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IMPROVING MEDICATION ADHERENCE: THE PROOF OF THE PUDDING WILL BE IN THE EATING

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Editorial for Liver Transplantation on "Shemesh et al. Trajectory of adherence behavior in pediatric and adolescent liver transplant recipients – the MALT cohort. Liver Transplantation 2017, e-pub ahead of print.

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Shemesh and colleagues conducted a unique prospective multi-site study, following the medication adherence behavior of 400 pediatric and adolescent liver transplant recipients who were on average 6.8 years post-transplant (range 1-17.4 years). In their paper, included in this Journal's issue, the authors investigated trajectories in adherence to tacrolimus from year 1 to year 2 of the MALT study data collection, with a Medication Level Variability Index (MLVI) of > 2 signaling nonadherence [1]. We can distill at least three important messages from their analyses. First, 24.5% of the participants were nonadherent in the first year and 28.5% in the second year of observation, suggesting that, at population level, nonadherence tends to increase over time. Second, the authors demonstrated that nonadherence is not a stable behavior, as about one in four non-adult liver transplant patients ($N=70/294$; 23.8%) switched their medication behavior, going from being adherent to nonadherent ($N=41/294$; 13.9%), or slightly less frequently the other way around ($N=29/294$; 9.9%). Third, the odds of being nonadherent in the second year were 6.5 times higher for patients being nonadherent already in the first year of the study, and these patients were also at the highest risk for developing a late acute rejection.

These observations largely confirm existing evidence. Other prospective studies, admittedly predominantly in the field of adult transplantation, likewise showed that adherence behavior might fluctuate over time. Using electronic monitoring as a continuous and sensitive measure of medication nonadherence, the group of Nevins and colleagues for instance showed that even kidney transplant patients with the highest medication adherence immediately post-transplant occasionally missed doses over time [2]. Moreover, other studies demonstrated that adherence seems to worsen with longer post-transplant time. The Swiss Transplant Cohort study, enrolling 1505 adult solid organ transplant patients, observed a continuous increase in immunosuppressive medication from 6 months to 3 years posttransplant [3]. Unfortunately, the MALT study included patients with a widely ranging post-transplant status. Hence, the authors could not ascertain the impact of post-transplant time on adherence trajectories. Finally, several research groups already demonstrated the detrimental impact of medication nonadherence on post-transplant clinical outcomes [4]. The dose-response association

between nonadherence and late acute rejections, discovered in the MALT study, certainly further contributes to this evidence base, particularly in the field of pediatric transplantation. The authors subsequently conclude eloquently that *"...nonadherence is likely to persist in the absence of interventions, and that monitoring of adherence and interventions to improve it should be expected to last for years if transplant outcomes are to be improved."*

We cannot concur more with this conclusion and almost every adherence paper in transplantation iterates the same message over and over again. The problem, however, is that this plea for a better adherence management in post-transplant long-term care does not seem to spin off in actual changes in practice patterns. Indeed, after the initial recovery period, most transplant programs continue to see their patients only occasionally at their outpatient transplant clinics, e.g. every 6 months or even once a year. These contacts are often short, mainly concentrate on running some blood work and medical examinations, and routine screening for behavioral or psychological problems seldom take place. These practice patterns presumably prevail at the eight centers participating in the MALT study also. More specifically, the authors indicate that most of the study centers have a social worker or psychologist, suggesting the availability of interdisciplinary care, but the authors do not describe whether these disciplines are also fully embedded in long-term care. The high nonadherence rates reported in their paper make us believe this is not the case. In addition, some transplant centers prefer not to seeing all patients at their outpatient clinic anymore, but refer them to specialists closer to the patients' homes. These physicians might only see a handful patients with a transplant within their practice, and might lack the expertise or resources to deal with adherence problems. Hence, in general, post-transplant follow-up is rather scattered and currently has predominantly a uni-disciplinary medical focus.

We therefore argue that transplantation needs to be managed like any other chronic condition, and that changes in transplant patients' adherence behavior will not happen overnight without reengineering the way we deliver care in the long-term post-transplant. Congruent with the definition

of a chronic disease [5], transplantation is a condition that persists over time, and although people can live relatively long with a transplant and resume day-to-day activities, their condition eventually will slowly deteriorate. Indeed, despite some transplant professionals believing otherwise, transplantation does not cure people. Lifelong medication intake and monitoring of graft function is needed, and onset of co-morbidities, such as hypertension, diabetes, cancer or hyperlipidemia, for instance, will further contribute to the burden of chronic illness over time. Moreover, as has also been demonstrated in the MALT study and by others, medication nonadherence elevates the risk of late acute rejection, and increasing evidence likewise shows that other behavioral (e.g. smoking) and psychosocial factors (e.g. depression) negatively impact graft and patient survival as well [6,7]. In congruence with the building blocks of the chronic care model, the goal of chronic illness management is therefore to ensure continuity and coordination of care and makes sure adherence support is structurally embedded in the long-term follow-up. Within such an approach, medical and allied health professionals, both within the transplant center and the community, closely work together with patients as active partners in their care, so that medical, adherence or lifestyle problems or psychosocial issues can be proactively managed.

Convincing evidence from other chronically ill populations like heart failure or diabetes shows that better chronic illness management spins off in improved clinical outcomes [8]. Likewise, two kidney transplant programs found a better adherence, fewer emergency visits and hospital readmissions in patients exposed to a transplant follow-up model based on the principles of chronic illness management [9,10]. We are therefore convinced that implementing a chronic illness management model within the field of solid organ transplantation, of which adherence support is an integral part, provides a fertile soil to reduce the number of graft losses and premature deaths over time.

So, what can be changed and how? In congruence with the recently published practice recommendations of the COMMIT group [11], medication nonadherence needs to be routinely and systematically assessed as what they call the “fifth vital sign”. The MLVI used in the MALT study is a

relatively easy method to do so. Yet, because this index can be calculated for tacrolimus only and given that at least three tacrolimus blood levels are needed to be able to calculate the index, we suggest supplementing this method by validated self-report tools, alongside any other indicators of poor adherence.

Regular assessment of adherence should furthermore go hand in hand with the monitoring of risk factors, so that nonadherence can be predicted and prevented, rather than to be remediated. Instead of selecting factors on an ad hoc basis, a theory-based approach is favored in order to select those factors that matter most. The Integrative Model of Behavior Prediction, for example, states that intention is the most important driver of behavior, yet poor knowledge and skills and the presence of barriers (defined as personal or environmental constraints hindering correct medication intake), might prevent patients from acting upon their intentions. Hence, measuring ones motivation, knowledge and medication skills, and barriers might be an excellent starting point in this regard. The COMMIT group presents a list of relatively short questionnaires to measure some of these risk factors.

By regularly screening patients' adherence behavior and risk factors at regular time intervals, risk stratification will become possible, so that professionals can offer tailored adherence interventions to patients needing them the most. The results of our MAESTRO-Tx study [12], alongside the efficacy of other recently published trials, makes us feel confident that nonadherence can be successfully remediated and that this likely will also improve long-term clinical outcomes.

Such an approach necessitates a multidisciplinary team, as we found that interdisciplinarity was associated with higher levels of chronic illness management in heart transplant centers [13]. These teams should also work together with professionals or services based in the community to ensure continuity and coordination of care. Moreover, training of staff members is essential, given that the current educational curricula of most healthcare professionals still do not incorporate many opportunities of skills development in adherence interventions. Training transplant teams in motivational interviewing might be a valuable first step in learning how to motivate people and engage

patients as active partners in their care. In addition, using eHealth offers multiple opportunities to monitor and support adherence within transplant program's routine care, and, if well developed and accepted by all relevant stakeholders, might help easing concerns about a lack of time, staffing or resources.

Yet, we realize that implementing such a care model is challenging and that centers cannot immediately "transplant" the ideal care model from paper to practice directly. We therefore believe the time is ripe for implementation science as the next generation of research in order to bring the much-needed innovation within solid organ transplantation. Implementation science is defined as "*the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices in routine practice, and hence, to improve the quality and effectiveness of health services*" [14].

We hope we convinced transplant professionals that structurally embedding adherence support in a follow-up model that is based on the principles of chronic illness management will bring the innovation needed to improve long-term outcomes. Hence, think "delivery system redesign" and start acting. The proof of the pudding will be in the eating!

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