Published in final edited form as:

Pediatr Transplant. 2015 June ; 19(4): 348–350. doi:10.1111/petr.12484.

Editorial: Longitudinal Stability of Medication Adherence: trying to decipher an important construct

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In this issue, Loiselle et al. (1) address an important construct that surprisingly has not been adequately investigated in the transplant literature—namely, the degree to which adherence to immunosuppression is a stable or a “shifting” phenomenon. The answer to this question holds some important implications for the field of transplantation. Those important implications include, as the authors highlight, that adherence is important in terms of disease and financial burden; we would like to add another important implication of this construct: whether adherence is a stable phenomenon or not might also have implications with regards to the decision to allow or not allow retransplantation in a nonadherent patient. If nonadherence is stable, then hoping that these behaviors improve might be futile, and therefore re-transplantation should not be offered; if unstable, then nonadherence should be presumed to be modifiable and not be used to determine transplant eligibility.

The authors found that the average rate of adherence in their sample did not change over time. However, individual patient adherence varied substantially—there were many patients whose adherence category shifted during the study period. The interpretation of this finding, if proven to be robust, is that patient-level decisions regarding adherence should assume that it is a shifting (unstable) phenomenon: past adherence is not a good indicator of future adherence. On the other hand, since on average the rate of nonadherence remains the same in an entire clinic population (different patients become more or less adherent, but the average remains the same), resource allocation decisions in entire clinics or programs should assume a stable need for resources to address this risk over time.

While the results are interesting and might prove to be correct, this study also illustrates the enormous challenges that are encountered when one tries to study the phenomenon of adherence in transplantation medicine. Those challenges can be summarized as issues of

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No conflict of interest.

inadequate sample size, selection bias, failure to pre-define a single primary hypothesis, measurement difficulties, and over-statement of clinical implications.

A small sample size with selection bias is the rule, rather than the exception, in studies that purport to investigate adherence in pediatric transplantation (2). First, it is extremely difficult to achieve an adequate sample size in this population unless a large number of centers are involved. Second, in any population, it is difficult to recruit nonadherent patients for a study, let alone follow them up (3), because the same patients who are unable to take their medications consistently are also less likely to come to clinic, less likely to participate in a study, and less likely to have adequate data follow-up. The resulting bias favors adherent patients as participants. The combination of a small (inadequately powered) sample size and a substantial selection bias leads to a high likelihood of spurious results.

The transplant field, fortunately, has recognized the issue of sample size limitations and created mechanisms to study phenomena related to behavioral constructs, such as nonadherence, within established consortia such as CTOT-C (4), SPLIT (5), and one smaller consortium (6) that is entirely dedicated to the study of adherence (MALT). Within those consortia, the promise of an adequate sample size can be realized. Manuscripts such as the one in this issue can be viewed as indicators of potentially important topics that can be taken up for further study in a multi-site trial. The problem of selection bias can be addressed in several ways, and again the transplant field is well positioned to minimize, or at least monitor, this issue. First, steps need to be taken to minimize patient burden and ensure adequate sampling methods. Second, a CONSORT-type diagram with CONSORT-type statements (7) of the discrepancy between patients who did and did not participate in this study must be provided in adequately powered studies, and any substantial differences should be discussed. Third, a comparison between the general outcomes in the study sample (e.g., rejection rates per patient year) with outcomes reported to data repositories such as the United Network for Organ Sharing (UNOS) or SPLIT can provide additional insight regarding whether the sample was representative, at least as far as rejection rates or other reported outcomes are concerned. This study provided none of those assurances; however, such rigor should not be expected and would be difficult to achieve in pilot studies or underpowered investigations. Rather, readers should assume that substantial selection bias is inevitable, and results in under-representation of severely nonadherent patients, in pilot and underpowered prospective investigations. Selection bias can be mitigated by a retrospective design in some circumstances, which means that sometimes results from retrospective studies are more powerful and generalizable than results from prospective studies in adherence research (2).

A failure to pre-define a single primary hypothesis is a common feature of pilot studies. Failure to register trials on sites such as clinicaltrials.gov or failure to specify a primary hypothesis, even if registered, result in a situation in which data are mined for results rather than used to establish (or refute) a fact. In this situation, the meaning of statistical tests is questionable, as our conventional reliance on a “p” value of 0.05 for significance is predicated on the existence of a pre-specified primary hypothesis. For unregistered studies that do not pre-specify a single primary hypothesis, study results should be considered exploratory rather than conclusive.

The issue of a lack of “gold standard” for measuring adherence has been previously reviewed (8) and is presented in the current manuscript as well. We caution against the tendency to assume (without supporting evidence) that multiple measures should be used to gain a more complete picture of adherence. For example, subjective measures (e.g. self-report) are considered to be low-quality measures of adherence in the broad literature of adherence research, while objective measures such as medication blood levels are considered to be higher quality (9). It is unlikely that coupling a high-quality measure with a low-quality measure will result in an aggregate measure that is superior to the high-quality measure when used alone. This is especially true if self-report vs. objective measures do not correlate with each other (as reported in the present study and others). Unless combined measures are decisively shown to be superior, the interpretation of the broad literature seems to be quite the opposite of the authors’ opinion (that combined measures are preferred). Combining multiple measures of varying levels of quality is time consuming and is not preferred – in our view, the “default” assumption should be that a single robust measurement technique (preferably, objective rather than subjective) is preferred (10).

Finally, the fact unfortunately remains that not even one randomized controlled trial has ever shown that it is possible to improve post-transplant outcomes by addressing nonadherence, and one robust trial in adults showed no improvement in medical outcomes (11). In that trial, adherence was improved, but the investigators recruited primarily patients who were highly adherent at baseline. Therefore, presumably, a marginal improvement in their already excellent adherence did not translate into improved medical outcomes. It is extremely difficult to engage seriously nonadherent patients in research for obvious reasons, and thus if they are not targeted specifically, studies tend to exclude them (2,3). Because no study has ever shown that it is possible to improve transplant outcomes by addressing adherence, it is premature to recommend that adherence be measured routinely, let alone targeted, in clinical practice: why measure it if it has never been proven that it can inform any successful intervention strategy?

In sum, the manuscript by Loiselle et al. is addressing an important topic. It should be read as a call to conduct rigorous trials that shed light on the longitudinal trajectory of adherence behavior in transplanted children. The transplant field, with its robust outcome measures that are reported to national repositories, highly successful and collaborative consortia, and invested interest in the topic, is well poised to answer some of the most intriguing questions raised in the current manuscript. It is time to take the study of adherence into the rigorous and exciting realm of well-powered multi-site clinical trials that would be able to decisively refute or prove rigorous, single, pre-specified hypotheses about the trajectory of nonadherence behavior and ways to address it. We hope that the authors of the manuscript, as well as the readers, see the manuscript in this issue as a first, and not the last, step in this direction.

Acknowledgments

Supported by NIH/NIDDK award # R01DK080740 (ES)

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