Adherence to Medication in Children With Liver Disease in India, the First Report – Every Journey Starts With a First Step!☆

Medical treatment of paediatric liver diseases has seen major advances in the past few decades leading to improved survival. Effective pharmacological agents are available for common disorders such as Wilson disease (WD), autoimmune liver disease (AILD), and some rare metabolic disorders (eg: bile acid synthetic disorder) that can obviate the need for liver transplantation (LT) in a considerable number of patients while immunosuppression after LT is the main stay of allograft survival. Post-transplantation immunosuppressive regimens ensure 1-, 5-, and 10-year recipient survival rates of 93.4%, 90.2%, and 87.5% respectively.[1] The outcomes largely depend on the adherence of the patient and the family to the therapeutic regimen agreed with their physician. Non-adherence (NA) could pertain to clinic and laboratory visits, pharmaceutical agents, dietary modifications or lifestyle changes. The role of medication non-adherence (MNA) in allograft rejection and mortality in children after transplantation is well recognised.[2] Studies in children from the western hemisphere have used various tools to identify NA in chronically ill children and in the post-transplantation scenario.[3,4] Suchismita *et al.* have addressed the paucity of information on MNA in children with liver disease from Northern India.[5] It may be assumed that differences in socio-economic and cultural variables between countries result in variations in the patterns and contributors of MNA and hence the need for the study. They define the frequency of MNA by interviewer-administered medication adherence measure (MAM) with a 4-week recall and identify barriers to adherence using the Child & Adolescent Adherence to Medication Questionnaire (CAAMQ) in patients with WD, AILD and recipients of LT.[6,7] The study is relevant to (i) define the magnitude of the problem of NA in the patient cohort, (ii) identify at-risk patients early based on known risk factors for NA and (iii) evaluate the effect of interventions directed towards improving adherence in the Indian subcontinent.

The tools used to assess MNA in children may be objective measures such as medication event monitoring systems, medication possession ratio and drug assays. Non-objective measures include questionnaires/interviews, opinions of nurses and doctors, retrospective chart review and validated questionnaires such as MAM. A combination of MAM and drug assays with balanced scores (multidimensional adherence classification system) has also been used.[3] It is well recognised that methodologic differences between studies are a likely contributor to the mixed findings of prevalence and risk factors.[8] A closer look at the study design of Suchismita *et al.*, provides an opportunity to better understand the methodologies while investigating NA. A cut-off of 20% has been used by the authors to define adherence and the categorisation is used in analysing the data. This approach may be controversial for various reasons. Firstly, the 20% cut-off is based on studies on anti-hypertensive medications, anti-diabetic medications, psychoactive medications, and anti-lipidemic medications. A similar validation was not possible in congestive cardiac failure. There is no data to suggest that this cut-off optimally predicts therapeutic failure, higher hospitalisation rates in the disorders studies by the authors, either in adults or children. Among paediatric recipients of renal allografts, a medication possession ratio (MPR) of less than 92% identified by categorising MPR into quartiles has been shown to be associated with higher rates of graft failure.[9] Such a cut-off is likely to vary depending on the severity/phase of liver disease, the time after transplantation and individual immunological propensity for rejection post-transplantation. It may be argued that 80% adherence to post-transplantation medications detected by MAM may be too low, especially in the early phase after transplantation, even for an immunologically tolerant organ such as the liver. Higher degrees of non-compliance may be tolerated many years after transplantation in an immunotolerant patient. Hence a uniform categorisation of NA for all patients lacks biological rationale. Such cut-offs are more relevant in the context of variations in drug levels. Cut-offs have been defined for standard deviation of tacrolimus levels to identify non-adherent paediatric liver transplant recipients at risk for biopsy-proven rejection.[10] Secondly, in the absence of a biological rationale, statistical analysis of a continuous variable as a dichotomised variable reduces the power of analysis and often leads to substantial loss of information. Any future attempt to accurately risk-assess patients for NA on a spectrum based on previously identified barriers might be impaired by placing patients into categories.

Abbreviations: WD: Wilson disease; AILD: autoimmune liver disease; LT: liver transplantation; MNA: Medication non-adherence; NA: Non-adherence; MAM: Medication adherence measure; CAAMQ: Child & Adolescent Adherence to Medication Questionnaire; MPR: Medication possession ratio

☆This article has not been published elsewhere in any language and it is not currently under consideration for publication elsewhere.

https://doi.org/10.1016/j.jceh.2022.11.015

MAM was developed as a self-reported questionnaire in the English language with a 7-day recall.[6] In the study by Suchismita *et al.*, MAM was administered by an interviewer who was one of the treating physicians (authors), in the vernacular with a 4-week recall. Often, using a tool outside the parameters within which it has been validated may lead to unreliable results. The longer duration of recall used in the author's study could incorporate a higher degree of recall bias in their evaluation which was not a factor in the original validation of the tool.[6] There are advantages and disadvantages to both self-reported and interviewer-administered questionnaires.[11] Interviewer-administered questionnaires suffer from social desirability bias introduced by the patients and the bias of the interviewer, especially in the context of treating physicians who are known to overestimate the adherence of their patients.[12,13] The demonstration of agreement between the responses of the patient and their parent does not negate the possibility of an interviewer bias. The disadvantages of self-reported questionnaires includes its non-applicability in illiterate patients and those with learning disabilities. Although the data on literacy and learning disorders are not evident from the study results, a proportion without formal education reported by the authors may have been illiterate. The authors' judgement favouring an interviewer-administered questionnaire may be appropriate in such a context but is ideally done with a cross-culturally validated questionnaire in the vernacular, validated in an interviewer-administered format, administered by a non-physician.[14,15] In the future, cross-cultural validations of questionnaires in Indian languages or validation of new questionnaires in the Indian context could set the stage for reliable data on effective interventions against MNA.

The authors used the CAAMQ questionnaire to assess the barriers to adherence, thoughts and emotions towards taking medications and suggestions from patients to improve adherence. It is important to note that data on barriers and adherence is available from both parents and the patients in the older age group. Such detailed data on barriers is likely to provide a direction to tailored interventions in their cohort. Interventions towards improving adherence have included mobile applications, use of pillboxes, drug minimisation, use of appropriate formulations, enhanced counselling, education, psycho-social support, phone calls, home visits, etc. The bad taste of medications seems to be a major determinant of MNA in the authors' experience. It may be worthwhile to revisit the nature of formulations available to these patients. Often crushed tablets are used in scenarios where age-appropriate liquid or dissolvable granular preparations are not available in the market. Highlighting these issues and advocacy from physicians could bring change. Services to help children swallow tablets would remedy the burden of reconstitution/administration for parents, decrease costs, address the issue of bad taste as a barrier as alluded to by the authors and hence possibly improve adherence.[16] Drug minimisation by revisiting the therapeutic regimens constantly could be helpful.[17] For example, once daily medications of Tacrolimus are used in older children who are on follow-up long after their transplantation. Also, the use of Zinc in WD is more relevant in young genetically proven cases who have no manifestations of the disease and in those with neurological disease who show worsening with chelators. Their use in combination with chelators has not been shown to improve efficacy, increase the number of medications, and often leads to an unmanageable and hence sub-optimal regimen as chelators, zinc, and food intake have to be spaced from each other.[18] The use of Zinc in such cases is restricted to those with demonstrable Zinc deficiency. Poor health-related quality of life scores in AILD is related to steroid doses used. Steroid minimisation should be targeted and may be beneficial in improving adherence in addition to reducing the side effects of steroids.

The attitude and behaviour of the patient and family towards medications are influenced by numerous psychosocial aspects. The data presented by the authors indicates living donor transplantation rate of 97.6% which is likely to be associated with the high rates of adherence reported by the authors in view of a possible higher sense of accountability in comparison to the social accountability expected in a cadaveric donor programme. Also, adherence tends to decrease with the duration of therapy and better-perceived health. The authors do not demonstrate an effect of duration of therapy on MNA but the median duration of drug intake was 36 months in the study which is considerably early in therapy. It would be interesting to note the longitudinal changes to MNA in the authors' patient cohort.

The age of patients has major bearing on adherence as the responsibility of medication administration transitions from the family to the patient in the adolescence. In addition, adolescence is characterised by major neurobehavioural and social changes that impact on their attitude to health, self-care, and adherence. The literature on adherence often report a greater risk of MNA in adolescents than in younger children even though there is evidence to the contrary as well.[3,9,17] Even though the authors detail the distribution of responsibility of administration in the under 12 years of age and older children and demonstrate higher risk of MNA with older age, the age distribution in each aetiology is not available. The remarkably low MNA of 2.4% reported in post-transplantation is possibly also related to the age group of the post-transplantation patients, with 83.3% of them <5 years of age. These patients invariably would have had their medications administered by their caregivers, unlike older children. From the available data, it seems likely that the children with WD and AILD are much older and self-administer medications. As mentioned earlier, adherence

is not a given in children where the caregiver administers medications. Parental employment, understanding of medications and disease, heath-seeking behaviour, psychological disorders in parents, socio-economic constraints and family distress can impact adherence where administration is by parents/care-givers.

NA also functions as a lead point to detect and alleviate psychological comorbidities known to be associated with the disease and NA.[19] Depressive symptoms and anxiety among paediatric renal and LT recipients are associated with illness-related uncertainty and lack of hope and depressive symptoms were associated with treatment NA.[20] Children with WD may have neuropsychological manifestations that impair adherence, the details of which are not apparent from the author′s data. Young people with AILD and associated mental health problems and certain illness perceptions are known to be more non-adherent.[21] Although, the directional causality between NA and depression and other co-morbidities is not known, an attempt at delineating NA and barriers to adherence should also be an opportunity to pro-actively seek out psychological co-morbidities and alleviating them.[22]

The authors have appropriately drawn attention towards influence of rural residence on adherence. The reasons could be multifactorial ranging from economic factors, geographical separation affecting access to healthcare, and health-seeking behaviour. Telemedicine in collaboration with local healthcare providers can be used for continuing education of parents, patients, and local healthcare providers. This could also facilitate monitoring and managing the disease during the phases that do not require speciality investigations or evaluation.[23] This might improve access to care and the confidence in care, thereby impacting adherence. More innovative hub and spoke solutions may be required for speciality lab investigations which are more centralised in the speciality centres, thus decreasing the need for travel to speciality centres.[24] This would involve state support and funding to be a reality and beyond the scope of a single speciality centre′s mandate except for advocating to initiate change.

The authors highlight the issue of adherence in paediatric hepatology in India.[5] Further in-depth understanding of the behaviour of their patients and their families using appropriate methodologies will provide the data to design effective and tailored interventions appropriate in the Indian context. We congratulate the authors for their first step in addressing this difficult problem.

CREDIT AUTHORSHIP STATEMENT

All authors contributed to the manuscript and approved the final manuscript.

FINANCIAL DISCLOSURE AND FUNDING

The authors have no financial relationships relevant to this article to disclose. No conflict of interests.

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21 November 2022.