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Adherence to medical recommendations and transition to adult services in pediatric transplant recipients

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Abstract

Purpose of review—Nonadherence to treatment recommendations, especially when associated with transition to adult care providers, account, by some estimates, for most organ rejections and death in long-term pediatric survivors of solid organ transplantations. It is therefore imperative that providers become familiar with the issues related to those major risks and ways to address them.

Recent findings—It is possible, and important, to routinely measure adherence to medications by using one of several available and proven methods of surveillance. There are numerous ways to improve adherence, and it is in fact possible to improve adherence and therefore outcomes in the transplant setting. The transition to adult services is a vulnerable period. The authors believe that it is possible to improve the transition process, and suggestions are presented in this review. However, solid research into interventions to improve transition is sorely lacking.

Summary—Nonadherence to medical recommendations is prevalent and leads to poor outcomes following otherwise successful pediatric transplantation. An especially vulnerable period is the time when a recipient transitions to adult care. Routine monitoring of adherence, evaluating and addressing barriers to adherence, and collaborative, multidisciplinary care are all expected to substantially improve adherence and reduce the risks associated with transition.

Keywords

Adherence; nonadherence; transition; pediatric; transplantation

Introduction

Nonadherence, defined by the World Health Organization (WHO) as a “the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (1), is common in children and adolescents who have received a solid organ transplant (2–6). Transplant recipients must self-manage a number of tasks including medication-taking responsibilities, completing required blood tests, and attending appointments (7) making adherence difficult. The consequences of nonadherence can be grim, including but not limited to increases in medical morbidity, irreversible graft damage, and significantly increased use of health care resources (8–10).

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There are other aspects of self-management in addition to those under the rubric of adherence. Many behaviors that constitute self-management have received little attention in the literature including scheduling appointments, speaking with health care providers at appointments and as needed in between visits, and autonomously seeking medical care when necessary (11). Furthermore, maintaining a healthy lifestyle and avoiding health risk behaviors, such as lack of exercise, poor diet, substance abuse, and unsafe sexual behavior, are important aspects of self-management (12).

Nonadherence to treatment recommendations may well be the most important reason for organ rejection in children and adolescents who are late survivors of a liver transplant (13). There is anecdotal evidence that during the process of transitioning health care management from caregivers to patients, adherence declines even further (14). Thus, it is imperative that practitioners familiarize themselves with these two interrelated, and often neglected, aspects of posttransplant care: helping patients adhere closely to recommendations, and ensuring that transition of care is done as smoothly as possible.

To this end, the present review describes a framework for evaluating and improving adherence in the transplant setting, and describes the issue of transition in some detail as well as suggests some ways to improve it.

Nonadherence – how to evaluate ?

Most patients who do not take their immunosuppressants will ultimately suffer a rejection, organ loss, and if not treated, death. Indeed, nonadherence counts for many if not most of the deaths of pediatric, and especially adolescent, transplant recipients who have an otherwise stable posttransplant course (5). In the opinion of the writers of the present review, the most challenging aspect in managing adherence is to identify the patients who are not adhering well to the regimen, before they present clinically with graft dysfunction. Simply asking is not good enough (8), as self-reported adherence bears little resemblance to reality: some patients who report that they are adherent may simply not be telling the truth, or are unable to do so. Conversely some patients who do report nonadherence may in fact be adhering well enough. Parent, physician, and nurses' impressions of adherence are inadequate too (8). It is also not very helpful to wait until an adverse outcome has already happened (i.e., the patient has a rejection) because by then, the damage was already done.

Fortunately, there are several ways to find out. Classic objective ways to assess whether a patient is taking the medication or not, and to what extent, include the following:

- A. Pill counts. One may count the patients' pills in each visit to find out how many have been taken. The disadvantages of this method are that it takes time, patients might not bring their medications consistently, and pills can be discarded by patients who do not take them.
- B. Medication refill rates. Can be obtained from the pharmacy that the patient is using, and then compared to the expected time of the refill. This method has been successfully used in research in transplant recipients (15) but unfortunately is rarely incorporated into practice. Downsides include that patients might get a refill but still not take the medicine, and also that obtaining this information consistently over time may be challenging, especially in cases where patients switch pharmacies or prescriptions.
- C. Medication blood levels and, especially, the degree of fluctuation between individual blood levels. The transplant setting has an advantage that is rarely encountered in other medical settings; medication blood levels are routinely evaluated as a part of standard care. It is possible to calculate the degree of variance

between individual blood levels over time by computing the Standard Deviation of such sets of levels (i.e., over a full year of review). The higher the fluctuation – the higher the S.D. – the less consistent is the medication taking by the individual. Several studies pointed to an S.D. level of between 2–4 as the threshold fluctuation, beyond which rejection is less likely (8, 16, 17). This innovative method has the potential to revolutionize the way nonadherence is assessed and treated in transplant settings, but it does have its caveats. It can only be used with patients who are prescribed a relatively stable dose. It cannot be used in inpatient settings, it cannot be used immediately posttransplant (as blood levels and prescribed medications vary widely then), and it cannot be used in situations in which medication absorption is transiently severely impaired.

- D.** Electronic monitoring. This usually involves the use of pill bottles with a computer chip that registers every opening of the bottle. While this method can and has been used successfully in research (18), it is yet to be adopted clinically because of several caveats that make its clinical use difficult (19). It is costly and can be cumbersome, and patients may elect not to use the bottle, it cannot be used for liquid preparations, significant time and some training are required to download and interpret the data, and patients might open the bottle without actually taking the medication. At this point, we believe that the use of electronic monitoring in clinical settings is best reserved for cases who are already strongly suspected of being nonadherent, to allow additional monitoring of these cases (20).

In conclusion: It is possible to monitor adherence in the transplant setting. In fact, because, on the one hand, adherence is extremely important to survival and, on the other hand, transplant settings are especially well suited for adherence monitoring, we believe that it is imperative to monitor adherence. We propose a “tiered” approach in which patients are asked about adherence as a first step. While those who say that they are adherent are not necessarily telling the truth, those who admit to nonadherence should be taken seriously. Second, a center might elect to routinely evaluate pill counts, refill rates, or medication blood levels as a part of standard practice and create “threshold” alert levels beyond which a patient's behavior receives more scrutiny. Third, for suspected or identified cases, continuous electronic monitoring may be warranted.

What to do when a patient is not taking the medications as prescribed?

The length and focus of this review is insufficient to provide a full and detailed review of interventions to improve adherence – there are, after all, full-length books and textbook chapters dedicated to this matter. Rather than provide a systematic and comprehensive review, we therefore aim to propose a common-sense approach towards issues related to improving adherence. This approach is neither exclusive nor is it the only one, and interested readers are encouraged to make use of specific texts that offer broader and more detailed reviews on this subject (i.e., 21).

To improve adherence, the first steps are general and apply to the entire patient population – not just to patients who are nonadherent. Practitioners might want to ensure that patients are being given adequate information about the regimen, and have the opportunity to ask questions. Consistent prescription practices, easy access to clinicians, and monitoring of adherence all might improve adherence in any patient. For patients who are either strongly suspected or confirmed of being nonadherent, more intensive approaches are warranted. This includes intensive monitoring of adherence, increasing the frequency of clinic visits (22), changing the prescribed regimen to a simpler or a more palatable one, interactive and detailed education, and evaluating risk factors and barriers to adherence and addressing them. Common risk factors that predispose patients to nonadherence include, but are not

limited to, patchy medical insurance coverage or low socioeconomic status, lack of family support including – at the extreme – child abuse (23), psychopathology including depression and posttraumatic stress disorder (20), and cognitive deficits including memory loss due to hepatic failure. In the opinion of the authors of the present manuscript, medication side effects are *not* common reasons for nonadherence. Although patients might stop taking a medication because of side-effects, so long as this issue is discussed in the open this cannot be considered nonadherence according to the WHO definition (1), because openly stopping a medication is *not* a “failure to follow the *agreed upon* recommendation” – it is simply a disagreement about the regimen. Conversely, if stopping the medications because of a side effect is not discussed with the prescriber, the issue is no longer exclusively due to the feared side effect but by definition has to do also with the reason that led the patient to hide his or her behavior from the prescriber. Thus, in spite of numerous studies that purport to show that medication side effects are common reasons for nonadherence, when using current definitions, side effects shouldn't be considered an important “stand alone” reason for such behavior. The clinically important point here is that prescribers should not assume that nonadherence is easily explained by medication side effect profiles. As a rule, clinicians should strive to find other reasons for the nonadherence even when a patient claims, after nonadherence is confirmed, that it was due to intolerance of side-effects (i.e., the next question should be, “why did you not speak with me about it ?”).

While it is certainly not the case that all risk factors can be treated successfully, many are amenable to treatment. Addressing some risk factors (i.e., mental health disorders) will require referral to specialists, but intervening to improve adherence should be considered the primary responsibility of any transplant team. While studies of interventions to improve adherence are few, the optimistic message from what we do know is that it is quite possible to dramatically improve adherence posttransplant, using methods as varied as increased monitoring, electronic or personal reminders (24), and possibly more intensive psychotherapeutic approaches. A caveat is that nonadherence per se is not considered a psychiatric disorder. Mental health providers are best equipped to handle mental health disorders (which are sometimes related to nonadherence) but do not necessarily have expertise in handling nonadherence per se. It therefore is imperative that clinicians who suspect or identify nonadherence engage in its treatment fully and without hesitation: there is a good chance that treatments/interventions will work.

Health care management while transferring to adult care centers

While there are interventions that may successfully target adherence, health management as a whole has been largely understudied. And yet successful transfer to the adult health care system may be dependent upon achieving mastery in managing one's own health care while still in the pediatric setting. Indeed, in adult settings, patients are expected to display behaviors consistent with self-management (e.g., independently discussing one's illness and or concerns with the treatment team, scheduling and attending appointments, etc; 25). A review describing elements of successful acquisition of self-management skills (26) states that “personal and medical independence of the patient are encouraged by promoting self-care and involvement in medical decision-making early and consistently in developmentally appropriate ways”. A study of CF patients found that self-management was associated with readiness for transfer to adult care providers (27). Conversely, lack of personal responsibility for health has been cited as a barrier to successful transition (26). In a study examining predictors of outcome during transfer to adult services among 360 patients with congenital heart defects (CHDs), 47% of the sample had successfully completed a physical transfer to adult services (28). This study examined medical, psychosocial, and service-related predictors of successful transfer. Among the subsample of patients in this study who completed psychosocial questionnaires, using dental antibiotic prophylaxis, absence of

substance use, attending cardiac appointments without family members, and documented recommendations in their medical chart for follow-up in adult services were associated with successful transfer. Factors related to successful transfer therefore centered on assumption of health care responsibility, adherence to treatment recommendations, and appropriate preparation.

The consequences of unsuccessful transfer to the adult health care system may be dire. In diabetic patients (29), clinic attendance decreased from 94% before transfer to 57% after transfer, which may signal tenuous self-management. In transplant recipients (30), eight out of ten young adult patients experienced graft loss after transfer. In seven of these cases, this outcome was considered unexpected and was likely related to nonadherence. Our group examined retrospectively whether adherence and accompanying medical outcomes deteriorated in transferred patients (14). We compared 14 recently transitioned patients to two cohorts of patients receiving care solely in either a pediatric or adult-oriented clinic. Adherence significantly declined both after transfer and relative to the comparison groups. Furthermore, four patients in the transferred cohort died at some point after leaving pediatrics while there were no deaths at any point in the other cohorts. This disturbing finding of increased mortality post transfer has also been observed among recently transferred CHD patients (31).

In the face of such risk, efforts to improve transfer to adult care facilities seem to be warranted. Yet, research efforts are lacking in this important field. Given the complete absence of prospective, controlled studies to evaluate even the most basic strategies to improve health care management during transition, we are forced to suggest recommendations based on common sense and clinical – anecdotal – experience. We believe that this process must be addressed while patients are still receiving care in pediatric settings, to ensure that patients are able to manage their own care well before transfer. Our group has found significant knowledge deficits in a variety of areas related to self-care in pediatric transplant recipients transferring to adult care facilities (32). For example, we found that less than half of the young adults surveyed schedule their own appointments, understand their health insurance, and only 58% order their own medications. Overall less than 50% of the respondents stated that they manage their own health care. Those deficits can be corrected before moving to another service. In addition, we believe that collaboration with adult care providers is essential to ensure a smooth transfer. Ideally, preparing for transferring should include input from the adult team regarding what skills they feel are essential to success in their service, and will also include feedback post-transfer.

Conclusions

Since the immediate post-transfer period is an extremely vulnerable time, and nonadherence to medications is a major risk, we believe that patients' adherence status should be regularly monitored, especially during before and during the transition period. Psychosocial and other risks should be evaluated and addressed in advance of the transfer of care. "Transition programs" have been established and proposed in numerous medical centers. Yet we believe that firm evidence is needed as to the efficacy of such interventions – and about the efficacy of different components in such programs – before they are widely adopted. To guide the efficient use of resources, systematic research efforts are essential and very much in need in this area.

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