

Chapter 11: Preventing, Detecting, and Treating Nonadherence

11.1: Consider providing all KTRs and family members with education, prevention, and treatment measures to minimize nonadherence to immunosuppressive medications. (Not Graded)

11.2: Consider providing KTRs at increased risk for nonadherence with increased levels of screening for nonadherence. (Not Graded)

KTRs, kidney transplant recipients.

Background

Adherence is 'the extent to which the patient's behavior matches the agreed-upon prescriber's recommendations' (255). At a recent consensus conference, this definition was modified to take into account the threshold of the effect of nonadherence on the therapeutic outcome. We have adopted this definition of nonadherence as 'deviation from the prescribed medication regimen sufficient to adversely influence the regimen's intended effect' (255). Nonadherence encompasses primary (at initiation) and secondary (subsequent) nonadherence, partial and/or total nonadherence, as well as the timing of medication use (256–260).

Rationale

- Nonadherence is associated with a high risk of acute rejection and allograft loss.
- Nonadherence may occur early and/or late after transplantation.
- The transition from pediatric to adult nephrology care may be a time when nonadherence is particularly common.
- Measures can be taken to reduce nonadherence and thereby improve outcomes.

Nonadherence is common in the first months after kidney transplantation and increases by duration of follow-up. The level of adherence affects clinical outcomes, and is associated with early and late allograft rejection, which reduces graft function and graft survival (261–263). Graft loss is sevenfold more likely in nonadherent compared to adherent individuals (264). In another study, nonadherence (missed appointments, fluctuating drug concentration) accounted for over a half of kidney allograft loss (265).

Nonadherence is multidimensional (255), although we have focused primarily on adherence with immunosuppressive medication use. Additional areas of nonadherence include prescribed diet; exercise; tobacco, alcohol and drug use; self-monitoring of vital signs, for example blood pressure, body weight and clinical appointments.

Satisfactory adherence to medication use is achieved when the gaps between dosing history and the prescribed regimen have no effect on therapeutic outcome. This pharmacoadherence definition emphasizes therapeutic outcome in contrast to specific medication intake or drug level. Measurement of outcome and drug levels is commonly used in the transplant population. Measurable parameters of pharmacoadherence are acceptance (whether the patient accepts the recommended treatment), execution (how well the patient executes the recommended regimen), and discontinuation (when the patient stops taking the medication) (264,266). Measurement of adherence can be by direct observation that medication was consumed, indirect measures that medication had been consumed or self-reporting (Table 9). Indirect measures include serum drug levels, biological markers, electronic monitoring, pill count and refill/prescription records. Since there is no perfect measure of adherence, consideration should be given to use more than one approach to measure adherence (267–270).

In organ transplant recipients, the average nonadherence rate was highest for diet (25 cases per 100 people per year), immunosuppressive medication (22.6 cases per 100 people per year), monitoring vital signs (20.9 cases per 100 people per year) and exercise (19.1 cases per 100 people per year) (264). Among KTRs, nonadherence with immunosuppressive medications was highest (35.6 cases per 100 people per year). Nonadherence to long-term medication is as high as 50% in developed countries and even higher

Table 9: Assessment of medication adherence (255,260)

Self-reporting medication use by patient
Collateral reporting of medication use by relatives, friends or caretakers
Patient diaries
Questionnaires
Laboratory tests (drug and metabolite levels)
Medical record review, outcomes
Prescription refills
Monitored pill counts
Electronic monitoring devices

Modified with permission (260).

Table 10: Risk factors for medication nonadherence (255,260)

Nonadherence behavior prior to transplantation
Psychiatric illness
Personality disorders
Poor social support
Substance abuse and other high-risk behavior
Adolescence
High education level
Time since transplantation (higher earlier)
Lack of adequate follow-up with transplant specialists
Inadequate pretransplant education
Multiple adverse effects from medications
Complex medication regimens

Modified with permission (260).

rates have been reported in developing countries (264). Meta-analysis showed that the odds of having a good outcome is 2.9 times higher if the patient is adherent (271).

Risk factors for nonadherence include long duration of treatment (with decline in rates of adherence over time), poor communication and lack of social support (Table 10). Risk factors for nonadherence can be categorized into four interrelated areas: patient/environment, caregiver, disease and medication. The patient/environment is central and interrelates with the other three categories. The primary patient–medication factors are side effects, regimen complexity, costs and poor access. Negative beliefs in medication and lack of medication knowledge have a moderate impact. Patient–caregiver factors include poor communication and poor aftercare/discharge planning (272–274). Patient–disease factors are primarily poor disease knowledge and insights, disease duration and comorbid psychiatric disease. A meta-analysis of 164 studies in the nonpsychiatric literature reported risk factors for adherence, including: age (adolescents less adherent), sex (girls more adherent than boys among pediatric patients), education level (positively associated with adherence in chronic disease) and socioeconomic status (positively correlated with adherence in adults) (275–277).

A team approach consisting of education, monitoring, recognition and intervention is essential to secure the benefit of transplantation. A combination of educational, behavioral and social support interventions provides the best results (Table 11) (271,278). Simplified drug regimens, pillboxes to organize medications, individualized instructions (particularly for travelers and night-shift workers), combining medication administration with daily routine activities and electronic devices can contribute to improve adherence.

Simply forgetting to take their pills is one of the most common reasons that patients give for missing doses of their medication (268). Patients should be counseled about various possibilities to integrate their medication administration into their daily routine. Pillboxes may be helpful for complex regimens consisting of multiple drugs with mul-

Table 11: A summary of interventions aimed at improving medication adherence

Education and medical intervention

- Ensure that patients know their medications by name, dosage and reason for prescription; reinforce these points during every clinic visit.
- Inform patients 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.
- Ensure the patients understand that they need to continue taking 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 visit and prescription refills.

Behavioral and psychosocial approaches

- Provide positive support to encourage adherent behaviors during preparation for transplant.
 - Encourage patient to demonstrate a track record of medication adherence and knowledge.
 - Encourage individual team members to 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 nonjudgmental approach to the discussion of adherence.
 - Address social problems such as insurance changes or difficulties at school or work.
 - Tailor interventions for nonadherence to its root cause.
 - Integrate taking medication into the daily routine.
 - Consider reminders such as digital alarms or alerts.
 - Provide ongoing education, discussion and easily accessible counseling.
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multiple daily dose-administration schedules. Electronic compliance devices, including alarms, are also available for improving medication adherence. The disease-management assistance system is a device that delivers a programmed voice message reminder at set times and has been applied in patients on antiretroviral therapy (279). Finally, an online pager or mobile phone system may improve adherence to medication regimens (280). However, except for the observation method, which can be onerous, all measures have significant disadvantages, primarily related to their lack of accuracy. Because there is no perfect measure of nonadherence, consideration should be given to use more than

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one approach to measure adherence. The overall approach to measure adherence requires individualization.

The number of prescribed medications and the dosing frequency has an effect on adherence rates (280,281). When a regimen is extremely complex, forgetfulness becomes a contributing factor to nonadherence (282). The complexity of a medication regimen is inversely proportional to the rate of adherence, with an increasing number of prescribed medications favoring nonadherence (283). Medications requiring twice-daily administration have resulted in greater adherence than those administered more than twice daily (284). The simplification of therapy strategies includes immunosuppressive as well as nonimmunosuppressive medications (e.g. antihypertensives). In addition, steroid- or CNI-sparing protocols should be considered for the benefit of reduction of number of drugs, and reduction of adverse events. Involving a clinical pharmacist may be helpful to provide comprehensive patient education regarding benefits and adherence effects of their medications. A significantly greater proportion of patients were adherent with their immunosuppressive medications at 1 year after transplant when a pharmacist was involved (284,285).

Behavioral change strategies have been applied in the clinical setting. Behavior modifications have been incorporated in six adherence-improvement RCTs in KTRs (286,287). The methods included behavioral contacting, education, skills training, feedback and reinforcement. These data indicated that such behavioral intervention is a very individualized process and adherence motivation needs to be patient-specific and updated continuously. Using the medication event-monitoring system to monitor monthly azathioprine adherence during a 6-month period in KTRs demonstrated a significant correlation with adherence and rejection-free survival in the first 6 months after transplantation (288).

Research Recommendations

- Additional prospective cohort studies are needed to establish the best measures of adherence and the association between adherence and outcomes.
- RCTs are needed to test interventions to improve adherence in KTRs.