SHOULD WE RETRANSPLANT A PATIENT WHO IS NONADHERENT?

A LITERATURE REVIEW AND CRITICAL REFLECTION

Dobbels F, PhD [1,2]; Hames A, DClinPsy [2]; Aujoulat I, PhD [3];

Heaton N, FRCS [2]; Samyn M, MD [2]

1 Center for Health Services and Nursing Research, Katholieke Universiteit Leuven, Leuven, Belgium

2 Institute of Liver Studies, King's College Hospital, London, United Kingdom

3 Pediatric Liver Transplant Program, Université Catholique the Louvain, Woluwe, Belgium

Running title: review on retransplantation after nonadherence

Address for correspondence

Fabienne Dobbels, PhD

Center for Health Services and Nursing Research

Katholieke Universiteit Leuven

Kapucijnenvoer 35/4

B-3000 Leuven

Belgium

Tel: +32 16 33 69 81

Fax: +32 16 33 69 70

e-mail: fabienne.dobbels@med.kuleuven.be

ABSTRACT

The majority of transplant centers around the world face an ethical debate whether to retransplant a young nonadherent patient. Nonadherence to life-long immunosuppressants presents a significant risk for graft loss, yet rates remain consistently high. Despite a number of these patients presenting for retransplantation, there is little evidence to guide professionals in their decision-making. This paper aims to provide such guidance, by systematically reviewing the existing outcome data for retransplantation in patients who are known to be nonadherent to their immunosuppressants. This review searched for original papers which addressed retransplantation of a solid organ, and included quantitative data on adherence or graft function. Only one original research paper was found to meet the inclusion criteria. This paper is reviewed, and details of the protocol to determine eligibility for retransplantation are summarised. The findings are discussed within the ethical context that transplant professionals work within, and the arguments for and against retransplantation are considered. The need for effective integration of adherence management into routine practice is highlighted, with an emphasis on reliable measurement of adherence throughout the patient's life. Examples of good practice are discussed, favouring prevention over cure.

Key words: literature review, non-adherence, adolescence, re-transplantation

INTRODUCTION

Solid organ transplantation is a routinely performed treatment option for selected patients with end-stage organ disease. Yet, transplantation does not cure patients: While one year survival after transplantation is excellent and has continued to improve over the last decades, long-term survival did not increase dramatically over time [1-4]. Identifying pathways to improve long-term post-transplant outcomes now presents one of the major challenges for transplant professionals across the globe [1, 6].

An increasing number of studies show that clinical outcomes are to a large extent dependent on a patient's ability to adhere to the complex and life-long immunosuppressive regimen. A meta-analysis reports that about 22.6 out of 100 adult transplant patients per year fail to take their immunosuppressive medications correctly [7]. A similar meta-analysis in pediatric populations, only reported 6 cases per 100 patients per year of follow-up, yet studies with a higher methodological quality, that used measurement methods other than chart review, and who focused exclusively on adolescent populations found much higher prevalences [9]. Individual studies typically report prevalences of nonadherence in pediatric populations of about 15% to 25%,. Yet, adolescents typically are at highest risk, with more than 50% of patients failing to take their medication correctly [9-11].

The clinical consequence of nonadherence can no longer be ignored: It is estimated to be responsible for about 50% (range 20-73%) of all late acute rejections and 15% (range 3-36%) of all graft losses [9-13], with mortality in the long-term post-transplant being much

higher in adolescents compared to younger patients and adults [2, 3, 5]. An elegant study of Pinsky and colleagues (2009) including both pediatric and adult kidney transplant patients showed that the medical cost at 3 years post-transplant was 21 600 USD higher for a nonadherent patient compared to an adherent patient [14]. Graft failure might be an important driver of the inflated individual cost of nonadherence.

These impressive numbers imply that a significant proportion of both adult and pediatric patients who lose their graft because of nonadherence will present for retransplantation. Overall, between 3 and 11% of patients are listed for retransplantation annually [15, 16], although it remains unclear how many are relisted due to nonadherence. Likewise, it is also possible that many nonadherent are not referred for relisting, as transplant centers would not consider offering a second chance to patients who lost their graft because of nonadherence.

While the decision whether or not to relist patients who lost their graft due to technical problems, primary non-function or hyperacute rejection is relatively easy, the decision to retransplant nonadherent patients is less straightforward, given that nonadherence is not easy to detect. Transplant teams face the question of whether the patient will be able to change their behaviour and adhere to the stringent immunosuppressive regimen after retransplantation and keep the second graft healthy, given also that the immunologic response to the graft will be different. This paper aims to summarize the available evidence on adherence and clinical outcomes after retransplantation in pediatric and adult patients who lost their graft because of nonadherence to the immunosuppressive regimen

and to provide guidance on managing these patients. The results of this systematic literature review will be discussed in the light of the ethical challenges professionals face during their decision making process.

METHODOLOGY

Inclusion- and exclusion criteria:

Eligible papers for this systematic review had to fulfil the following inclusion criteria:
1) Papers should address patients undergoing retransplantation of a solid organ (heart, liver, lung, kidney, pancreas or intestine); 2) Papers should provide original quantitative data on adherence to the immunosuppressive medication after retransplantation of patients who lost their first graft because of nonadherence and 3) the paper is written in a language understood by a member of the research teams (i.e. English, Dutch, French, German, Italian). The reference list of eligible papers was scrutinized for additional references we might have missed when applying our search strategy. Papers were excluded if 1) only a case report was described without quantitative data on a cohort of patients; 2) no original data were provided (e.g. editorials or reflection papers); or 3) the results only described how many patients lost their organ because of nonadherence, without providing follow-up adherence or clinical follow-up data after retransplantation; or 4) papers who only describe survival or graft function after retransplantation, without reporting adherence rates after retransplantation or referring to the underlying reason for retransplantation.

Search strategy:

In concordance with systematic review methodology and the PRISMA guidelines [17], two authors independently reviewed the PUBMED database, from inception to April 1, 2011,

using the following search string: (retransplant* OR re-transplant* OR graft loss OR graft failure OR rejection) AND (patient noncompliance [MESH] OR noncomplian* OR non-complian* OR nonadheren* OR non-adheren*). A similar search string was used for the database CINAHL and PSYCHINFO.

Study selection:

In a first phase, all titles and abstracts were screened against inclusion and exclusion criteria. In the next phase, the full text of all abstracts deemed to be potentially relevant by at least one of the abstract reviewers were ordered and evaluated against inclusion and exclusion criteria again. Inconsistencies in decision making within this second phase were solved based on consensus between both reviewers.

Data extraction:

Information was extracted from each study on a) bibliographic details (author, journal, year of publication, and language) b) content of decision making process and c) results of retransplantation in view of adherence to the immunosuppressive regimen or graft function.

RESULTS

Figure 1 depicts the results of the search strategy. After title and abstract screening, the full-texts of 27 abstracts were evaluated against inclusion and exclusion criteria, identifying 3 original research papers investigating nonadherence to the immunosuppressive regimen in patients who underwent a retransplant [18-20]. Two papers were published in 1995 by Troppmann and colleagues, but refer to the same study [18, 19], and the study published in 2009 by Dunn and colleagues reports on a larger sample and follow-up data of this initial cohort of patients, leaving us with only one paper to answer our research question [20].

The authors identified 114 kidney transplant patients (3.3% of all graft losses; of which 33 in late adolescence or young adulthood) who admitted they lost their graft because of nonadherence to their immunosuppressive medication and who underwent a mandatory protocol to determine their eligibility for retransplantation, i.e:

1) a discussion between the candidate and the medical staff about nonadherence and strategies to prevent nonadherence after retransplantation
2) an evaluation by allied health professionals to further investigate potential barriers to adherence
3) Proof of full adherence to the current medical regimen, removal of all risk-factors having contributed to previous nonadherence, and completion of all recommendations made by the allied health team

Figure 2 presents the results of the screening process, showcasing the following interesting observations:

1) Only 75/114 patients decided to follow the protocol (65.8%), of which only 48 (64%) met the eligibility criteria for retransplantation (i.e. 42% of all patients who lost their graft due to overt nonadherence).

2) Seven out of 27 (25.9%) who did not qualify for retransplantation and 9 out of 39 (23%) patients who decided not to pursue with the Minnesota protocol, managed to be listed for retransplantation elsewhere.

3) Of the 35 patients who underwent retransplantation for nonadherence at the University of Minnesota, chart review showed repeated nonadherence in 20 (57%) patients, compared to 43% of the 14 previously nonadherent patients retransplanted elsewhere. Pediatric patients showed a lower rate of repeated nonadherence compared to adults (38% versus 55.3%, respectively).

4) At 5 years follow-up, patients retransplanted for nonadherence had a significantly worse actuarial rejection free survival compared to patients retransplanted for other reasons (N= 552) (i.e. 49% vs. 59.7%) and a tendency towards decreased death-centered graft survival (75.4% vs. 78%) and chronic rejection free graft survival (64.1% vs. 74.2%).

DISCUSSION

With only one paper having been published, the evidence base to judge whether patients losing their graft because of nonadherence to the immunosuppressive regimen should be retransplanted is hard to answer. The cohort study of the University of Minnesota [20] generated the following key messages: 1) recurrence of nonadherence is prevalent despite having implemented a screening protocol; and 2) clinical outcomes are poorer in those being retransplanted for overt nonadherence compared to patients undergoing retransplantation for other reasons.

This study leaves us with several questions: One could argue that everybody deserves a new chance in life, yet at the same time this is not possible, forcing us to find ways to identify those patients who have maximum chances with a second graft. Despite using a standardized screening protocol prior to relisting, it is not clear, however, from the above-mentioned study which long-term follow-up interventions were in place to support patients' adherence in the long term after retransplantation. The protocol stresses that all risk factors resulting in nonadherence should be modified before one is eligible for relisting, yet, one might wonder whether this is feasible in patients who did not undergo kidney transplantation, for whom life-saving options like dialysis are not available and hence might not leave much time for remediation. On the other hand, this might not be a valid argument: While patients with an emergency need for retransplantation are typically those with primary graft failure or hyperacute rejection, the consequences of nonadherence such as late acute rejection or chronic rejection often play out more slowly

over time, leaving sufficient time to conduct a thorough assessment determining eligibility for a retransplant.

Also, a large portion of patients (i.e. about 35%) decided not to engage in the screening process, but were relisted or underwent retransplantation at another center. The reasons why they declined screening at their own transplant center and went to a different center remain known. It is likely that some patients will hop from center to center, until one is willing to admit them to their waiting list. However, other transplant centers would easily be able to determine that the person had already received a transplant. It is unlikely that the new center would at least not ask patients where they received their transplant and why they don't want to be considered for retransplantation at their original center. Even if the patient is not disclosing their past nonadherent behavior, the medical charts requested from the original transplant center will most likely contain information on the reason of graft failure.

To our knowledge, no guidelines have been published on whether or not to retransplant nonadherent patients. The absence of objective guidelines on retransplantation that ideally are followed at each and every transplant center in a consistent manner contribute to this worrisome phenomenon. This is not unique to retransplantation, as large differences exist between centers in the degree of risk they are willing to take in performing transplants in patients with medical or psychosocial co-morbidities, including nonadherence. Moreover, organ availability in specific countries might also influence whether patients are relisted or not. Admittedly, outcomes were similar among patients transplanted in Minnesota and elsewhere, questioning whether availability of mandatory

screening protocols would have a huge impact on improving retransplantation outcomes. Even with a rigorous protocol in place, outcomes were still worse in patients retransplanted for nonadherence compared to those retransplanted for other reasons.

With this limited evidence in mind, then what rational or ethical arguments do we have to decide whether or not to retransplant a nonadherent patient? Table 1 lists the most prevailing arguments in favor of or against retransplantation [21-36], and shows that many of these arguments come down to a conflict between an obligation to an individual and an obligation to an entire group of patients.

Arguments against retransplanting nonadherent patients

Irrespective of organ type or underlying reason for primary graft failure, international registry reports have clearly demonstrated that patient and graft survival is inferior in both adults and pediatric patients undergoing retransplantation compared to outcomes after primary transplantation [22-25]. The study of Dunn and colleagues showed that outcomes after retransplantation were also poorer in those transplanted for prior nonadherence [20]. In addition, more than half of the patients show recurrent nonadherence, even after establishing a pattern of adherence long enough to meet the requirements of their screening protocol. Theoretical models to explain health behavior likewise show that past behavior, in our case adherence to the immunosuppressive medication, is a very powerful predictor of future nonadherence [26, 27]. Presumed failure to take individual responsibility for maintaining good graft function could hence be used as a reason to

deny further access to transplantation. Indeed, in a time of worsening donor organ shortage and expanding waiting lists, many transplant centers are concerned not to waste another organ for somebody who might not be able to take care of it [21, 28]. Within this context, the principle of utilitarism that focuses on the greatest amount of good for the largest number of people could ethically justify why patients with graft failure are not relisted for transplantation [29-30]. Along the same lines, retransplantation would conflict with the principle of distributional justice: This assumes fairness and equal treatment of every patient and might imply, especially in times of organ scarcity, that once a patient has received a transplant, he or she is no longer in contention for another organ and priority is given to those on the waiting list for a first transplant.

Arguments in favor of retransplanting a nonadherent patient

Despite outcomes after retransplantation in general being poorer than after a first transplant, more recent studies show that satisfactory outcomes are nevertheless possible in well-selected patients [25, 31]. For kidney transplant patients, retransplantation might also be more cost-effective and yield better outcomes than dialysis [32]. Moreover, while about half of the patients in the study of Dunn and colleagues showed recurrent nonadherence post-retransplantation, the other half proved capable of changing their medication taking behavior [20]. Similarly, existing theoretical models on behavior change and empirical evidence show that adherence to medication is possible, with a positive impact on clinical outcomes as well [33, 34]. Admittedly, intervention studies in transplantation specifically [35], and in chronic illness populations in general [33] are limited and often of a poor

methodological quality, but, if well-designed, are able to improve patients self-management with regard to medication taking. Intervention studies all start from the common premise that nonadherence can be treated like any other illness or problematic behavior, and that patients can learn from their past mistakes by taking up responsibility for their future life. This attitude mirrors the issues surrounding access to liver transplantation for patients with alcoholic-related end-stage liver disease who are eligible for transplantation after a thorough psychosocial screening: a large group of patients remain abstinent after transplantation and have good clinical outcomes relative to other indications for liver transplantation [36]. This might also be true for patients losing their grafts during adolescence or young adulthood, who might become more responsible for their self-management as they grow older. Interestingly, nonadherence in the study of Dunn and colleagues in those being initially transplanted in adolescence was lower after retransplantation compared to adults [20]. It is commonly accepted that biological, psychological, social and developmental processes contribute to the inflated risk for nonadherence in young patients, yet, their tendency for risk taking behavior seems to disappear when growing up.

From an ethical point of view, withholding a retransplant might equal withdrawing care. Given that the patient will die without a retransplant (maybe with the exception of kidney patients who have dialysis as a life-saving option), this might clash with the ethical principles of benevolence and nonmaleficence, and hence the obligation towards maximizing an individual's well-being primes above the problem of organ shortage at a society level [21, 30]. Finally, one might not forget that the patient included in the cohort

study of Dunn and colleagues all admitted to be nonadherence (i.e. overt nonadherence) [20]. Moreover, only 3.3% of the graft losses where attributed to nonadherence, which is a much lower prevalence compared to the 15-35% rates reported elsewhere [9-11]. Given that it is hard to predict who is adherent or not, and that nonadherence is often a covert phenomenon, it is questionable whether these patients could be "punished" for being honest with the transplant team. If the chance of receiving a retransplant is at stake, non-disclosure of adherence problems will become even more prevalent, and should be understood as an act of self-protection when facing death at the time of graft failure. It is also worthwhile mentioning that outcomes in those who avoided the selection protocol in the study of Dunn and colleagues and were transplanted elsewhere had similar outcomes than the patients screened and transplanted in Minnesota.

Moving forward

While each of the above arguments undoubtedly has value, they exclusively focus on "fixing" problems when the initial transplant fails, leaving preventive strategies entirely out of the pro-con debate. Recent policy reports and practice guidelines [37-39], however, recommend that adherence management should become an integral part of chronic illness management. Unfortunately, we are not good at detecting nonadherence, with problematic behaviors remaining unnoticed until serious clinical consequences become apparent. In contrast to current (transplant) healthcare systems that are mainly medically oriented, focusing predominantly on fixing acute health problems, clinical practice should hence be redesigned towards a chronic care model that treats transplantation as a chronic

condition and strives towards delivering excellent self-management support to patients in view of immunosuppressive medication taking. A growing body of evidence in asthma, diabetes and rheumatoid arthritis shows that care models incorporating self-management support show superior outcomes compared to those lacking such outcomes [40]. A limited number of intervention studies also found a positive effect on adherence and self-management in transplant populations [35, 41, 42]. It is therefore highly likely, yet to be further proven, that supporting patients in becoming active and knowledgeable partners in managing their transplantation might result in enhanced post-transplant treatment outcomes. If successful, this approach might be a much sought after solution to the problem of suboptimal clinical outcomes in the long-term after transplantation.

So, how can this system change be realized? Given that medication adherence might fluctuate over time, and that even the most adherent patients miss doses over time, as shown by the study of Nevins and colleagues [43], it becomes abundantly clear that medication adherence should be monitored regularly during life-long follow-up. Interestingly, we learned that many adolescent patients are unaware of their problematic behaviour and are convinced they are perfectly adherent [44]. Other patients experiencing rejections or graft loss might be accused of nonadherence, while there biological vulnerability for poor outcomes has nothing to do with improper medication taking behaviour. Ideally, every patient should be considered at risk for nonadherence, until the contrary is proven [45]. Adherence management therefore necessitates regularly measuring adherence, ideally starting prior to transplantation, in combination with transplant professionals who are committed to exploring the reasons behind a patient's problematic

behaviour, and implementing tailored interventions to address the underlying causes from pre-transplant onwards. Two recent systematic reviews and the Transplant360 website might provide guidance on how medication and its barriers can be assessed in a validated, comprehensive way in the reality of busy outpatient clinics [46-48].

At the same time, blaming the patient for losing their graft because of nonadherence is easy if the healthcare system is not equipped to offer patients adequate support to self-manage their chronic condition. As a starting point, professionals need to be trained in adherence assessment and management. A systematic review across diverse chronic illness populations showed that training the communication skills of professionals specifically targeting on adherence management resulted in significantly higher adherence rates [49]. No studies have looked at communication skills of transplant nurses and professionals in relation to adherence and self-management; and whether improving their adherence management skills improves transplant patients adherence, presenting certainly an avenue for additional research with a huge spin-off for clinical practice.

To conclude, it is time for a paradigm shift from cure to prevention, with "*measurement being the first step that leads to control and eventually to improvement. If you can't measure something, so you can't understand it. If you can't understand it, you can't control it. If you can't control it, you can't improve it*" [James Harrington [50]].

Contribution of authors:

All authors contributed significantly to this manuscript:

Fabienne Dobbels: Design of the review, data analysis and interpretation, drafting the manuscript

Anna Hames: data analysis and interpretation, critical revision of the manuscript

Isabelle Aujoulat: data interpretation, critical revision of the manuscript

Nigel Heaton: data interpretation and critical revision of the manuscript

Marianne Samyn: data analysis and interpretation, critical revision of the manuscript.

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Figure 1: flow chart with the results of the search strategy

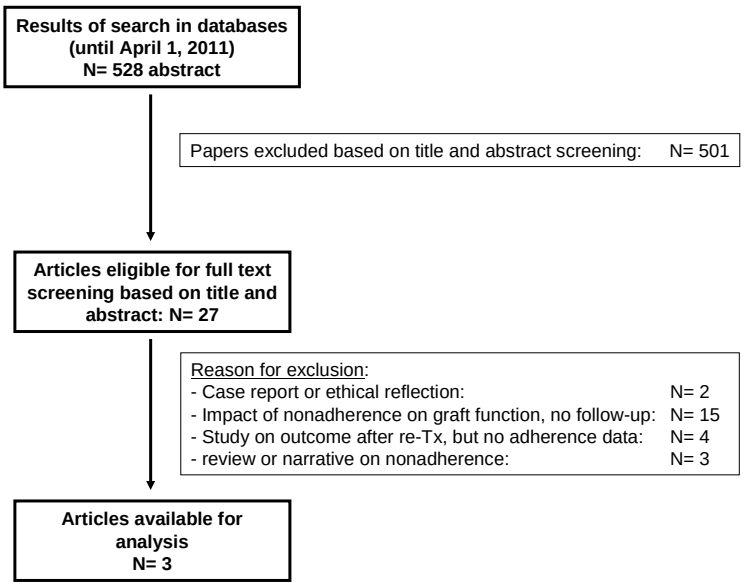
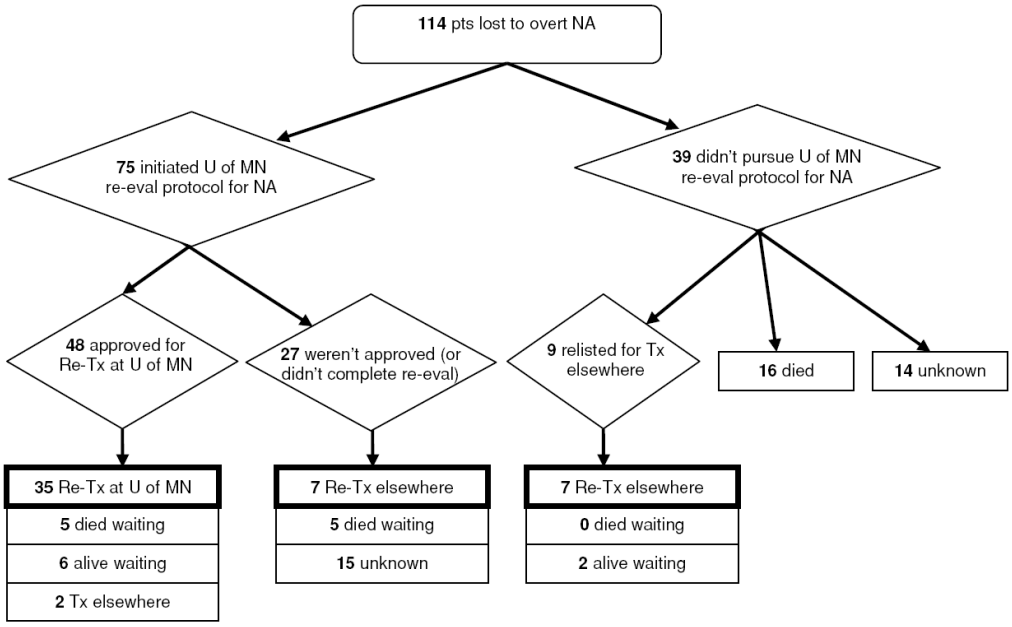


Figure 2: Results of the screening process of candidates for retransplantation due to nonadherence in the study of Dunn and colleagues [15] (figure on page 1340 copied with permission of the editor)



* NA= nonadherence; U of MN= University of Minesota; re-eval= re-evaluation; Tx= transplantation

Table 1: arguments in favour and against retransplantation in nonadherent patients

Arguments against retransplantation
- Organ scarcity: patients on the waiting list could be disadvantaged [21, 29, 30]
- Outcomes after re-Tx are inferior compared to outcomes after primary Tx [22-25]
- Principle of justice and utilitarism in patient care [29, 30]
- Past (nonadherent) behaviour is a predictor of future (nonadherent) behaviour [26, 27]
Arguments in favour of retransplantation
- Retransplant in kidney Tx more cost-effective and better outcomes than dialysis [25, 31, 32]
- Principles of nonmaleficence and benevolence in patient care [21, 28-30]
- Patients admitting to be nonadherent cannot be punished for their honesty [37]
- Evidence shows that behavioral change is possible [33-36]