec 23; 351 (26): 2715-29
2. Gaston RS. Maintenance immunosuppression in the renal transplant recipient: an overview. Am J Kidney Dis 2001; 38 (S6): S25-35
3. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005; 353 (5): 487-97
4. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Adv Ther 2005 Jul-Aug; 22 (4): 313-56
5. Marinker M, Blenkinsopp A, Bond C, et al., editors. From compliance to concordance: achieving shared goals in medicine taking. London: Royal Pharmaceutical Society of Great Britain, 1997
6. Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med 2005 May 23; 165 (10): 1147-52
7. Greenstein S, Siegal B. Compliance and noncompliance in patients with a functioning renal transplant: a multicenter study. Transplantation 1998; 66: 1718-26
8. Siegal BR, Greenstein SM. Postrenal transplant compliance from the perspective of African-Americans, Hispanic-Americans, and Anglo-Americans. Adv Ren Replace Ther 1997; 4: 46-54
9. Raiz LR, Kilty KM, Henry ML, et al. Medication compliance following renal transplantation. Transplantation 1999; 68: 51-5
10. Gaston RS, Hudson SL, Ward M, et al. Late renal allograft loss: noncompliance masquerading as chronic rejection. Transplant Proc 1999; 31: S21-3
11. Nevins TE, Kruse L, Skeans MA, et al. The natural history of azathioprine compliance after renal transplantation. Kidney Int 2001; 60: 1565
12. Hilbrands LB, Hoitsma AJ, Koene RA. Medication compliance after renal transplantation. Transplantation 1995; 60: 914-20
13. Chisholm MA, Vollenweider LJ, Mulloy LL, et al. Renal transplant patient compliance with free immunosuppressive medications. Transplantation 2000; 70: 1240-4
14. Loghman-Adham M. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. Am J Manag Care 2003; 9: 155
15. Kiley DJ, Lam CS, Pollak R. A study of treatment compliance following kidney transplantation. Transplantation 1993; 55: 51-6
16. Vlaminck H, Maes B, Evers G, et al. Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. Transplantation 2004; 4: 1509-13
17. Shaw RJ, Palmer L, Blasey C, et al. A typology of nonadherence in pediatric renal transplant recipients. Pediatr Transplantation 2003; 7: 489-93
18. Laederach-Hofmann K, Bunzel B. Noncompliance in organ transplant recipients: a literature review. Gen Hosp Psychiatry 2000; 22 (6): 412-24
19. Jarzembowski T, John E, Panaro F, et al. Impact of noncompliance on outcome after pediatric kidney transplantation: an analysis in racial subgroups. Pediatr Transplant 2004 Aug; 8 (4): 367-71
20. Nevins TE. Non-compliance and its management in teenagers. Pediatr Transplant 2002; 6: 475-9
21. Beck DE, Fennell RS, Yost RL, et al. Evaluation of an educational program on compliance with medication regimens in pediatric patients with renal transplants. J Pediatr 1980; 96: 1094-7
22. Butler JA, Roderick P, Mason JC, et al. Frequency and impact of nonadherence to immunosuppressant following renal transplantation: a systematic review. Transplantation 2004; 77: 769
23. Chapman JR. Compliance: the patient, the doctor, and the medication? Transplantation 2004; 77 (5): 782-6
24. Morrissey PE, Reinert S, Gohh R, et al. Factors contributing to acute rejection in renal transplantation: the role of noncompliance. Transplant Proc 2005; 37: 2044-7
25. Dobbels F, Vanhaecke J, Desmyttere A, et al. Prevalence and correlates of self-reported pretransplant nonadherence with medication in heart, liver, and lung transplant candidates. Transplantation 2005 Jun 15; 79 (11): 1588-95
26. Dew MA, Roth LH, Thompson ME, et al. Medical compliance and its predictors in the first year after heart transplantation. J Heart Lung Transplant 1996; 15: 631-45
27. De Geest S, Abraham I, Moons P, et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. J Heart Lung Transplant 1998; 17: 854
28. Shemesh E, Shneider BL, Savitzky JK, et al. Medication adherence in pediatric and adolescent liver transplant recipients. Pediatrics 2004 Apr; 113 (4): 825-32
29. Shemesh E. Nonadherence to medications following pediatric liver transplantation. Pediatr Transplantation 2004; 6: 600-5
30. Shemesh E, Lurie S, Stuber ML, et al. A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. Pediatrics 2000; 105: E29
31. Sweet SC, Wong H-H, Webber SA, et al. Pediatric transplantation in the United States, 1995-2004. Am J Transplant 2006; 6: 1132-52
32. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, et al. Growing pains: nonadherence with the immunosuppressive regimen

in adolescent transplant recipients. Pediatr Transplant 2005; 9: 381-90

33. Kalb LM, Loeber R. Child disobedience and noncompliance: a review. Pediatrics 2003; 111: 641-52
34. Schneider J, Kaplan SH, Greenfield S, et al. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. J Gen Int Med 2004; 19 (11): 1096-103
35. Rosenow EC. Patients' understanding of and compliance with medications: the sixth vital sign? Mayo Clin Proc 2005; 80 (8): 983-7
36. Butler JA, Peveler RC, Roderick P, et al. Modifiable risk factors for non-adherence to immunosuppressants in renal transplant recipients: a cross-sectional study. Nephrol Dial Transplant 2004; 19 (12): 3144-9
37. Chisholm MA. Enhancing transplant patients' adherence to medication therapy. Clin Transplant 2002; 16 (1): 30-18
38. Steiner R. Medication noncompliance: implications for transplant professionals [online]. Available from URL: http://www.medscape.com/viewprogram/3639 [Accessed 2006 May 5]
39. Aardex. MEMs [online]. Available from URL: http://www.aardex.ch/aardex/index.htm [Accessed 2006 May 23]
40. Feldman HI, Hackett M, Bilker W, et al. Potential utility of electronic drug compliance monitoring in measures of adverse outcomes associated with immunosuppressive agents. Pharmacoepidemiol Drug Saf 1999; 8: 1-14
41. Butler JA, Peveler RC, Roderick P, et al. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. Transplantation 2004 Mar 15; 77 (5): 786-9
42. Andrade AS, McGruder HF, Wu AW, et al. A programmable prompting device improves adherence to highly active antiretroviral therapy in HIV-infected subjects with memory impairment. Clin Infect Dis 2005; 41: 875-82
43. Safren SA, Hendriksen ES, Desousa N, et al. Use of an on-line pager system to increase adherence to antiretroviral medications. AIDS Care 2003; 15 (6): 787-93
44. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 1999; 23 (8): 1296-310
45. Urquart J. Patient non-compliance with drug regimens: measurement, clinical correlates, economic impact. Eur Heart J 1996; 17 Suppl. A: 8-15
46. Chisholm MA, Mulloy LL, Jagadeesan M, et al. Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications. Clin Transplant 2001; 15 (5): 330-6
47. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990; 150: 1881-4
48. Bennett WM, Lindsley J, Buss WC. The effects of age and dosage route on experimental cyclosporine nephrotoxicity. Transplantation 1991; 51: 730-1
49. Hardinger KL, Park JM, Schnitzler MA, et al. Pharmacokinetics of tacrolimus in kidney transplant recipients: daily versus once daily dosing. Am J Transplant 2004; 4: 621-5
50. First MR, Fitzsimmons WE. New drugs to improve transplant outcomes. Transplantation 2004; 77 (9 S): S88-92
51. Schubert M, Venkataramanan R, Holt DW, et al. Pharmacokinetics of sirolimus and tacrolimus in pediatric transplant patients. Am J Transplant 2004; 4: 767-73
52. Sarwal MM, Yorgin PD, Alexander S, et al. Promising early outcomes with a novel, complete steroid avoidance immunosuppression protocol in pediatric renal transplantation. Transplantation 2001 Jul 15; 72 (1): 13-21
53. Shapiro R, Basu A, Tan H, et al. Kidney transplantation under minimal immunosuppression after pretransplant lymphoid depletion with thymoglobulin or campath. J Am Coll Surg 2005 Apr; 200 (4): 505-15
54. Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005; 80 (9): 1233-43
55. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. Am J Health Syst Pharm 2003; 60 (7): 657-65
56. Roter DL, Hall JA, Merisca R, et al. Effectiveness of interventions to improve patient compliance: a meta-analysis. Med Care 1998; 36 (8): 1138–1161
57. Troppmann C, Benedetti E, Gruessner RWG, et al. Retransplantation after renal allograft loss due to noncompliance: indications, outcome, and ethical concerns. Transplantation 1995; 59: 467-71
58. Nevins TE, Matas AJ. Medication noncompliance: another iceberg's tip. Transplantation 2004 Mar 15; 77 (5): 776-8

Correspondence: Dr *Paul E. Morrissey*, Division of Organ Transplantation, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, USA.
E-mail: Pmorrissey@lifespan.org